Textile-enabled Bioimpedance Instrumentation for Personalized Health Monitoring Applications

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Licentiate Thesis in Applied Medical Engineering
Stockholm, Sweden 2013
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Royal Institute of Technology
School of Technology and Health
Stockholm, Sweden 2013
Dedicated to Evelyn
Abstract

A growing number of factors, including the costs, technological advancements, an ageing population, and medical errors are leading industrialised countries to invest in research on alternative solutions to improving their health care systems and increasing patients’ life quality. Personal Health System (PHS) solutions envision the use of information and communication technologies that enable a paradigm shift from the traditional hospital-centred healthcare delivery model toward a preventive and person-centred approach. PHS offers the means to follow patient health using wearable, portable or implantable systems that offer ubiquitous, unobtrusive bio-data acquisition, allowing remote access to patient status and treatment monitoring.

Electrical Bioimpedance (EBI) technology is a non-invasive, quick and relatively affordable technique that can be used for assessing and monitoring different health conditions, e.g., body composition assessments for nutrition. EBI technology combined with state-of-the-art advances in sensor and textile technology are fostering the implementation of wearable bioimpedance monitors that use functional garments for the implementation of personalised healthcare applications.

This research studies the development of a portable EBI spectrometer that can use dry textile electrodes for the assessment of body composition for the purposes of clinical uses. The portable bioimpedance monitor has been developed using the latest advances in system-on-chip technology for bioimpedance spectroscopy instrumentation. The obtained portable spectrometer has been validated against commercial spectrometer that performs total body composition assessment using functional textrode garments.

The development of a portable Bioimpedance spectrometer using functional garments and dry textile electrodes for body composition assessment has been shown to be a feasible option. The availability of such measurement systems bring closer the real implementation of personalised healthcare systems.

Keywords personal healthcare systems • electrical bioimpedance • wearable • portable • monitoring • textrodes • body composition • chronic kidney disease • ambient assisting living • wireless sensor
Preface

This PhD research has been conducted under a double PhD agreement degree between the School of Technology and Health (STH) at the Royal Institute of Technology (KTH) in Sweden and the School of Telecommunications (EUITT) at the Technical University of Madrid (UPM) in Spain.

This research was performed at the University of Boras (HB) in Sweden under the supervision of Professor Kaj Lindecrantz from KTH and Dr. Fernando Seoane from KTH and HB in Sweden; additionally with the collaboration of Professor Miguel Angel Valero and Dr. Ivan Pau de la Cruz from UPM in Spain.
List of Appended Papers

The thesis includes the following appended papers, which they will be referred and numbered by Roman numerals. The complete papers are attached as appendices at the end of this document.


Division of work between authors. Each author’s contribution at different stages of the reported studies is given in the following paragraphs. Names are shorted alphabetically by Surname and do not reflect any further weight in contribution.

Paper I

Ferreira and Sanchez under the supervision of Bragos and Seoane contribute the experiment design and idea. Data acquisition was executed by Ferreira and Sanchez. Data analysis was performed by Ferreira, Sanchez and Seoane. The study was reported by Bragos and Seoane.

Paper II

Ferreira developed the analog-front end used for the experiment and Ansede, Ferreira and Seoane contribute to the study design. Data acquisition was carried out by Ansede. Data analysis was performed by Ansede and Ferreira and reported by Ferreira and Seoane.

Paper III

Ferreira design and implemented the bioimpedance spectrometer used for the experiment. Ferreira and Seoane contribute to the data acquisition and data analysis. The study was reported by Ferreira.
Other scientific contributions


“Bioimpedance-Based Wearable Measurement Instrumentation for Studying the Autonomic Nerve System Response to Stressful Working Conditions”. J. Ferreira, R. Buendia, L. Alvarez et al. XV. International Conference on Electrical Bio-Impedance (ICEBI) and XIV. Conference on Electrical Impedance Tomography (EIT), Heilbad Heiligenstadt, Germany, 2013 (Accepted for publication)

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I would especially like to thank my parents Daniel Ferreira and Catalina González as well as my brother Pablo for their guidance and support through life. Finally, I would like to express my deepest gratitude to my girlfriend Evelyn Lebis for her love, patience and never ending support.

*Muchas gracias a todos!*

*Javier Ferreira*

*March, 2013*
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# Abbreviations and Symbols

## Abbreviations

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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>AFE</td>
<td>Analog Front End</td>
</tr>
<tr>
<td>BCA</td>
<td>Body Composition Assessment</td>
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<tr>
<td>BIS</td>
<td>Bioimpedance Spectroscopy</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CVC</td>
<td>Current to Voltage Converter</td>
</tr>
<tr>
<td>DDS</td>
<td>Direct Digital Synthesis generator</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual Energy X-Ray Absorptiometry</td>
</tr>
<tr>
<td>DFT</td>
<td>Discrete Fourier Transform</td>
</tr>
<tr>
<td>EBI</td>
<td>Electrical Bioimpedance</td>
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<td>EBIS</td>
<td>Electrical Bioimpedance Spectroscopy</td>
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<tr>
<td>EC</td>
<td>Extra Cellular</td>
</tr>
<tr>
<td>ECF</td>
<td>Extra Cellular Fluid</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass</td>
</tr>
<tr>
<td>GND</td>
<td>Ground Potential</td>
</tr>
<tr>
<td>HD</td>
<td>Haemodialysis</td>
</tr>
<tr>
<td>HHD</td>
<td>Home Haemodialysis</td>
</tr>
<tr>
<td>IC</td>
<td>Intra Cellular</td>
</tr>
<tr>
<td>ICF</td>
<td>Intra Cellular Fluid</td>
</tr>
<tr>
<td>ICT</td>
<td>Information and Communication Technologies</td>
</tr>
<tr>
<td>INA</td>
<td>Instrumentation Amplifier</td>
</tr>
<tr>
<td>LC</td>
<td>Lung Composition</td>
</tr>
<tr>
<td>LPF</td>
<td>Low Pass Filter</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NLLS</td>
<td>Non-Linear Least Square</td>
</tr>
<tr>
<td>PD</td>
<td>Peritoneal Dialysis</td>
</tr>
<tr>
<td>PGA</td>
<td>Programmable Gain Amplifier</td>
</tr>
<tr>
<td>PHS</td>
<td>Personalized Healthcare Systems</td>
</tr>
<tr>
<td>RR</td>
<td>Respiration Rate</td>
</tr>
<tr>
<td>SMT</td>
<td>Surface Mount Technology</td>
</tr>
<tr>
<td>SoC</td>
<td>System-on-Chip</td>
</tr>
<tr>
<td>SPP</td>
<td>Serial Port Profile</td>
</tr>
</tbody>
</table>
STD  
TBC  
TBW  
Textrode  
TRS  
VCV  

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Units</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$</td>
<td>rad/s</td>
<td>Angular frequency</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>-</td>
<td>Dimensionless Cole parameter Alpha</td>
</tr>
<tr>
<td>$\tau$</td>
<td>sec</td>
<td>Relaxation time constant</td>
</tr>
<tr>
<td>$C_m$</td>
<td>farads</td>
<td>Membrane Capacitance</td>
</tr>
<tr>
<td>ECF</td>
<td>liters</td>
<td>Extra Cellular Fluid content</td>
</tr>
<tr>
<td>$f_c$</td>
<td>Hz</td>
<td>Characteristic Frequency</td>
</tr>
<tr>
<td>$H$</td>
<td>cm</td>
<td>Body Height</td>
</tr>
<tr>
<td>ICF</td>
<td>liters</td>
<td>Intra Cellular Fluid content</td>
</tr>
<tr>
<td>$R_\infty$</td>
<td>$\Omega$</td>
<td>Resistance at infinite frequency</td>
</tr>
<tr>
<td>$R_0$</td>
<td>$\Omega$</td>
<td>Resistance at zero frequency</td>
</tr>
<tr>
<td>$R_e$</td>
<td>$\Omega$</td>
<td>Resistance Extracellular Medium</td>
</tr>
<tr>
<td>$R_i$</td>
<td>$\Omega$</td>
<td>Resistance Intracellular Medium</td>
</tr>
<tr>
<td>TBW</td>
<td>liters</td>
<td>Total Body Water content</td>
</tr>
<tr>
<td>$W$</td>
<td>kg</td>
<td>Body Weight</td>
</tr>
<tr>
<td>$Z_{ep}$</td>
<td>$\Omega$</td>
<td>Electrode polarization impedance</td>
</tr>
<tr>
<td>$Z_{TUS}$</td>
<td>$\Omega$</td>
<td>Impedance of the tissue under study</td>
</tr>
<tr>
<td>$\rho$</td>
<td>$\Omega \cdot m$</td>
<td>Electrical Resistivity</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>$(\Omega \cdot m)^{-1}$</td>
<td>Electrical Conductivity</td>
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Chapter 1

Introduction

A growing number of factors including rising costs, technological advancements and an ageing population, are prompting industrialised countries to invest in research on alternative solutions for improving their health care systems and increasing patients’ life quality. In the EU, for example, the health care systems already account for approximately 9% of the gross domestic product (EU-FP7-ICT-C5 2012), and the ageing of the population is generating immense pressure to increase this number.

Personal Healthcare System (PHS) offers the means to follow a patient’s health by using wearable, portable or implantable systems. These systems offer ubiquitous, unobtrusive bio-data acquisition for the purpose of deriving important information about patient health statuses and to provide feedback to the patient to assist in disease prevention, treatment and lifestyle management. PHS provides health professionals with comprehensive monitoring and diagnostic data that will help them to improve the diagnostics and offer more effective care to their patients. The PHS are formed from different elements; a typical PHS is formed from the following elements: biomedical sensors that could be wearable, portable or implantable, communications interfaces such as wireless technologies, and intelligent signal processing to assist professionals or patients in decisions and in knowledge management.

The use of PHS provides continuous health monitoring, disease management and ambient assisted living, which is expected to offer continuity of care, to improve patients quality of life and to rationalise healthcare. The monitoring of physiological signals with portable, unobtrusive ubiquitous measurement devices is an essential component for the proliferation of home health monitoring applications allowing remote access to patient status and treatment monitoring.

In recent years several projects have been funded under the EU’s Seventh Framework Programme (FP7) that support the development of Information and Communication Technologies (ICT) for the development of health sciences, material sciences and neurosciences. For example, the MyHeart project IST-2002-507816 (Habetha 2006) was a case study for the development of a PHS for the prevention and monitoring of patients with cardiovascular diseases. MyHeart was focused on the development of smart electronics, smart textile systems and custom services to monitor cardiovascular patients at home. The project was tested in several hospitals and patient’s homes across Europe, where data were collected, with the goal of
CHAPTER 1 INTRODUCTION

analysing and obtaining health parameters that could indicate the patient’s status. The STELLA project IST-028086 (STELLA EU Project 2012) aims to develop new techniques for implementing flexible and stretchable electronics for the development of body measurement sensors as well as new ways of electronic interconnections in flexible and stretchable materials to be used in biomedical applications.

Electrical Bioimpedance (EBI) measurements have been used extensively as a tool for monitoring and diagnosing many diseases, e.g. skin cancer detection (Aberg, Geladi et al. 2005), lung oedema detection (Beckmann, Van Riesen et al. 2007), cardiac stroke volume assessment (Bernstein 2010) or body composition assessment (Van Loan, Withers et al. 1993, Moissl, Wabel et al. 2006). EBI technology compared with other methods presents a quick, non-invasive and relatively affordable assessment of tissue composition. EBI technology combined with the latest advances in sensor and textile technology (Beckmann, Neuhaus et al. 2010, Marquez, Seoane et al. 2013) are enabling the implementation of home-based personalised healthcare applications that are based on EBI technology.

1.1 Research objectives

The aim of my studies is to research new technologies that could facilitate the implementation of wearable body monitoring sensors, which could be integrated in functional textile garments for the implementation of PHS. The body sensors are used to monitor biosignals such as electrocardiograms, temperature, body position or bioimpedance-related signals. These portable devices are designed to be unobtrusive and ubiquitous, and are specifically designed to work with textile sensors and to be integrated seamlessly into functional textile garments.

More specifically, this work has been focused on the development of a bioimpedance portable monitor that uses dry textile electrodes to monitor body fluid distribution and that could enable the implementation of PHS, e.g., in patients who suffer from Chronic Kidney Disease (CKD) and who require the maintenance of an euvoletic state through homecare dialysis.

According to the aforementioned requisites, two research questions for the evaluation of the concept have been identified:

- Is it possible to implement a portable-wearable Bioimpedance Spectrometer that has similar performance to the clinical measuring devices?
- Is it possible to perform Bioimpedance Measurements using functional garments and textile electrodes for the implementation of Personal Healthcare Systems with the aforementioned portable-wearable Bioimpedance Spectrometer?

These research questions have been tested in this thesis, and the research tasks performed here were aimed at demonstrating that a small and portable system could take measurements as well as commercial equipment, that textile electrodes could be used with bioimpedance systems to monitor body fluids and that the development of a PHS for CKD could be a feasible option for using bioimpedance technology and functional textile garments.

Although the goal of my research studies is aimed toward enabling monitoring on PHS using textile-enabled measurement instrumentation, such at PHS has not been implemented yet; only the first steps regarding the development of monitoring instrumentation have been validated in this study.
1.2 Thesis overview

This thesis report is structured in a total of six chapters and three appended publications that have resulted from this research. Following this introduction, Chapter 2 provides a general review and introduction to Electrical Bioimpedance theory, measurement techniques and the application of bioimpedance for body fluid assessment. Chapter 3 describes the system requirements and materials that are used for the development of a portable bioimpedance spectrometer, including the description of the dry textile electrodes garment used. The results obtained in this work are summarised in Chapter 4; the first part of Chapter 4 covers the implementation results for the portable bioimpedance spectrometer, and the second part covers the system validation, in which measurements of total body composition are performed using dry Textrode garments. In Chapter 5, the results are discussed, and the conclusions are drawn. To finalise, Chapter 6 presents the future work is presented, and describes how the obtained results of this thesis are intended to be used and validated in a personalised healthcare system for chronic kidney disease patients.
Chapter 2

Electrical Bioimpedance Measurements

2.1 Introduction

Biological tissues are primarily composed of cells and fluids. For example in the human body, the muscle tissue comprises long and tubular cells called myocytes, which contract to produce force. The cell is considered to be the basic structural and functional unit of all biological organisms, and it can exist as an independent unit of life. A cell is formed by a lipid bilayer membrane surrounding the cell, known as the cell membrane, which isolates the Intracellular (IC) medium from the Extracellular (EC) medium. The IC space contains the cell organelles, the cell nucleus and other cell components. The EC space, which surrounds the cells, is divided into two major sub compartments: the interstitial fluid and the blood plasma.

Because of the existence of free ions, Sodium (Na\(^+\)), Potassium (K\(^+\)), Chlorine (Cl\(^-\)), and protein ions that are contained in the IC and EC mediums, biological tissue can be considered to be an electrolyte that has electrical properties. Therefore, the IC and EC mediums are considered to be ionic conductors, and the lipid cell membrane is considered to behave as a capacitor because of its dielectric properties.

Early studies of biological tissues and electricity contributed to the discovery and characterisation of electrical properties in tissue (Fricke and Morse 1925, Schwan 1957). H. Fricke presented the electrical equivalent model of blood cells, which is based on the assumption that the cells are suspended in the EC medium with electrical properties. This model, apart from being a precise model, has been fully acknowledged and extensively used with acceptable results. Fricke’s representation model is shown in Figure 2.1, where \( R_e \) represents the resistance of the extra cellular medium, \( R_i \) represents the resistance of the EC medium and \( C_m \) represents the capacitance of the cell membrane. From Fricke’s Model in Figure 2.1, it is clear that the current will flow through different paths depending on the frequency. At low frequencies, the current will flow mainly through the EC medium. At higher frequencies the modelled cell membrane capacitor will act as a shunt that allows current to flow through the IC medium.
Although Fricke’s circuit model is a good model for a suspension of cells, it is less accurate for the more complex structures that constitute the human body. Other models, such as the Cole Model (Cole 1940), have been proposed and used, which shows a better agreement with the empirical data. Currently, the Cole Model is used in several EBI applications for tissue characterisation such as Body Composition Analysis. The Cole Function and Model will be introduced in the following sections.

The passive electrical properties of biological tissue exhibit a certain dependency on the frequency of the externally applied electrical field. The conductivity ($\sigma$) and permittivity ($\varepsilon$) are passive electric properties of biological tissue that are expressed as a function of the frequency. The conductivity indicates how easily the free charges move through a medium, and it is related to the conductance. The permittivity is the measure of the resistance that is encountered when an electric field is formed in a dielectric medium. The permittivity is also expressed as the ability to permit the storage of electric energy in a dielectric medium; this measurement is related to the conductance.

The impedance of the biological tissue varies with the frequency and four specific dispersions windows have been identified: $\alpha$, $\beta$, $\delta$ and $\gamma$ (Schwan 1994, Schwan 1999), see Figure 2.2. The main contributions of these dispersions are explained as follows:

- $\alpha$ dispersion: This dispersion appears between 1 mHz and 1 kHz, and the mechanisms that contribute to this dispersion window are not fully clear (Schwan 1994).
- $\beta$ dispersion: This dispersion is caused by the cellular structure of the tissue, which has poorly conducting membranes: the dispersion window is located between 1 kHz and 100 MHz.
- $\delta$ dispersion: This dispersion appears between the $\beta$ and $\gamma$ dispersions, and its influence is caused by amino acids and proteins in the frequency range of hundreds of MHz and a few GHz.
- $\gamma$ dispersion: This dispersion is caused by dipolar mechanisms in polar media such as salts, proteins and water: this dispersion is found between 100 MHz and 100 GHz.

The $\alpha$ and $\beta$ dispersion windows are quite relevant for clinical applications, because in these dispersion windows, most changes in the electric properties of human tissue occur, such as the accumulation of fluids or cell structure changes.
2.2 Electrical Bioimpedance measurements

The electrical impedance of a material is the opposition that the material offers to the flow of electrical charges through it. For materials that have a biological origin, the term Electrical Bioimpedance (EBI) is used. To characterise the electrical tissue properties, an external energy source is needed: in EBI measurements, the source of the energy is either an injected current or a voltage that is applied to the biological material. The resulting voltage or current is measured, and the impedance is obtained by applying Ohm’s Law.

To characterise the electric properties over a frequency range, the most common method is to use one single frequency excitation signal at a time to extract the current and voltage signals and to characterise the impedance over a frequency range. This procedure will be repeated \(n\) times when performing a frequency sweep (Pallàs-Areny and Webster 2001). Another proposed method uses an excitation signal that is formed by the summation of \(n\) signals at different frequencies, called multi-sine or chirp excitation. Compared to a single excitation signal (Bragos, Blanco-Enrich et al. 2001, Sanchez, Vandersteen et al. 2012), this approach has the advantage of accomplishing the impedance characterisation in a shorter amount of time compared with the frequency sweep methods.

2.2.1 Measurement electrode configuration

Depending on the EBI Application, there are two methods for obtaining the impedance value: exciting with a controlled current or with a controlled voltage. Each method has its own advantages and disadvantages (Grimnes and Martinsen 2008), but the most common technique uses controlled current for excitation and measures the resulting voltage. The excitation current should be chosen to comply with the standard IEC-60601-1 for ensuring patient safety and electrical currents (International Electrotechnical Commission 2010). Throughout the remainder of this thesis, controlled current excitation is assumed.
A typical EBI measurement requires two, three or four contact points (Grimnes and Martinsen 2008) to measure the voltage and current values. The impedance is then obtained through Ohm’s Law, see Equation (2.1), where $\omega$ is the frequency in [rad/s].

$$Z(\omega) = \frac{V(\omega)}{I(\omega)}$$  \hspace{1cm} (2.1)

In a 2-electrode or bipolar EBI measurement, two electrodes are used to inject the current, and the same electrodes are used to sense the resulting voltage. In Figure 2.3, an example of an EBI bipolar configuration measurement of the lower part of the leg is displayed (a), and the general bipolar configuration equivalent electrical circuit is shown in (b), where $I_m(\omega)$ is the constant current, $Z_{ep1}(\omega)$ and $Z_{ep2}(\omega)$ are the electrode polarisation impedances, $Z_{tus}(\omega)$ is the measured impedance, and the differential amplifier is used to obtain the voltage $V_m(\omega)$. The measurement impedance can be expressed in terms of its equivalent electric circuit equation displayed in Equation (2.2).

$$Z_{m,2e}(\omega) = \frac{V_m(\omega)}{I_m(\omega)} = \frac{V_{zep1}(\omega) + V_{ztus}(\omega) + V_{zep2}(\omega)}{I_m(\omega)}$$ \hspace{1cm} (2.2)

Because the electrical current flows through the sensing electrodes, the voltage drop across $Z_{ep1}(\omega)$ and $Z_{ep2}(\omega)$ is included in the measured voltage together with the voltage over $Z_{tus}(\omega)$. Assuming that the electrode polarisation impedances are approximately equal, the measured impedance equation $Z_{m,2e}(\omega)$ is shown in Equation (2.3).

$$Z_{m,2e}(\omega) = \frac{V_m(\omega)}{I_m(\omega)} = \frac{I_m(\omega) \cdot \left(2 \cdot Z_{ep}(\omega) + Z_{tus}(\omega)\right)}{I_m(\omega)} = 2 \cdot Z_{ep}(\omega) + Z_{tus}(\omega)$$ \hspace{1cm} (2.3)

For a 4-Electrodes or Tetrapolar configuration, two electrodes are used to inject the current and two electrodes are used to sense the resulting voltage. In Figure 2.4, the tetrapolar EBI measurement of the lower part of the leg (a) as well as the typical tetrapolar electrical circuit (b) are displayed. In Figure 2.4 (b), the impedances of the electrodes used to inject current are $Z_{ep1}(\omega)$ and $Z_{ep2}(\omega)$, and the impedances of the
electrodes that are used to sense the voltage are $Z_{ep3}(w)$ and $Z_{ep4}(w)$. The impedance is calculated according to Equation (2.4).

$$Z_{m,4e}(\omega) = \frac{V_m(\omega)}{I_m(\omega)} = \frac{V_{zep3}(\omega) + V_{ztus}(\omega) + V_{zep4}(\omega)}{I_m(\omega)}$$  \hspace{1cm} (2.4)$$

Assuming an ideal differential amplifier, the measured impedance can be expressed as in Equation (2.5).

$$Z_{m,4e}(\omega) = \frac{I_m(\omega)Z_{ztus}(\omega)}{I_m(\omega)} = Z_{ztus}(\omega)$$  \hspace{1cm} (2.5)$$

Because the input impedances $Z_{ina+}$ and $Z_{ina-}$ of an ideal differential amplifier are infinite, the currents and voltages in the electrode polarisation impedances $Z_{ep3}(\omega)$ and $Z_{ep4}(\omega)$ are equal to zero; therefore, the measured impedance $Z_m(\omega)$ is equal to $Z_{ztus}(\omega)$. This advantage over a bipolar configuration makes the tetrapolar configuration the most commonly used configuration.

### 2.2.2 The skin-electrode interface

Electrodes constitute an interface between the electronic currents in the measuring electronic instrumentation and the ionic currents that flow in the tissues. Typically, a non-invasive skin electrode is formed by a metal conductor, e.g. Silver, and an electrolytic gel, e.g., Silver-Chloride, which is applied to the skin surface, see Figure 2.5. The human skin is composed of three primary layers: the epidermis, the dermis and the hypodermis, also called the subcutaneous layer. The epidermis is the primary barrier between the outside world and the interior of the body, and it is primarily composed of dead cells that act as a dielectric membrane that is semi-permeable to ions. The dermis and subcutaneous layers are beneath the epidermis and contain some biological components that behave as ionic conductors, such as the hair follicles, sweat glands and blood vessels.
The electrodes that are used for EBI measurements are typically non-invasive and they are placed on the skin surface. In Figure 2.5, the different electrode-skin layers (a) and the equivalent circuit model (b) are depicted. Each skin layer has an equivalent electrical model (Neuman 2009). The $C_{\text{skin}}$ and $R_{\text{skin}}$ represent the electrical behaviour of the epidermis, and the dermis and subcutaneous layer is represented by a resistor $R_{\text{tissue}}$. Conventional skin electrodes are provided with an electrolyte gel layer that enables the transfer of ionic currents and that is modelled by the resistor $R_{\text{gel}}$, and the interface electrode-electrolyte is represented by $C_{\text{DoubleLayer}}$ and $R_{\text{DoubleLayer}}$, Figure 2.5.b. The elements $V_{\text{HalfCell}}$ and $V_{\text{skin}}$ are generated by an accumulation of charges between the layers; this effect is known as the “Helmholtz double layer” effect.

Advances in textile materials and conductive yarns allow the development and validation of Textile Electrodes (Textrodes) for use with EBI measurements (Medrano, Beckmann et al. 2007, Beckmann, Neuhaus et al. 2010, Marquez, Seoane et al. 2013). Dry textrodes present high electrode-skin impedance because of the absence of electrolytic medium between the electrode and the skin: this effect is reduced sometime after the electrode has been applied and the skin starts sweating, which allows ions that are present in the sweat to function as an electrolytic interface. Factors such as the textile structure, the choice of textile-conductive materials, and the skin hydration status could affect the textrode performance, and their influence must be taken into consideration when textrodes are used. The proliferation of the use of textrodes together with their performance improvements enable a handful of novel and emerging applications, such as in the field of home healthcare and personal health systems.

As discussed in the previous section, the skin-electrode impedance polarization can play an important role in the estimation of the impedance $Z_{\text{tissue}}$, especially for 2- and 3-electrode configurations. Measurement errors could occur due to several factors such as the use of non-ideal electronic instrumentation, the presence of high electrode polarisation impedance, stray capacitances or the presence other types of artefacts (Bogónez-Franco, Nescolarde et al. 2009, Buendía, Bogónez-Franco et al. 2012). Therefore, to minimise all of the possible errors, the selection of electrodes and the electronic designs must be considered in the development of EBI measuring systems.
2.2.3 Sine correlation estimation method

Several possible methods exist for estimating the impedance value after the voltage-current signals have been obtained. These methods include Fast Fourier Transform (FFT) techniques, Sine Correlation methods (Pallas-Areny and Webster 1993), Gain-Phase Detectors (Yuxiang, Jue et al. 2006) and Lock-In Amplifiers, among others.

One of the most widely used techniques is the Sine Correlation method, which is also called Quadrature Demodulation, and its functional block diagram is depicted in Figure 2.6. The injected current $I_m(t)$ flows through the unknown impedance $Z$, and the resulting voltage $V_m(t)$ is multiplied by the in-phase and in-quadrature signals, which will be averaged to obtain the impedance real $Re(t)$ and imaginary $Im(t)$ component values.

Let us consider that the frequency $\omega$ is equal to the impedance frequency analysis, see Equation (2.6), then the injected current $i_m(t)$ has the value shown on Equation (2.7), and the measured voltage $v_m(t)$ will be equal to Equation (2.8).

$$if \ \omega = \omega_m \rightarrow Z(\omega_m) = |Z(\omega_m)| \cdot e^{j\theta(\omega_m)}$$ (2.6)

$$i_m(t) = I_0 \cdot Sin(\omega_m t)$$ (2.7)

$$v_m(t) = |Z(\omega_m)| \cdot I_0 \cdot Sin(\omega_m t + \theta_z(\omega_m))$$ (2.8)

In the sine correlation method, the measured voltage will be multiplied by the in-phase and in-quadrature signals, and by using double angle relationships the components $v_Q(t)$ and $v_I(t)$ are obtained, see Equations (2.9) and (2.10) below.

$$v_Q(t) = v_m(t) \cdot Sin(\omega_m t) = \frac{|Z(\omega_m)| \cdot I_0}{2} \cdot [\cos(\theta_z(\omega_m)) - \cos(2\omega_m t + \theta_z(\omega_m))]$$ (2.9)

$$v_I(t) = v_m(t) \cdot Cos(\omega_m t) = \frac{|Z(\omega_m)| \cdot I_0}{2} \cdot [\sin(\theta_z(\omega_m)) + \sin(2\omega_m t + \theta_z(\omega_m))]$$ (2.10)
If the signals are averaged over a time $t_c = n/\omega_m$ that is equal to $n$ periods of the analysis frequency $\omega_m$, then the terms of $\cos(\ldots)$ and $\sin(\ldots)$ in both equations will be equal to zero, which leaves only the DC component of the signal. The average signals $V_{avgR}(t)$ and $V_{avgI}(t)$ are obtained as shown in see Equations (2.11) and (2.12), below.

$$V_{avgR}(t) = \frac{i_0}{2} \cdot (|Z(\omega_m)| \cdot \cos(\theta_Z(\omega_m))) = \frac{i_0}{2} \cdot Re(Z(\omega_m)) \quad (2.11)$$

$$V_{avgI}(t) = \frac{i_0}{2} \cdot (|Z(\omega_m)| \cdot \sin(\theta_Z(\omega_m))) = \frac{i_0}{2} \cdot Im(Z(\omega_m)) \quad (2.12)$$

Finally, to obtain the Real $R_m$ and Imaginary $X_m$ components from the measured impedance, a gain factor equal to $a = \frac{2}{i_0}$ is applied, as in Equations (2.13) and (2.14), below.

$$Re(t) = a \cdot V_{avgR}(t) = R_m \quad (2.13)$$

$$Im(t) = a \cdot V_{avgI}(t) = X_m \quad (2.14)$$

One critical point that is present in this method is the signal averaging stage: when the averaging time is not equal to $n$ periods of the analysis frequency $\omega_m$, the estimated impedance values will contain an error.

Different implementations of this estimation method are employed, where the signals are digitalised by either an ADC or a DAC, which allows a processor or microcontroller to perform part of the mathematical operations and the storage of the information digitally for future calculations (Pallas-Areny and Webster 1993, Yuxiang, Jue et al. 2006).

### 2.3 EBI for body composition assessment

The use of EBI technology for the estimation of Body Composition Assessments (BCA) offers a quick, inexpensive and non-invasive measurement procedure compared with clinical methods such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or Dual Energy X-Ray Absorptiometry (DEXA). These clinical methods are used as “Golden Standards” for BCA and they offer better accuracy and consistency compared to EBI methods; however they require expensive equipment that is usually located in clinics or hospitals. Traditional methods are invasive and require procedures such as blood samples, exposure to X-Ray radiations or the administration of contrast agents, which make these methods unsuitable for continuous monitoring applications.

The use of EBI spectroscopy measurements, Cole modelling and Hanai mixture theory has become one of the most common approaches for estimating BCA parameters (Van Loan, Withers et al. 1993, Matthie 2008). The following sections will introduce all of the factors that are related to the acquisition of BCA parameters from EBI spectroscopy measurements.
2.3.1 Cole modelling

In 1940, Kenneth S. Cole presented the empirical Cole function, see Equation (2.15) (Cole 1940). The Cole function is a complex non-linear function that models and experimentally fits EBI measurements in the \( \beta \) dispersion range, between several kHz and a few hundreds of MHz. The equation is defined by four parameters \( R_0, R_\infty, \alpha, \tau \) and the independent variable \( \omega \) that represents the natural frequency.

\[
Z(\omega) = R_\infty + \frac{R_0 + R_\infty}{1 + (j\omega\tau)\alpha} \tag{2.15}
\]

In Equation (2.15), the parameter \( R_0 \) represents the resistance at zero frequency, which contains information about the conductivity of the EC medium. \( R_\infty \) represents the resistance at a high frequency that includes information about the conductivity of both mediums, the EC and the IC: the parameter \( \tau \) is the relaxation time constant, which is the inverse of the natural frequency \( \tau = 1/\omega_\tau \), and \( \alpha \) is a dimensionless parameter for which there is no clear explanation regarding its origin.

The Fricke’s Model and the Cole Function are quasi-compatible. The EC medium resistance \( R_e \) is equal to the resistance at zero frequency \( R_0 \), as in Equation (2.16): at high frequency, the ionic currents flow through the EC and IC mediums. Therefore, the IC medium resistance \( R_i \) can be obtained as shown in Equation (2.17), and the membrane capacitance can be extracted using the Cole parameter \( \tau \).

\[
R_e = R_0 \tag{2.16}
\]

\[
\frac{1}{R_\infty} = \frac{1}{R_e} + \frac{1}{R_i} \tag{2.17}
\]

To obtain the four Cole parameters, the measurement data are fitted to the Cole function using computational methods that will find the Cole parameters that approximate as close as possible the experimental data. One implemented method is to fit the data to the semicircle in the impedance plane (Kun and Peura 1999). This method offers a good estimation of \( R_0, R_e \) and \( \alpha \), but the estimation of the parameter \( \tau \) is less accurate because this method does not account for the frequency information of the EBI measurements. The Non Linear Least Square (NLLS) fitting method is also used extensively to fit the Cole model in the different planes, such as the magnitude plane or the imaginary plane, and it has shown good results compared with other fitting methods for the estimation of Cole parameters for their use in BCA applications (Buendia, Gil-Pita et al. 2011, Nordbotten, Tronstad et al. 2011).

2.3.2 Total body composition analysis

Measurements of the Total Body Composition (TBC), also called the Total Right Side (TRS), are taken using a tetrapolar configuration and by placing the electrodes on the right side between the wrist and the ankle, with the subject lying in a supine position see Figure 2.7. The EBI spectroscopy data obtained from the measurement is fitted to the Cole Function and the obtained parameters \( R_0 \) and \( R_\infty \) are used to obtain the Intra Cellular Fluid (ICF) and Extra Cellular Fluid (ECF) resistances, as shown in Equations (2.16) and (2.17).
One of the most accepted approaches for estimating the ECF content from TRS EBI measurements was proposed by De Lorenzo et al. (De Lorenzo, Andreoli et al. 1997). This method is based on Hanai’s Mixture conductivity theory (Hanai 1968), as shown in Equation (2.18).

\[
ECF = K_e \left( \frac{H^2 \cdot \sqrt{W}}{R_e} \right)^{2/3} \tag{2.18}
\]

In Equation (2.18), the ECF parameter is in litres, H is the height in cm, W is the weight in kg, \(R_e\) is the resistance of the ECF Equation (2.16) in Ohms, and \(K_e\) is a dimensionless constant that depends on the shape factor of the human body, which is considered to be the sum of 5 cylinders. Experimental studies have suggested that the constant \(K_e\) for males is equal to \(K_{e,m} = 0.306\) and for females is \(K_{e,f} = 0.316\) (Van Loan, Withers et al. 1993).

The ICF volume is calculated as proposed by (De Lorenzo, Andreoli et al. 1997) and is depicted in Equation (2.19). In the Equation, \(R_i\) is the resistance of the ICF, and \(K_p\) is the resistivity ratio of the ICF and ECF, which for males is equal to \(K_{p,m} = 3.82\) and for females is equal to \(K_{p,f} = 3.40\).

\[
\left( 1 + \frac{ICF}{ECF} \right)^{5/2} = \frac{R_e + R_i}{R_i} \cdot \left( 1 + K_p \frac{ICF}{ECF} \right) \tag{2.19}
\]

New approaches by (Moissl, Wabel et al. 2006) propose the correction of Hanai’s theory for the calculation of ICF and ECF while considering the effect of the Body Mass Index (BMI). Therefore the ICF and ECF can be obtained by Equations (2.20) and (2.21), as follows:

\[
ECF_{BCS} = k_{E_{BCS}} \left( \frac{H^2 \cdot \sqrt{W}}{R_e} \right)^{2/3} \tag{2.20}
\]
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\[ ICF_{BCS} = k_{ICW} \left( \frac{H^2 \cdot \sqrt{W}}{R_i} \right)^{2/3} \]  \hspace{1cm} (2.21)

Where \( k_{ECW} \) and \( k_{ICW} \) are functions of BMI and can be obtained as follows:

\[ k_{ECW} = \frac{0.188}{BMI} + 0.2883 \]  \hspace{1cm} (2.22)

\[ k_{ICW} = \frac{5.8758}{BMI} + 0.4194 \]  \hspace{1cm} (2.23)

This new approach suggested by Moissl, Wabel et al. 2006 was obtained by a cross-validation study on 152 test subjects, where EBI Spectroscopy measurements were compared with dilution methods. The ECF was obtained with a precision of 0.4 ± 1.41 litres compared with the dilution methods.

Another method, which was suggested by Jaffrin M. Y. et. al. (Jaffrin and Morel 2008) is used to estimate TBW from the FFM, and applies EBIS analysis and DEXA measurements. The TBW is obtained using the following Equations (2.24) and (2.25).

\[ TBW = k_t \left( \frac{H^2 \cdot \sqrt{W}}{R_{oo}} \right)^{2/3} \]  \hspace{1cm} (2.24)

\[ k_t = \left( \frac{K_b \cdot \rho_{wn}}{D_b} \right)^{2/3} \]  \hspace{1cm} (2.25)

In Equation (2.25), \( K_b \) is the shape factor that has a value of 4.3, \( \rho_{wn} \) is the resistivity that for men is equal to 104.3 Ω·m and for women is equal to 100.5 Ω·m, and \( D_b \) is the body density, which has a value of 1.05. In this approach, the Total Body Water (TBW) can be obtained by adding the ICF and the ECF. The Fat Free Mass (FFM) can be obtained by the empirical relationship, which states that the 73.2% of the FFM is water (Van Loan, Withers et al. 1993, Jaffrin and Morel 2008), see Equation (2.26).

\[ FFM = \frac{TBW}{0.732} \]  \hspace{1cm} (2.26)
Chapter 3

Materials and Methods

This chapter introduces the materials and methods that are used for the implementation of portable EBI spectrometer devices. The first part will enumerate some of the system requirements that are considered for the development of the portable EBI prototype spectrometer. Subsequently, the novel System-on-Chip (SoC) Impedance Network Analyser AD5933 from Analog Devices Inc. (Analog Devices Inc. 2013) will be introduced; additionally, a custom Analog Front End (AFE) that enables the use of the SoC AD5933 for EBI measurements will be described. Finally, the Textrodes and traditional electrodes that are used for the validation of the system will be described.

3.1 Portable EBI spectrometer requirements

The requirements have been kept very general in terms of the specific EBI application; therefore factors such as usability requirements, wearability or system integration aspects, or critical factors for the implementation of a Personalized Healthcare Systems PHS are not considered in these first studies. The portable device will allow its use for different EBI applications, where the instrumentation can be customised to perform impedance measurements over different impedance ranges, e.g., in terms of the Total Body Composition or Segmental measurements.

This thesis discusses the development of a portable and wearable EBI spectrometer that can perform measurements using textile electrodes and functional garments with integrated textile electrodes. Therefore, some of the identified system requirements are the following:

- **System accuracy**: the implemented monitoring device should perform measurements that are equivalent to commercial EBI spectrometers.
- **Patient electrical safety**: the device must fulfil the requirements for patient electrical safety that are imposed by the standard IEC-60601-1 for medical electrical equipment (International Electrotechnical Commission 2010).
- **Portability**: the device should be small, lightweight, and battery operated, and it should be equipped with wireless communications, which enable its integration as portable-wearable device in home-care applications.
The choice of electronic components for the implementation of the portable EBI monitor is based on the previously listed requirements; therefore factors such as power consumption, chip dimensions and printed electronic circuit technology are the key elements for the device implementation.

3.2 The system-on-chip impedance network analyser

The novel SoC Impedance Network Analyser AD5933 is, to date, the only SoC solution that incorporates all of the functional components that are necessary to characterise the impedance over a frequency range using a bipolar configuration. A typical measurement of the frequency range is from 1 kHz to 100 kHz: the impedance dynamic range is from 1kΩ to 10MΩ, with a system accuracy of 0.5%, and it is provided with a serial I2C interface to control the internal functions and the measurement retrieval. The AD5933 can operate with a single power supply between 2.7v and 5.5v; it consumes only 33mW at 3.3v and has dimensions equal to 8x6x2 mm (Analog Devices Inc. 2013).

The main AD5933 functional blocks are depicted in the diagram in Figure 3.1. They are also listed below:

- **The Stimulation Stage**: This stage is formed by a Direct Digital Synthesizer (DDS) which generates the digital sine waves that could be configured for the specific impedance excitation frequency, denoted as \( w_n \), a 12-bit Digital to Analog Converter (DAC) and a Programmable Gain Amplifier (PGA) which adapts the generated voltage that will be applied to the Impedance \( Z_{TUS(w)} \).

- **The Receiver Stage**: This stage is formed by a Current to Voltage Converter (CVC), a Voltage Amplifier, an antialiasing Low Pass Filter (LPF) and a 12-bit Analog to Digital Converter (ADC). The receiver stage will adapt and convert the flowing current through \( Z_{TUS(w)} \) into a voltage that will be fed to the following stage.

- **The Impedance Estimation Stage**: This stage uses 1024 sample points from the signals that are generated by the DDS module, \( \cos[w_n n] \) and \( \sin[w_n n] \), and the digitalised input signal \( x[n] \) to estimate the real and imaginary impedance values using the single Discrete Fourier Transform (DFT) method, see Equations (3.1) to (3.3).

- **The chip control stage**: This stage is formed by the I2C Core module that control all of the chip functions and stores all of the measurement results among other parameters; see the AD5933 datasheet for further details.
To characterise the impedance over a frequency range, the AD5933 uses a frequency sweep; thus, each time that a single frequency point is analysed, the sequence is repeated at a different frequency until the entire spectrum is obtained. For each frequency, the AD5933 will obtain 1024 samples of the output and input signals to estimate the real and imaginary component values performing a 1024-point single frequency DFT analysis, which is also denoted as the Sine Correlation Method in the digital form previously introduced.

\[
X_{(\omega n)} = \sum_{n=0}^{1023} \left( x[n] \cdot \cos[\omega n \cdot n] - j \cdot \sin[\omega n \cdot n] \right) = Re_{(\omega n)} - j \cdot Im_{(\omega n)} \tag{3.1}
\]

\[
Re_{(\omega n)} = \sum_{n=0}^{1023} x[n] \cdot \cos[\omega n \cdot n] \tag{3.2}
\]

\[
Im_{(\omega n)} = \sum_{n=0}^{1023} x[n] \cdot \sin[\omega n \cdot n] \tag{3.3}
\]

To obtain the Impedance Magnitude and Phase values, the obtained real and imaginary components must be adjusted by a calibration factor, check datasheet for the complete operation procedure (Analog Devices Inc. 2013). The calibration factor is obtained by performing a frequency sweep over a known impedance value. The manufacturer suggests that a middle single point or two-point calibration method using a resistor could be used to characterise the system over a frequency range. In the next section the calibration methods will be discussed in more detail.

There are several factors that make the AD5933 unsuitable for the acquisition of EBI measurements. For example:

- Bipolar measurement configuration: Because of this factor, the electrode impedance polarisation is also included in the measured impedance; thus applications of spectral characterisation are basically discarded.
- Voltage-driven measurement: This factor makes it almost impossible to have control over the injected current. This problem can constitute a safety hazard because the injected current can be larger than the values that are established by the electrical safety standard IEC-60601-1.
- The dynamic impedance range is between 1kΩ and 10MΩ, and most of the EBI measurements are below 1kΩ. An application note suggests that lower impedances can be measured using an additional external operational amplifier, but still the measurement system is voltage-driven and has a bipolar configuration.
- The applied voltage contains a DC voltage level that is required to operate with a single power supply; a DC voltage will lead to polarisation of the electrodes.

Because the AD5933 is not suitable to be used in EBI applications, an Analogue Front End (AFE) is required to ensure that these factors are minimised or removed. The suggested AFE will modify the AD5933 voltage-controlled bipolar device into a current-controlled tetrapolar configuration that will ensure patient safety and that is capable of measuring impedances below 1kΩ, as expected in a human body.
3.2.1 Custom analog-front-end

The suggested AFE (PAPER I) (Seoane, Ferreira et al. 2008) is depicted in Figure 3.2, where the functional diagram blocks are shown; note that the interface electrodes between the AFE and the Z\textsubscript{TUS} are not present in this representation. The AFE converts the AD5933 voltage-controlled bipolar configuration to the current-controlled tetrapolar configuration that is presented at the Z\textsubscript{TUS} side. The functional block diagram of the AFE is based on the following two functional units:

- **Voltage to Current Converter:** The output voltage from the AD5933 is filtered by a High Pass Filter (HPF) to remove the DC component, and the HPF output drives a Voltage to Current Converter (VCC) that generates a current that is injected into the Tissue Under Study (TUS). The injected current will generate a voltage drop across the Z\textsubscript{TUS} that will be measured by the next functional unit.

- **Current to Voltage Converter:** The voltage across the Z\textsubscript{TUS} is sensed by an Instrumentation Amplifier (INA), which will amplify the generated voltage at Z\textsubscript{TUS} and also add dc voltage that is equal to the voltage power supply divided by 2, to make the signal dynamic range agree with the input dynamic range of the AD5933. The INA generated voltage will be converted to a current signal and will feed to the AD5933 input pins.

The implementation and validation of the suggested AFE will be discussed in the following sections. To implement the portable EBI monitor, the selection of electrical components used in the implementation of the AFE functional blocks is important.

3.3 Traditional and textile electrodes

The portable EBI monitor was evaluated in human subjects by performing EBI measurements. Therefore, two types of electrodes were used: traditional gel Silver-silver chloride (Ag/AgCl) electrodes and custom-made strap garments that incorporate t extrodes.
Chapter 3  Materials and Methods

The 3M gel Ag/AgCl electrodes, shown in Figure 3.3 right side, belong to the category of non-polarisable electrodes, which allow the transfer of charges with minimum voltage generation at the skin-electrode. The electrodes are formed by a conductive and sticky electrolytic gel that is in contact with the skin, and an electrically conductive snap button which allows the connection with the electronic instrumentation.

The functional textrode straps (Marquez Ruiz 2013), which are shown in Figure 3.3 left side, were used to obtain total right side EBI measurements, and its design allows the correct placements of electrodes to avoid as much as possible any electrode placement variability. Each strap incorporates two separate inner layer of conductive fabric that are in contact with the skin and that are used as electrodes. The conductive fabric material is a knitted silver coated fabric P130+B from the manufacture Shieldex Technik-Tex, which is made of 78% polyamide and 22% elastomer and is coated with 99% conductive silver particles with an approximate resistivity lower than $2 \, \Omega/\text{sq}$. The electrode areas are provided with an inner layer of foam that applies pressure to the conductive fabric, to improve the skin-electrode contact area. The outer layer is made of blue synthetic wrap-knitted fabric. The straps are provided with Velcro fasteners and snap buttons on each textrode for the electronic interconnection.

Figure 3.3  Functional straps with incorporated textrodes for TRS EBI measurements (left) and Ag/AgCl 3M traditional electrodes (right).
Chapter 4

Implementation and Validation
Results

This chapter presents the steps that are taken for the implementation of the portable EBI monitor as well as the validation results. First, the accuracy of the AD5933+AFE is studied to evaluate the performance in several EBI applications. Then, the results of the hardware that was developed are shown, and a description is provided of the portable EBI monitor components. Additionally, a subsection that discusses the different calibration methods is introduced. Finally, the portable EBI monitor performance is studied, where dry textile electrodes are used to obtain TRS EBI measurements.

All of the measurements that were obtained with the AD5933+AFE are compared against the same measurements obtained with the commercial EBI spectrometer SFB7 from ImpediMed Ltd. (ImpediMed 2011). In these studies, the SFB7 is considered to be “Golden Standard” or reference measurement equipment. The SFB7 performs EBI spectroscopy measurements in a tetrapolar configuration from 4 kHz up to 1 MHz, with 256 discrete frequency points that are logarithmic distributed. The SFB7 and BioImp PC software that was used provided Cole modelling and Hanai mixture theory to assess TBW, ECF and ICF (Van Loan, Withers et al. 1993). The SFB7 is FDA and CE certificated as portable medical device.

4.1 Analog-front-end validation for EBI applications

The first tests (PAPER I and PAPER II) were performed to evaluate the accuracy of the suggested AD5933+AFE for the acquisition of EBI measurements (Seoane, Ferreira et al. 2008, Ferreira, Seoane et al. 2010). The AD5933+AFE was evaluated for three EBI application cases that evaluate the system accuracy with different spectral responses: the Total Body Composition (TBC), the Respiration Rate (RR) and the Lung Composition (LC), where a 2R1C circuit model for each EBI application was used to compare the accuracy of the AD5933+AFE against the commercial EBI spectrometer SFB7. Using a frequency range off 5 to 100 kHz, the measurements from both devices were processed with the software BioImp from ImpediMed to obtain the Fricke’s circuit model components $R_c$, $R_e$ and $C_m$, and in addition, the spectral measurement errors of both devices were obtained.
In Figure 4.1, the resistance and reactance relative measurement error spectrum plots are displayed for TBC (a), RR (b) and LC (c). As can be seen, the errors with both devices are low, with a maximum relative error below 4% for the AD5933+AFE and below 2% for the SFB7. In the case of TBC (a), the resistance relative error is below 1% for both devices.
The estimated Fricke’s electrical components $R_c$, $R_e$ and $C_m$ were obtained for each EBI measurement, and their average values are shown in Table 4.1. The SFB7 presents a smaller error for all of the parameters except for the estimation of $C_m$. The AD5933+AFE presents lower standard deviation values in all of the cases compared with the SFB7.

Table 4.1 SFB7 vs. AD5933+4E-AFE, 2R1C Estimated Parameters Error and Accuracy

<table>
<thead>
<tr>
<th></th>
<th>TBC</th>
<th>RR</th>
<th>LC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SFB7</td>
<td>AD+AFE</td>
<td>SFB7</td>
<td>AD+AFE</td>
<td>SFB7</td>
<td>AD+AFE</td>
</tr>
<tr>
<td>$R_e$</td>
<td>Average Value (Ω)</td>
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<td>914.15</td>
<td>58.33</td>
<td>57.89</td>
<td>81.37</td>
</tr>
<tr>
<td></td>
<td>Standard Deviation</td>
<td>0.1594</td>
<td>0.0423</td>
<td>0.0177</td>
<td>0.0077</td>
<td>0.0193</td>
</tr>
<tr>
<td></td>
<td>Relative Error</td>
<td>0.04%</td>
<td>0.36%</td>
<td>0.29%</td>
<td>1.03%</td>
<td>0.16%</td>
</tr>
<tr>
<td>$R_i$</td>
<td>Average Value (Ω)</td>
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<td>676.3</td>
<td>25.60</td>
<td>26.00</td>
<td>22.25</td>
</tr>
<tr>
<td></td>
<td>Standard Deviation</td>
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<td>0.1280</td>
<td>0.0493</td>
<td>0.0238</td>
<td>0.0498</td>
</tr>
<tr>
<td></td>
<td>Relative Error</td>
<td>0.14%</td>
<td>1.64%</td>
<td>0.08%</td>
<td>1.63%</td>
<td>0.44%</td>
</tr>
<tr>
<td>$C_m$</td>
<td>Average Value (nF)</td>
<td>3.34</td>
<td>3.37</td>
<td>74.56</td>
<td>74.08</td>
<td>46.67</td>
</tr>
<tr>
<td></td>
<td>Standard Deviation</td>
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<td>0.0003</td>
<td>0.0444</td>
<td>0.0181</td>
<td>0.0149</td>
</tr>
<tr>
<td></td>
<td>Relative Error</td>
<td>2.22%</td>
<td>1.47%</td>
<td>1.50%</td>
<td>2.14%</td>
<td>2.16%</td>
</tr>
</tbody>
</table>

After the first AD5933+AFE EBI accuracy evaluations were completed, a portable unit was developed using Surface Mount Technology (SMT) components with the best available materials that allowed its integration into a reduced size. The portable EBI unit results are shown in the following section.
4.2 Portable EBI spectrometer unit

The developed portable spectrometer (called AD-EBIS) that was based in the AD5933+AFE is shown in Figure 4.2. The AD-EBIS has a size of 90 x 50 x 17 mm and a total weight of 70 g. Compared with the reference spectrometer SFB7, the AD-EBIS has truly portable dimensions. The achieved specifications are listed as follows:

- Frequency range: from 5 kHz to 270 kHz, with up to 512 discrete points.
- Injecting current: value of 100 $\mu$A$_{\text{rms}}$ DC free.
- Communications: Bluetooth 2.1 wireless communications with SPP.
- Power supply: Li-ion battery powered with up to 2 h of continuous measurements
- Provided with a user button, acoustic and two LED indicators.

The Cole plot for a TRS EBI measurement (PAPER III) obtained with the AD-EBIS using dry Textrodes is shown in Figure 4.3, where the displayed Cole parameters for the measurement were obtained using curve fitting in the impedance plane.

The following Table 4.1 displays a comparison of the physical and electrical properties for the implemented AD-EBIS, and the commercial spectrometers SFB7 from ImpediMed and BCM from Fresenius.
4.2.1 System component description

The general functional block diagrams of the implemented AD-EBIS unit are shown in Figure 4.4. The device was encapsulated in a plastic box that incorporates the electronic PCB and the 950 mAh Li-ion battery. The following sections will cover the descriptions for each device module.

4.2.1.1 Microcontroller PIC24F

The main AD-EBIS component is a PIC24F microcontroller from Microchip Inc. that contains the firmware program that controls the impedance functions and the different modules. The microcontroller PIC24FJ256GB106 was chosen for its powerful set of peripherals and the low power characteristics that are especially designed for portable applications. Some of the main features are:

- 16-bit architecture with a CPU speed of up to 16 MIPS
- 256 kB of Flash code memory and 16 kB of RAM memory
- Multiple standard interfaces; 3xI2C, 3xSPI, 4xUART or a 10-bit ADC among other peripherals
- 16-bit hardware multiplier and divider unit
- nanoWatt power managed modes, with 100nA in Sleep mode
- Operating voltage from 2v to 3.6v
- Reduced dimensions, with 12x12x1 mm for the 64-pin version

The AD-EBIS firmware was programed using high-level ANSI C programing and the Microchip MPLAB C30 compiler. The PIC24F firmware implemented all high level functions to perform both impedance measurements and data retrieval. The impedance measurements were stored temporally in the internal RAM memory for later transmission using the Bluetooth protocol. The AD-EBIS was connected to a PC station that had a PC developed application that retrieves the measurement and storage of all of the EBI measurements digitally on the PC for later processing.

4.2.1.2 The AD5933 impedance analyser

The AD5933 was connected using a serial I2C port configured with a frequency clock of 400 kHz, and an external clock oscillator circuit of 16 MHz with a frequency stability of ±50 PPM was used. The output voltage was selected to 1.98 v_{pp} with a DC bias of 1.48 v. The recommended AD5933 impedance frequency range is from 1 kHz
to 100 kHz (Analog Devices Inc. 2013), but it can be programmed for frequencies up to 450 kHz. Therefore, some of the following sections cover the AD-EBIS accuracy evaluating different frequency analysis ranges.

### 4.2.1.3 The analog-front-end

As described in previous sections, the AFE was implemented in two stages: a voltage to current conversion stage and an input current to voltage conversion stage, see Figure 3.2 in Chapter 3. The AFE was developed with 1% precision resistors and 5% tolerance capacitors, using SMT components with a form factor of 0603.

The high pass filter was implemented as a second order Sallen-Key topology, with a unity gain, a cut frequency at $f_c=0.97$ Hz and a quality factor equal to $Q = 0.67$. The Voltage to Current Converter (VCC) was implemented with an operational amplifier in a transadmittance amplifier circuit. The VCC gain was configured to $133 \, \mu A/v$, which yielded an injecting current of $94 \, \mu A_{rms}$. The Instrumentation Amplifier (INA) was configured with a gain of $7.09 \, v/v$, and the selected INA has a CMR of 120 dB.

The AD-EBIS was calibrated using a multipoint calibration method, where the calibration factor was obtained for each impedance excitation frequency and was stored in an external memory. To achieve the highest possible precision, floating point variables were used in the PIC24F firmware. The different calibration methods and their accuracies are presented in the following sections.

### 4.2.1.4 Wireless communications

The system was provided with Bluetooth communication using the Serial Profile Port (SPP) which emulates serial cable RS-232 communications. The commercial module RN42 from Robin Networks Inc. was used (RobinNetworks 2013); this Bluetooth module provided the best available option in terms of the power consumption and space requirements for the implementation of the portable unit. Some of the RN-42 characteristics are:

- Fully qualified Class 2 Bluetooth 2.1 + EDR module, with communication ranges up to a 20 m distance.
- On-board embedded Bluetooth stack, with no host processor requirements.

![Figure 4.4 Block diagram for the custom AD-EBIS portable unit.](image)
- SPP with UART maximum data rates of 240 Kbps slave and 300 Kbps master.
- Low power consumption; 26 μA sleep, 3 mA connected and 30 mA transmitting.
- Reduced dimensions of 13.4 x 5.8 x 2 mm with 1.3 grams of weight
- Secure communications with 128-bit encryption.

The module RN-42 was configured in slave mode to use encrypted communications and password pairing protection; therefore, the AD-EBIS unit could be used only by an authorised Bluetooth master device.

4.2.1.5 User interfaces

The AD-EBIS was provided with a user button to switch the unit on and off, two LED indicators to display the battery and Bluetooth status, an acoustic buzzer indicator, and one enhanced mini-B female USB connector for the supply of power to charge the battery and also for the connection of the measuring leads.

The enhanced mini USB connector supported the standard USB communications and had an extra line of 5 pins in the connector bottom part for other types of communications, which was used for the measuring leads in the AD-EBIS. The electrode cable assembly used an enhanced mini-b male USB connector that only allows the connection to an enhanced mini-b female USB connector, which avoids the connection of the electrode cable to other USB mini-b compatible devices. By using the same USB port for charging and measuring, thus eliminating the risk of performing measurements while the unit is connected to a power supply for charging the battery (International Electrotechnical Commission 2010).

4.2.2 Calibration methods

As introduced in Chapter 2, to obtain the impedance real and imaginary values, the sine correlation method averages the in-phase and the in-quadrature signals over an n-number of complete cycles of the injected signal. Averaging over an interval that includes an incomplete cycle will lead to an erroneous estimation. The AD5933 always uses 1024 sample points at a sampling rate of 1 MHz to perform the impedance estimation, see Chapter 3. Typically, no integer relation exists between the averaging interval and the period length of the excitation signal; this constraint is compensated for through a calibration procedure.

The AD5933 must be calibrated using a known impedance to obtain the calibration factor, which reduces the static system errors as much as possible. The manufacturer recommends the calibration using a single or two point method, but a multipoint calibration method was selected to obtain the maximum system performance for each frequency point.

The system calibration results from using two methods were obtained: a single resistor R of 604 Ω with 0.1% precision and a 2R1C impedance formed by a series of a resistor of 1210 Ω @ 0.1% and a capacitor of 1 nF @ ±5%, both of them in parallel to a resistor of 604 Ω @ 0.1%. The 2R1C circuits were selected to emulate as much as possible an EBIS measurement.

A set of 20 measurements that use each calibration method were obtained, when measuring a different 2R1C circuit formed by a series of a resistor of 1000 Ω @ 0.1% and a capacitor of 1.5 nF @ ±5%; both of them were in parallel to a resistor of 330 Ω @ 0.1%. The magnitude and phase measurement errors with both calibration methods are shown in Figure 4.5.
Chapter 4  Implementation and Validation Results

As shown in Figure 4.5, the magnitude measurement errors for both methods were below 1.5%, although the 2R1C method presented a lower value. In the case of the phase measurement error both methods presented high error values; for the 2R1C method the error was 16%, and for the R method, the error was 45%. Comparing both methods, the 2R1C calibration presented a lower error than the R calibration, but the 2R1C calibration method nevertheless presented an error of 11% at 450 kHz, which for some EBI applications might not be accepted.

4.2.3 System accuracy

The AD-EBIS system performance (PAPER III) was evaluated against the SFB7 spectrometer by performing a set of 30 complex EBI measurements in a 2R1C circuit. The impedance spectra were obtained as well as the absolute measurement errors of both devices.

The average resistance and reactance measurement spectra are shown in Figure 4.6.a. Both of the devices presented good performance, and only a slight deviation at high frequencies was present in the reactance part for the AD-EBI spectrometer from frequencies higher than 250 kHz.

The resistance and reactance absolute errors are displayed in Figure 4.6.b. The AD-EBIS presented lower error in the resistance portion compared with the SFB7, but in the reactance, the AD-EBIS presented an error that was greater than 5% above 270 kHz approximately, while the SFB7 had an error that was lower than 4%. The standard deviations (STD) are also displayed in the same figure, where the SFB7 presented a lower value compared with the AD-EBIS, and in both cases the STD was below 0.5 Ω.
4.3 Dry textrode TRS EBI measurement results

The AD-EBIS and the SFB7 spectrometer were used to obtain TRS EBI measurements (PAPER III) on three healthy subjects using dry Textrodes. A set of 20 measurements were taken with each device on each subject. To analyse the upper frequency limit effect, three frequency ranges, 5-100 kHz, 5-200 kHz and 5-450 kHz were used, and the Cole parameters on each range were obtained using the ImpediMed BioImp software.
The obtained complex EBI measurements with both devices displayed similar results, where the AD-EBIS had a high frequency deviation in the reactance part. In Figure 4.7.a, the averaged EBI measurements were used to display the resistance and reactance plots for subject 1, where a deviation in the reactance part for the AD-EBIS could be observed at frequencies that were higher than 200 kHz. In Figure 4.7.b, the same measurements were used to display the average impedance plot. Despite the differences in the reactance spectrum plot, the obtained impedance plots with both devices were almost the same, which made it difficult to observe any visible differences.

The software BioImp from ImpediMed was used to extract the Cole parameters \( R_o, R_w \) and \( f_c \) from the TRS EBI measurements with both devices, for each subject and for the three frequency ranges. The averaged Cole parameter values are displayed in Table 4.3, where the obtained Cole parameters values in the ranges of 5-100 kHz and 5-200 kHz were very similar.
Table 4.3 TRS Cole parameter estimation for SFB7 and AD-EBIS spectrometers.

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Device</th>
<th>( R_0 (\Omega) )</th>
<th>( R_\infty (\Omega) )</th>
<th>( f_C (kHz) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( S_1 )</td>
<td>( S_2 )</td>
<td>( S_3 )</td>
</tr>
<tr>
<td>5-100</td>
<td>AD-EBIS</td>
<td>510,4</td>
<td>566,9</td>
<td>546,3</td>
</tr>
<tr>
<td></td>
<td>SFB7</td>
<td>509,6</td>
<td>562,8</td>
<td>546,4</td>
</tr>
<tr>
<td>5-200</td>
<td>AD-EBIS</td>
<td>511,8</td>
<td>567,9</td>
<td>547,8</td>
</tr>
<tr>
<td></td>
<td>SFB7</td>
<td>511,1</td>
<td>564,0</td>
<td>547,7</td>
</tr>
<tr>
<td>5-450</td>
<td>AD-EBIS</td>
<td>514,2</td>
<td>568,8</td>
<td>549,5</td>
</tr>
<tr>
<td></td>
<td>SFB7</td>
<td>511,9</td>
<td>564,5</td>
<td>547,9</td>
</tr>
</tbody>
</table>

In Table 4.4, the AD-EBIS Cole parameter mean absolute deviation is shown. The extracted AD-EBIS Cole parameters at each frequency were calculated against the obtained SFB7 Cole parameters for the frequency range of 5-450 kHz were used as reference Cole parameter values. The estimations of \( R_0 \) and \( R_\infty \) were very similar, with a difference in the two values of below 1%; however, the estimation of the characteristic frequency \( f_c \) had a higher deviation. Note that the fitting method that was used can influence such a difference, because the EBI measurement frequency content is not used; only the real and imaginary part are used for the estimation.

Table 4.4 Total mean relative difference for the AD5933-EBIS against SFB7 Cole parameters in the frequency range 5-450 kHz.

<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>( R_0 (%) )</th>
<th>( R_\infty (%) )</th>
<th>( f_c (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-100 kHz</td>
<td>0,06</td>
<td>0,10</td>
<td>2,33</td>
</tr>
<tr>
<td>5-200 kHz</td>
<td>0,19</td>
<td>0,64</td>
<td>1,71</td>
</tr>
<tr>
<td>5-450 kHz</td>
<td>0,49</td>
<td>0,99</td>
<td>6,76</td>
</tr>
</tbody>
</table>
Chapter 5

Discussion and Conclusions

In this chapter, the results given in Chapter 4 are used to evaluate the two hypotheses that were introduced in Chapter 1. This chapter is divided into two sections. The first section discusses the developed portable spectrometer, and the second section is dedicated to the bioimpedance measurements with dry Textrodes.

5.1 Portable Bioimpedance spectrometer development

The first validation results indicated that the proposed analogue-front-end combined with the impedance spectrometer integrated circuit based on sine correlation estimation methods, the AD5933, can indeed perform EBI measurements in the frequency range from 5 kHz to 100 kHz (PAPER I and II). The spectral measurement errors that were produced with both devices over the 2R1C circuits are usually low; in the worst case studied, the error drops below 4% for the RR measurements. The first results confirm that the implementation of a portable spectrometer is a viable option using the proposed instrumentation.

The implemented portable spectrometer has the dimensions of 90x50x17 mm, a weight of only 70 g, standard Bluetooth communications and it is provided with batteries. These portable features compared with other commercial devices, e.g., SFB7 or BCM in Table 4.2, make the developed portable bioimpedance spectrometer more suitable that other devices for applications in which the size and weight are important factors, such as in wearable and homecare applications.

The spectral plots obtained with the developed spectrometer AD-EBIS measuring 2R1C circuits (PAPER III) indicate that the spectrometer can perform accurate impedance measurements well above the upper frequency limits that were previously reported, 100 kHz in (Seoane, Ferreira et al. 2008, Ferreira, Seoane et al. 2010) and 200 kHz in (Bogónez-Franco, Bayés-Genis et al. 2010). The AD-EBIS presents a good accuracy compared with the reference spectrometer SFB7 on the 2R1C measurements; it shows a smaller error in the resistance spectrum measurement but a noticeable error in the reactance spectrum at frequencies above 270 kHz.

The results obtained with different calibration methods indicate that this type of bioimpedance spectrometer, which is based on sine correlation estimation methods, presents lower measurements error when the spectrometer is calibrated by an
impedance circuit rather than with a simple resistor. The magnitude error is below 0.75 % for the 2R1C method and is below 1.5 % with the resistor method, but the maximum phase error at 450 kHz, which is calibrated with a resistor, is almost 50% compared with 10% when calibrating with a 2R1C circuit.

The use of the developed spectrometer for the implementation of personalised healthcare systems will require a more in-depth study to analyse the measuring instrumentation requirements for a successful implementation of the PHS. In future studies, it will be necessary to address factors such as system maintenance, measurement reliability or system calibration assurance among others.

5.2 Bioimpedance measurements using functional garments

The results presented here include the feasibility of obtaining accurate Total Right Side (TRS) EBI spectroscopy measurements using the custom made portable AD-EBIS with dry Textrodes for Cole parameter estimations and its future use for Body Composition Assessments (BCA).

Despite the clear deviation that is observed in the reactance at high frequencies for the TRS measurements on Subject 1, Figure 4.7, the Cole parameter estimation performed on the EBIS data measured up to 450 kHz with the AD-EBIS and produces very similar values for $R_0$ and $R_m$ compared with the estimations from the EBIS measurement performed with the SFB7. This observation arises from the the fact that the impedance plots produced by the EBIS measurements taken with the two spectrometers are almost identical, see Figure 4.7.b, and because the curve fitting to the Cole function implemented by the BioImp software from ImpediMed fits the EBIS data in the impedance plane; it is expected that similar impedance plots will produce similar values for $R_0$ and $R_m$.

Nevertheless, the differences that were observed when estimating the Cole parameters, $R_0$ and $R_m$ using the AD-EBIS, are below 1% compared with the reference spectrometer SFB7. Because the estimation of the body fluid distribution from the EBIS data currently depends only on the estimates of $R_0$ and $R_m$, it is very likely that the AD-EBIS spectrometer in combination with the Textrode garment would be useful for BCA applications.

For the assessment of the body fluid distribution, the broadest approach to estimate the Cole parameters is to fit the EBI spectral data to a depressed semicircle, thereby using only the resistance and the reactance measurement data and ignoring the frequency information. This fitting approach is vulnerable to the reactance deviation that is present at high frequencies for the AD-EBIS; therefore the upper frequency must be reduced up to 270 kHz where the phase error has an acceptable error value of 5%.

Currently, other methods are proposed to estimate the Cole parameters using Non-Linear Least Square (NLLS) iterative fitting, where the frequency information contained in the measurement is used(Ayllon, Seoane et al. 2009, Buendia, Gil-Pita et al. 2011). The method proposed by Buendia et al. suggests using the modulus of the Cole function as the function model that is used by NLLS fitting, to extract the Cole parameters. Using this approach to estimate the Cole parameters suggests that the portable AD-EBIS that uses only the magnitude spectral data in the whole frequency from 5 kHz to 450 kHz could be used where the magnitude error value is below 1%.
Studies performed on the dependence of the upper frequency limit as well as the number of frequency points for the estimation of the Cole parameters by Buendia et al. (Buendia, Gil-Pita et al. 2011) suggest that using an upper frequency limit of 250 kHz with a maximum of 16 frequency points produces similar Cole parameter estimation errors compared with using an upper frequency limit of 1 MHz with 256 frequency points. These results combined with using NLLS to the modulus of the Cole function suggest that the developed spectrometer could perform measurements that are as accurate as commercial spectrometers, such as the SFB7, for the estimation of body fluid distribution.

The developed portable AD-EBIS presents good accuracy compared with the reference spectrometer SFB7 in spite of the phase frequency deviation (PAPER III). The availability of Textrode garments and reduced size spectrometers such as the one presented in this thesis research will enable the development of wearable measuring instrumentation that could be incorporated into functional garments.
Chapter 6

Future steps toward Personalised Health Monitoring Applications

The development of a portable Bioimpedance spectrometer that uses functional garments and dry Textrodes for the evaluation of body composition assessment has been shown to be a feasible option after the obtained results, and the use of this type of systems for the development of Personalised Healthcare Systems (PHS) is a step closer to a real implementation.

The use of a PHS in a clinical environment requires the contribution of many research fields for its successful implementation, and during my research studies new questions have arisen that are related to the development of body sensor instrumentation:

*Does a medical device that is going to be used in a personalised healthcare application have special design requirements compared with conventional medical devices? What requirements are needed to guarantee measurement reliability or system maintenance among the many other factors?*

In addition to fulfilling the standards for patient electrical safety (International Electrotechnical Commission 2010) or the Medical Devices Directives (European Commission 2007), other types of requirements must be contemplated for the correct development of personalised health systems. Factors such as usability, trustworthiness, system maintenance or interoperability must be studied. To evaluate the requirements that are needed for the development of body sensor instrumentation, the strategy is to use a case study in which a PHS for chronic kidney disease patients is implemented, and this approach will help to examine all of the system requirements for the correct implementation. These types of system requirements will be elaborated as design guidelines that will help future developments of body instrumentation sensors in PHS for clinical use.

This section starts with an introduction to the concept of personal health systems and its conforming elements, delineating some of the existing barriers for the implementation of these types of systems in clinical environments. The following section covers a proposed novel personal healthcare system for Chronic Kidney Disease patients that incorporates EBI measurements for the assessment of the patient euvoletic state.
6.1 Personalised health systems

The use of Information and Communication Technologies (ICT) as a tool for enhancing the quality, accessibility and efficiency of health care systems has been supported extensively by the European Commission since the launch of the action plan eEurope 2002 (European Commission 2000). In spite of the substantial progress in the field of eHealth applications, barriers still exist, and they must be addressed to foster the opportunities that eHealth applications offer.

Personal Health Systems (PHS) solutions envision the use of ICT and other technologies to enable a paradigm shift from the traditional hospital-centred healthcare delivery model toward a preventive and person-centred model. The European project PHS2020 (Codagnone 2009) was focused on identifying the existing gaps and proposing a number of research roadmaps to turn PHS into reality. Within the PHS2020 project and with the collaboration of many experts the following definition was elaborated:

Personal Health Systems assist in the provision of continuous, quality controlled, and personalised health services to empowered individuals regardless of location. They consist of:

a) Ambient and/or body (wearable, portable or implantable) devices, which acquire, monitor and communicate physiological parameters and other health related context of an individual (e.g., vital body signs, biochemical markers, activity, emotional and social state, environment);

b) Intelligent processing of the acquired information and coupling of it with expert biomedical knowledge to derive important new insights about individual’s health status.

c) Active feedback based on such new insights, either from health professionals or directly from the devices to the individuals, assisting in diagnosis, treatment and rehabilitation as well as in disease prevention and lifestyle management.

The PHS definition is a good approach to identifying and framing all of the different elements that are present in this type of solution. The underlying concept is to empower the individual’s health responsibility while reducing the costs of the current healthcare system.

Notwithstanding the potential benefits of PHS applications, there are still barriers that hinder the deployment of eHealth solutions. New action plans from the European commission, such as the eHealth Action Plan 2012-2020 (European Comission 2012), target the identification of barriers and recommendations for the implementation of eHealth applications. Some of the identified barriers are the following:

a) Lack of awareness of and confidence in eHealth solutions among patients, citizens and healthcare professionals

b) Lack of interoperability between eHealth solutions

c) Limited large-scale evidence of the cost-effectiveness of eHealth tools and services

d) Lack of legal clarity for health and wellbeing mobile applications and the lack of transparency regarding the utilisation of data collected by such applications

e) Inadequate or fragmented legal frameworks including the lack of reimbursement schemes for eHealth services

f) High start-up costs involved in setting up eHealth systems
g) Regional differences in accessing ICT services and limited access in deprived areas

The eHealth Action Plan 2012-2020 addresses the barriers and also the following operation objectives:

- a) Achieving wider interoperability of eHealth services
- b) Supporting research, development and innovation in eHealth and wellbeing to address the lack of availability of user-friendly tools and services
- c) Facilitating uptake and ensuring wider deployment
- d) Promoting policy dialogue and international cooperation on eHealth at global level

Current attempts in the area of PHS's standardisation are the one proposed, for example, by the Continua Health Alliance (Continua Health Alliance 2012) or the white paper resulting from the HeartCycle Project (Lekka, Reiter et al. 2008). The HeartCycle document gives an overview of the current certification procedures for PHS in Europe, identifying major gaps and drawing recommendations. Nevertheless, more effort must be applied regarding the standardisation, quality assurance and interoperability of systems to empower the potential of eHealth applications.

6.2 Monitoring applications for Chronic Kidney Disease patients

Managing and taking care of patients with chronic diseases accounts for over 75% of the healthcare costs in developed countries. One of the most resource-demanding diseases is CKD, for which 10-12% of the population shows signs of different stages of this disease. There are more than 2.5 million patients with end-stage renal disease who require dialysis treatment, where 75-90% of the patients perform in-centre haemodialysis (HD) treatment in specialised centres, and 10-25% of the patients use a home-based dialysis treatment such as peritoneal dialysis (PD) or home haemodialysis (HHD).

Compared to in-centre HD, PD and HHD require certain patient training and specialisation for performing the therapy procedures out of the clinical environment,
which sometimes leads to unexpected problems in the treatment, such as infections or hydration imbalances.

The use of ICT and other technologies for the implementation of PHS could facilitate a shift in dialysis care from the hospital to home, ensuring a better quality of treatment, improving the patient’s quality of life and also reducing the costs of the healthcare system. In home dialysis, HHD or PD, it is quite important to monitor and adjust the treatment to allow the patient’s euvolemic state to be maintained constantly during the treatment, which avoids dehydration or over-hydration stages. With a device that provides a reliable indicator of the body composition, the homecare dialysis therapy could be delivered with much better precision, which would increase the treatment quality and promote the use of PD among the patients that follow HD.

To achieve such a PHS or “tele-nephrology system” with the capability of supporting homecare dialysis, the system should comply with several requirements:

- The system should be user-centred from design to operation, accounting for the needs of the patients.
- A videoconference system should be available for performing tele-consultations.
- Dedicated home-monitoring equipment for body fluid volume distribution assessment should be incorporated, including a bioimpedance spectrometer and functional garments with textile electrodes, such as the technology developed in this work.
- An efficient distribution system for the dialysis products and medications should ensure continuous functioning of the home therapy.
- An IT platform that integrates all of the elements of the system ensuring, data collection, communication and visualisation.

In Figure 6.1, an example PHS for CKD patients is depicted, where the system is built on several components, such as a weight scale, a bioimpedance spectrometer for body fluid distribution, a patient software interface, communication infrastructure and a remote server, among others.

This case study will help to identify and frame all of the system requirements that are needed for the proliferation and development of these types of PHS applications. Factors such as usability, and interoperability will be contemplated during the execution of the project to extract the system requirements for the development of body sensors. The aim will be to obtain a draft of recommendations for development of body sensor devices that will be used in PHS.

Furthermore, repeatability is a critical issue for a clinical measurement, and it is a major challenge when implementing a PHS that features bioimpedance measurements. In this case, the placement of the electrodes is crucial. The integration of the electrodes into functional garments where the electrodes are in fixed positions could be the key to overcoming this repeatability issue. Studies to analyse the body fluid distribution and dry weight assessment will be conducted using the developed sensorised garment, such as the garment developed by Marquez et. al. (Marquez, Seoane et al. 2013). Aspect such as usability and system integration will also be analysed when performing measurements, which will help to identify the body sensor requirements for the implementation and proliferation of PHS.
CHAPTER 6  FUTURE STEPS TOWARD PERSONALISED HEALTH MONITORING APPLICATIONS
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References


Appended Work
Paper I

An analog front-end enables electrical impedance spectroscopy system-on-chip for biomedical applications

Abstract

The increasing number of applications of electrical bioimpedance measurements in biomedical practice, together with continuous advances in textile technology, has encouraged several researchers to make the first attempts to develop portable, even wearable, electrical bioimpedance measurement systems. The main target of these systems is personal and home monitoring. Analog Devices has made available AD5933, a new system-on-chip fully integrated electrical impedance spectrometer, which might allow the implementation of minimum-size instrumentation for electrical bioimpedance measurements. However, AD5933 as such is not suitable for most applications of electrical bioimpedance. In this work, we present a relatively simple analog front-end that adapts AD5933 to a four-electrode strategy, allowing its use in biomedical applications for the first time. The resulting impedance measurements exhibit a very good performance in aspects like load dynamic range and accuracy. This type of minimum-size, system-on-chip-based bioimpedance measurement system would lead researchers to develop and implement light and wearable electrical bioimpedance systems for home and personal health monitoring applications, a new and huge niche for medical technology development.

An analog front-end enables electrical impedance spectroscopy system on-chip for biomedical applications

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Abstract
The increasing number of applications of electrical bioimpedance measurements in biomedical practice, together with continuous advances in textile technology, has encouraged several researchers to make the first attempts to develop portable, even wearable, electrical bioimpedance measurement systems. The main target of these systems is personal and home monitoring. Analog Devices has made available AD5933, a new system-on-chip fully integrated electrical impedance spectrometer, which might allow the implementation of minimum-size instrumentation for electrical bioimpedance measurements. However, AD5933 as such is not suitable for most applications of electrical bioimpedance. In this work, we present a relatively simple analog front-end that adapts AD5933 to a four-electrode strategy, allowing its use in biomedical applications for the first time. The resulting impedance measurements exhibit a very good performance in aspects like load dynamic range and accuracy. This type of minimum-size, system-on-chip-based bioimpedance measurement system would lead researchers to develop and implement light and wearable electrical bioimpedance systems for home and personal health monitoring applications, a new and huge niche for medical technology development.

Keywords: electrical bioimpedance spectroscopy, system-on-chip, four-electrode method

(Some figures in this article are in colour only in the electronic version)
1. Introduction

The continuous progress of medical applications of electrical bioimpedance spectroscopy (EBIS) (Aberg et al. 2005, Moissl et al. 2006, Caduff et al. 2006), combined with recent advances in textile electrode technology (Pacelli et al. 2006, Paradiso and De Rossi 2006), enable the development of bioimpedance-based measurement systems for home monitoring (Medrano et al. 2007, Vuorela et al. 2007) and personal monitoring (Scheffler et al. 2003).

Traditionally, wearable systems for on-body measurements have focused on the acquisition of biosignals and activity monitoring, in the line of the EU project Wealthy IST-2001-37778 (Paradiso et al. 2004). The European Commission has specifically supported several textile-based healthcare projects, e.g. BIOTEX IST-2004-016789, CONTEXT IST-2004-027291, MERMOTH FP6-IST-508272, MyHeart IST-2002-507816, OFSETH IST-2005-027869, PROETEX IST-2004-026987 and STELLA FP6-IST-028086. Currently, it is possible to find commercial products for personal healthcare monitoring, e.g. Lifeshirt® of Vivometrics® and adiSTAR® of Adidas.

Often the acquired signals are ECG and heart rate with electrodes, movement with accelerometers and respiration rate with piezoelectric and/or inductive sensors. EBI has not been among the typical measurements for monitoring until recently. Initially, EBI measurements target the respiration activity rate by impedance pneumography (Paradiso and De Rossi 2006, Seppä et al. 2007), heart failure by impedance cardiography (Amft and Habetha 2007) and even body composition by bioelectrical impedance analysis (Hännikäinen et al. 2007). Nowadays it is possible to find a commercially available, single-frequency ambulatory bioimpedance monitor for cardiac assessment: AIM-8 manufactured by Bio- Impedance Technology, Inc.

A concise review of wearable systems for physiological measurements can be found in Hännikäinen et al. (2007). For comprehensive and detailed information about healthcare applications of smart textiles, see Van Langenhove (2007).

AD5933 is the first commercially available impedance network analyzer implemented in a single integrated circuit, and it allows us to take an important step from portable to wearable applications. The complexity of the impedance measurement system is reduced to basically one integrated circuit plus additional analog circuitry for signal conditioning, to meet the requirement for electrical bioimpedance (EBI) applications.

AD5933 alone is not suitable for EBI measurements on patients, or for several EBI applications, due to several factors, e.g. dc excitation, a voltage-driven system with large output impedance and a two-electrode system. In this work, we propose and validate the addition of an analog front-end (AFE) to fully adapt the AD5933 circuit to a four-electrode strategy. In this way, the deflection signal is adapted for on-body measurements. The resulting system is a multifrequency measurement system with very few ICs which is suitable for wearable applications.

2. Methodology

2.1. Materials

The core of the measurement system is the impedance network converter integrated circuit AD5933. The impedance measurement system by itself is the evaluation board for the AD5933 circuit provided by Analog Devices Inc., the EVAL-5933EB4.

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4 See www.analog.com.
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The AFE is implemented with general application op-amp circuits, instrumentation amplifiers and voltage references. An adaptation circuit for measurements of small impedance has been used as recommended by Analog Devices.

The software used to control AD5993 and display the impedance measurements is provided with the evaluation board. This software application has been adapted for correct four-electrode operation with Visual Basic 6.0.

All the documentation related to the AD5933 evaluation board, schematics, user manual and software is available at the Analog Devices Inc. website.

2.2. Accuracy test

Impedance measurements have been performed on pure resistive loads as well as on a 2R-1C series circuit; note the absence of physical electrodes or any equivalent dummy. The measurements have been done with and without the AFE in the frequency range from 5 kHz to 100 kHz.

To study the error performance and its dependence on the load dynamic range, a pure resistive load has been measured at 10 kHz and its deviation from the theoretical value has been calculated. The value of the working load has been changed from 50 Ω to 1.6 kΩ.

To study the frequency performance of the measurement system, the 2R-1C series circuit has been used as a measurement load, measuring both resistance and reactance.

2.3. Four-electrode validation

To validate the proper implementation of the four-electrode technique, impedance measurements have been performed on a 2R-1C series circuit phantom. The measurements have been done by modeling the electrodes with an equivalent electrical circuit. The electrode-equivalent circuits have been connected in series with the phantom and the four leads, for both injection and measurement. The elements and values of the equivalent circuit have been selected to model the effect of the electrode polarization impedance, Z_{EP}.

3. Electrical bioimpedance instrumentation

Electrical bioimpedance measurements are most often performed as deflection measurements by measuring the response of the system to an external electrical excitation (Pallás-Areny and Webster 2001). Current is injected in the tissue under study (TUS) and the voltage drop caused in the load is measured or, reciprocally, the voltage is applied to the TUS and the correspondingly caused current through the TUS is measured. In either case, a generator for the excitation signal is required as well as a sensing stage to measure the response of the TUS.

Once the response to the excitation in voltage or current is measured by the system, the next step in an impedance measurement system is the impedance estimation process. This functional block estimates the complex impedance from the electrical measurements obtained, and there are several approaches to implementing this function. Sine correlation and Fourier analysis are choices often selected.

The electrodes are a critical element of an EBI measurement system; they function as an electronic-to-ionic interface between the electronic conductor in the measurement leads and the ionic conductor in the load, i.e. biological tissue. This interface can be described as a parallel circuit of a variable resistance R_{E} and a variable capacitance C_{E}; in addition, there is also a variable voltage source U_{EP} at the interface, as depicted in figure 1. The electrode impedance as well as the skin–electrode contact impedance can influence the impedance
Figure 1. Equivalent model for the electrical interface, ionic–electronic, responsible for the electrode impedance $Z_{EP}$ and its connection with the working load.

measurement to a very great extent, especially when the measurement setup is implemented as a two-electrode system.

In the two-electrode method, the same pair of electrodes is used to excite and to measure the response of the tissue. Therefore the impedance of the electrode, see figure 1, will be added to the impedance of the load. For instance if current is injected and voltage is measured, then the voltage measurement will contain the voltage drop caused in the TUS as well as the voltage drop caused in $C_E$ and $R_E$.

The four-electrode method is a robust electrode setup that reduces the influence of the electrode impedance and the skin–electrode contact impedance. This method uses a pair of electrodes to excite the TUS and a different pair of electrodes to measure the response. In the case of current excitation, electrical current does not flow through the sensing electrodes because of the high input impedance of the differential amplifiers. Therefore, the sensed voltage does not contain any voltage drop caused by $C_E$ and $R_E$ (Pallàs-Areny and Webster 2001).

3.1. AD5933 impedance converter

AD5933 is a two-electrode impedance measurement system, with a large dynamic range of the measurement load. According to the datasheet, AD5933 is able to measure loads ranging from 1 kΩ to 1 MΩ, although the auxiliary resistor connected to the input feedback resistor (RFB) should be tailored for the specific range.

The AD5933 integrated circuit contains all the necessary elements to implement a fully integrated impedance spectrometer—in this case, a waveform generator, a voltage source output, a current measurement input, a Fourier-based impedance estimator and even a serial communication port. See figure 2.

Note that the impedance estimation method is based on the Fourier analysis decomposition of both the reference signal and the measurement signal. In this case the reference signal represents the applied voltage, while the measurement signal represents the current through the measurement load. The DFT block provides the result as the ratio of reference over measurement, i.e. volts over amperes, thus impedance in Ω, as indicated in (1). In this manner, the REAL and IMAGINARY registers contain resistance and reactance information, respectively:

$$\frac{\text{REFERENCE SIGNAL}}{\text{MEASUREMENT SIGNAL}} = \frac{V_{\text{OUT}}(\omega)}{I_{\text{IN}}(\omega)} = Z(\omega) \text{ (}\Omega). \quad (1)$$
3.2. **AD5933 as a bioimpedance device**

The first point to note is that the AD5933 circuit is a two-electrode impedance measurement device. This fact by itself limits severely the range of application of usage, e.g. applications of spectral characterization are basically discarded since the impedance measurement obtained will also contain the electrode polarization impedance as well as the electrode–skin impedance.

Another important limitation of AD5933 is a safety issue: the voltage output contains a dc level, \( V_{bias} \), which is different from the dc level at \( V_{in} \), namely \( V_{dd}/2 \). This imbalance produces a dc voltage across the electrodes and the TUS, introducing dc current in the TUS, which can be a health hazard for the patient.

Moreover, AD5933 is a voltage-driven measurement system without any control over the injected current. This might be a safety hazard issue since the injected current can be larger than the limits set by IEC-60601.

Most often, values of EBI measurements fall within the range of tens or hundreds of Ohms than in the range of thousands of ohms. According to the specifications in the datasheet, the lower limit of AD5933 is \( 1 \, k\Omega \). This fact might be an additional limitation, depending on the application, to performing measurements of bioimpedance.

Nevertheless, AD5933 can perform measurements of loads below \( 1 \, k\Omega \) when the output voltage is attenuated by an op-amp in inverting configuration as indicated in figure 3.

3.3. **Analog front-end specifications**

The AFE must guarantee that the impedance measurement system is totally adapted to perform reliable four-electrode measurements of EBI according to the following specifications.

(i) The electrical safety of the patient must be ensured.
(ii) The dynamic range of measurement must be as expected in a human body.
(iii) The AFE must operate at any frequency supported by AD5933.
Figure 3. Attenuation circuit to adapt AD5933 for measurements of small impedance. The circuit proposed by Analog Devices in the datasheet of the evaluation board for AD5933. Note that 1.98 Vpp is the output for AD5933 functioning in Range 1 operation mode. Note that the resistive values used for implementing the circuit are 1 kΩ and 4.13 kΩ for $R_{\text{att}}$ and $R_{\text{in}}$ respectively, and the op-amp was TL082.

In order to achieve the aforementioned requirements, besides having an excitation and sensing ports totally independent of each other, i.e. four-electrode measurement setup, the AFE must block the flow of dc current through the TUS while simultaneously ensuring that the value of the ac current complies with the safety regulations imposed by IEC-60601. All these must be provided by the AFE while keeping the signal input and output signals of the AD5933 circuit within operational levels, i.e. avoiding current or voltage saturation.

3.4. System function and interfaces

The AFE is an interface between AD5933 and the TUS. As such, it must have the proper input and output stages to seamlessly interconnect to each of them. For a better understanding of the following description, it is advised to follow the block diagram depicted in figure 4.

In short, we could consider the AFE as a combination of two voltage-to-current converters (V2CC), one in the direction from AD5933 to the TUS and another from the TUS to AD5933.

Since AD5933 applies voltage and expects a current flowing into its RFB input, the AFE interfacing with AD5933 has a voltage input and a current output. The current source output expressly generates the current resulting from the ratio of $V_{\text{out}}$ and the impedance of the TUS, which is the current expected by AD5933 at the RFB input.

At the TUS side, the AFE has a current source as output while the input is a differential voltage measurement channel. The current source excites the TUS with an adjustable current. In this case, a current of 350 $\mu$A rms has been selected, thus fully complying with IEC-60601 for measurements above 3.5 kHz.

In essence, the AFE operation can be described as follows: after the removal of the dc bias component from the voltage output of AD5933 with a high-pass filter at the input of the first V2CC. The ac voltage from $V_{\text{out}}$ drives a voltage-controlled current source (VCCS) injecting an ac current $I_{\text{out}}$ into the TUS. Note that $I_{\text{out}}$ is directly proportional to $V_{\text{out}}$. The ac current $I_{\text{out}}$ causes a voltage drop at the TUS, which is sensed by the second V2CC and, since the voltage drop at the TUS drives the second V2CC, an ac current proportional to the voltage drop in the
TUS is generated. Finally, a dc component is added to the ac current generated. This added dc component is equivalent to \( dc_{bias} \) originally removed from \( V_{out} \). Note that the total gain introduced by the cascade combination of both V2CC together with the resistor \( R_{REF} \) at the input RFB sets the upper limit of the load dynamic range:

\[
V_{DAC_{\text{max}}} \geq R_{REF} \times g_{m2} \times g_{m1} \times V_{out} \times Z_{\text{TUS_{max}}}. 
\]

Even when carefully selecting the transconductance functions \( g_{m1} \) and \( g_{m2} \) of the V2CCs in (3), the total gain of the AFE can be set to 1. The AFE introduces a critical change in the impedance estimation process implemented by AD5933. Originally, AD5933 implemented the impedance estimation by performing the quotient of a voltage signal over a current signal, assigned to the reference signal and the measurement signal respectively. The AFE modifies such signal assignment in such a way that the operation performed by AD5933 is the quotient between a current signal over a voltage signal, i.e. amperes over volts, corresponding with the admittance of the measurement load instead. This issue has to be considered by the software application when handling the estimated immitance data:

\[
\begin{align*}
\text{REFERENCE SIGNAL} & \quad V_{\text{OUT}}(\omega) \\
\text{MEASUREMENT SIGNAL} & \quad I_{\text{IN}}(\omega) \\
\end{align*}
\]

\[
\frac{I_{\text{OUT}}(\omega)}{I_{\text{IN}}(\omega)} = \frac{I_{\text{load}}(\omega)}{g_{m2}} \times \frac{1}{g_{m1}} \times \frac{1}{Z(\omega)} = Y(\omega).
\]

4. Performance results

4.1. Accuracy

The performance of the EBI measurement system can be observed in figures 5 and 6. Figure 5 contains the measurement error obtained at 10 kHz for measurements of resistive loads with both measurement arrangements, as follows.
Figure 5. Impedance measurement error for measurements at 10 kHz with both measurement arrangements. Note that the calibration has been done with a resistive load of 1000 Ω.

Figure 6. Parametric impedance plot of theoretical and measured values of a series 2R-1C circuit. $R_s = 68$ Ω, $R_p = 130$ Ω and $C = 100$ nF. Frequency range: 5–100 kHz. Note that since the TUS used in this measurement is an electrical phantom, there is no electrode polarization impedance present, $Z_{EP}$.

(i) Four-electrode setup using the AFE. The bar is plotted with discontinuous trace.
(ii) Two-electrode setup using the attenuation circuit described in figure 3. The bar is plotted with solid trace.

In general, the measurement error is kept very low for most of the impedance range, especially for values near the calibration value, 1000 Ω.

In figure 6, the parametric plot reactance versus resistance contains the impedance values of a 2R-1C series model. For comparison, the measurements obtained with AFE, without
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Figure 7. A lead imbalance experiment to test the proper implementation of the four-electrode method.

AFE and with the attenuation circuit are plotted together with the theoretical value. Note that the electrical series circuit is the measurement load as such, and therefore there is no electrode polarization impedance of any kind present in these measurements.

It is easy to note, in the impedance plots in figure 6, the remarkable agreement between the theoretical values and the measurement done with the AFE, especially at high frequencies. Note that the frequency range of the measurement is 5–100 kHz, increasing clockwise as indicated in the plots.

In figure 6, it is also possible to observe that the measurements performed with AD5933 and the attenuator circuit do not match the theoretical values as well as those with the AFE.

Another significant result to remark is the asymptotic behavior of the measurements performed with AD5933 alone. These measurements apparently indicate the lower limit of the impedance measurement range.

4.2. Electrode polarization avoidance

The effect of electrodes has been modeled by adding impedances to the measurement leads. The goal pursued with the addition of these impedances is to simulate the effect of the electrode polarization impedance $Z_{ep}$. The electrode model used for this experiment is depicted in figure 7(c). Impedance measurements have been done with two different setups: symmetric and asymmetric, as depicted in figures 7(a) and (b) respectively, and the results of the corresponding measurements are plotted in the impedance parametric plot in figure 8. The plot contains the value of the measurements, dotted trace and discontinuous trace for the symmetric case and the asymmetric case, respectively, and for comparison the theoretical value of the measurement load is plotted with the continuous trace.

5. Discussion

5.1. On the application of AD5933 for electrical biomedical impedance

The reported measurements strongly indicate that the AD5933 impedance converter by itself cannot be used for any application EBIS where proper electrical characterization is needed. This result was expected, since AD5933 performs two-electrode measurements only.
Figure 8. The parametric impedance plot of a series 2R-1C circuit. $R_s = 68 \ \Omega$, $R_p = 130 \ \Omega$ and $C = 100 \ \text{nF}$, with impedance in leads modeling the effect of electrodes. Frequency range: 5–100 kHz. Note that the value for the capacitor in the theoretical calculations is the nominal value, while the value for the resistors $R_s$ and $R_p$ is the value measured at measured dc.

In addition to this limitation, the excitation signal generated by AD5933 is not dc free and the signal is injected by a voltage source. An important consequence of the voltage excitation is that the current through the load is dependent on the impedance value of the load as well as on the electrode polarization impedance. Since the value of the working load, mostly the electrode polarization impedance, can change with time, the current through the tissue can exceed the limit imposed by IEC-60601.

Another important limitation regarding the voltage source of AD5933 is that its minimum output impedance, $R_{out}$, is $200 \ \Omega$. Such a value is very high for a voltage source, especially when the working load can be very small, as in electrical bioimpedance applications. Moreover, apparently AD5933 cannot measure loads smaller than $130 \ \Omega$ approximately. See figure 6. This lower limit is related to the voltage source, $R_{out}$ of $200 \ \Omega$ and $5.8 \ \text{mA} \ \text{Vpp}$ of the ac output current. With a maximum current of $5.8 \ \text{mA}$ and a voltage source providing around $1.9 \ \text{Vpp}$, the minimum load is approximately $330 \ \Omega$, including $200 \ \Omega$ of $R_{out}$. This might not be a limitation in practice, since in a bioimpedance application the presence of the electrodes will increase the value of the working load.

5.2. Frequency performance with a whole single dispersion capacitive system

The measurements obtained with the proposed measurement system and the theoretical values agree significantly well in the whole frequency range. In this frequency range, we should not expect large parasitic effects in RC dummy circuits. Nevertheless, in a wearable application the measurement scenario is much more hostile, and the existence of parasitic capacitances might ruin the measurements. AD5933 has a built-in function for calibration, but at this point it is unknown to what extent such a feature will contribute to minimizing this type of negative effect.

5.3. Accuracy performance and load dependence

The reported experimental results indicate that the introduction of an external AFE does not significantly worsen AD5933. As expected, the results suggest that the best performance
An analog front-end enables electrical impedance spectroscopy system on-chip

is obtained when the measurement load approximates to the calibration load. In a typical application of electrical bioimpedance, the target load will have a dynamic range much smaller than the impedance range considered in these tests. Therefore it is most likely that the impedance measurement system will be able to keep, for each specific application, the high accuracy reported in figure 5.

5.4. Four-electrode setup

The four-electrode technique is successfully implemented with the AFE, as the measurements with simulated electrodes and particularly the asymmetric test show. The only source of concern is the observed deviation of both measurements at low frequencies from the theoretical value. This deviation may be due to the fact that the theoretical value for the circuit is calculated with the nominal value and not with the real value of the test components. The circuit overcomes the intrinsic limitation of the two-electrode structure of the AD5933 device. Note that measurements with the original two-electrode setup of AD5933 would have produced impedance values in the range of several kΩ, including the impedance of the electrode equivalent model (Ferreira and Sanchez 2007).

5.5. Limitations

The only foreseen limitation for this type of device is the upper limit frequency. A maximum high frequency of 100 kHz is not enough for certain EBI applications, especially when the purpose of the measurement is to characterize the full beta dispersion. In the datasheets provided by Analog Devices, the option to measure above 100 kHz is considered. We have not tested the performance of AD5933 above the recommended frequency range in this work because the objective of the work was to adapt AD5933 for EBI measurements.

Regarding safety issues of the AFE due to the excitation current, the implemented solution as such can be used to measure EBI at frequencies down to 3.5 kHz, complying with IEC-60601. Simply by adjusting the transconductance of the first VCCS in the AFE, the output current can be adjusted to perform measurements of EBI at lower frequencies.

6. Conclusions

The analog front-end proposed in this paper complies with the initial requirements. It implements a complete four-electrode measurement system, and completely adapts AD5933 for electrical bioimpedance measurements. This achievement is obtained by the addition of very few ICs, in essence only two, and a few passive components. This simple analog front-end, in combination with the unique system-on-chip impedance spectrometer, reduces the size and complexity of the electronics of an EBI measurement system.

The development of wearable home-monitoring devices can benefit to a very large extent from such reduction in size and complexity, while it allows the implementation of EBI measurement systems with target sizes similar to mobile phones or even watches. The availability of such minimal monitoring devices would contribute substantially to spreading the use of EBI measurement for home monitoring and wearable applications.

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Paper II

AD5933-based Spectrometer for Electrical Bioimpedance Applications

Abstract

To build an Electrical Bioimpedance (EBI) spectrometer using the Impedance Measurement System-On-Chip AD5933 together with a 4-Electrode Analog Front End (4EAFE) has been proven practicable. Such small measurement devices can make possible several new applications of EBI technology, especially when combined with functional textiles, which can enable wearable applications for personal health and home monitoring. After the implementation and functional validation of the 4E-AFE-enabled spectrometer, the next natural step is to validate for which EBI applications the 4E-AFE-enabled system is suitable. To test the applicability of this novel spectrometer on several EBI applications, 2R1C equivalent models have been experimentally obtained and impedance spectroscopy measurements have been performed with the system under study and with the SFB7 EBI spectrometer manufactured by ImpediMed. The 2R1C circuit parameters have been estimated with the BioImp software from the spectra obtained with both EBI spectrometers and the estimated values have been compared with the original values used in each circuit model implementation. The obtained results indicated that the 4E-AFE-enabled system cannot beat the performance of the SFB7 in accuracy but it performs better in preciseness. In any case the overall performance indicates that the 4E-AFE-enabled system can perform spectroscopy measurements in the frequency range from 5 to 100 kHz.

AD5933-based Spectrometer for Electrical Bioimpedance Applications

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Abstract. To build an Electrical Bioimpedance (EBI) spectrometer using the Impedance Measurement System-On-Chip AD5933 together with a 4-Electrode Analog Front End (4E-AFE) has been proven practicable. Such small measurement devices can make possible several new applications of EBI technology, especially when combined with functional textiles, which can enable wearable applications for personal health and home monitoring. After the implementation and functional validation of the 4E-AFE-enabled spectrometer, the next natural step is to validate for which EBI applications the 4E-AFE-enabled system is suitable. To test the applicability of this novel spectrometer on several EBI applications, 2R1C equivalent models have been experimentally obtained and impedance spectroscopy measurements have been performed with the system under study and with the SFB7 EBI spectrometer manufactured by ImpediMed. The 2R1C circuit parameters have been estimated with the BioImp software from the spectra obtained with both EBI spectrometers and the estimated values have been compared with the original values used in each circuit model implementation. The obtained results indicated that the 4E-AFE-enabled system cannot beat the performance of the SFB7 in accuracy but it performs better in preciseness. In any case the overall performance indicates that the 4E-AFE-enabled system can perform spectroscopy measurements in the frequency range from 5 to 100 kHz.

1. Introduction
Over recent years, advances in different technological fields like electronics, physics and materials have made possible to embed complex functional systems into a single integrated circuit producing the System-on-Chip technology. As a result of such technological advances a whole impedance spectrometer is available on a single integrated circuit: the AD5933 [1] from Analog Devices. Such a level of integration together with advances made in textile technology, especially in the development of textile electrodes suitable for applications of Electrical Bioimpedance (EBI) [2], might enable wearable applications for personal health and home monitoring based in EBI measurements.

In this work the performance of a custom-made EBI spectrometer based on the AD5933 in combination with a 4-electrode Analog Front End [3] is evaluated when measuring 3 different
impedance loads modeling three typical EBI applications: Total Body Composition (TBC), Respiration Rate (RR) and Lungs Composition (LC), also known as Pulmonary Edema [4].

2. Materials and Methods

2.1. Spectrometers and 2R1C models

Two different spectrometers have been used in this work: the ImpediMed SFB7 and a custom-made device based in the AD5933 in combination with an analog front-end to enable 4-electrode impedance measurements [3].

![Image of 2R1C parallel bridge model](image)

Figure 1. 2R1C parallel bridge model

The measurements have been performed on a 2R1C parallel electrical model representing biological tissue, see Figure 1. The values of the model parameter to build the 2R1C models, $R_e$, $R_i$, and $C_m$, were extracted from experimental EBI measurements with the software BioImp [5]. The 2R1C have been build to produce an impedance complex spectrum similar to experimental impedance spectra obtained in the aforementioned applications. The resistors used in the model belong to the E-24 series and a potentiometer was used to trim the values of the circuit parameters, see Table 1, to obtain the intended impedance spectrum.

<table>
<thead>
<tr>
<th>EBI Application</th>
<th>$R_e$ (Ω)</th>
<th>$R_i$ (Ω)</th>
<th>$C_m$ (nF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBC</td>
<td>917.5</td>
<td>665.4</td>
<td>3.42</td>
</tr>
<tr>
<td>RR</td>
<td>58.5</td>
<td>25.58</td>
<td>75.7</td>
</tr>
<tr>
<td>LC</td>
<td>81.5</td>
<td>22.15</td>
<td>47.7</td>
</tr>
</tbody>
</table>

2.2. Methods

Using both impedance spectrometers, 100 impedance measurements were performed in the frequency range 5 to 100 kHz on each experimentally-based 2R1C circuit model. For each EBI application the average complex spectrum from the measurements was obtained for each of the impedance spectrometers. A comparison between the resistance and the reactance spectra obtained from each spectrometer has been done.

Using the software BioImp applied on the measured impedance spectra obtained with each of the spectrometers, the value of the 2R1C circuit parameters was estimated and the obtained estimation error was studied to perform a comparison between the SFB7 and the AD5933-based spectrometer.
3. Results

3.1. Spectral Measurements

The reactance and resistance spectra from the impedance measurements for the different EBI applications are plotted in Figure 2. As it is denoted in all the spectral plots, the spectra obtained with both devices are perfectly overlapped for both the resistance and the reactance. Only a small deviation at high frequency can be observed on the reactance of for TBC and RR on Figure 2.b) and 2.d) respectively.

![Figure 2. Resistance and reactance spectrum plots from the measurements obtained with the AD5933-based spectrometer in continuous and SFB7 in dashed trace, respectively.](image)

3.2. 2R1C Circuit Parameters Estimation

The average values estimated for the 2R1C parameters from the impedance measurements obtained with both spectrometers are indicated in Table 2. For each of the applications, the relative differences respect the real values of the circuit components, as indicated in Table 1, are indicated by the relative error. The Standard Deviation obtained with both spectrometers for the estimation of each of the parameters is also indicated. For all the applications and all the parameters with the exception of the estimation of C_m for TBC, the SFB7 exhibit a smaller error than the AD5933-based spectrometer. Regarding to the Standard Deviation, it is the AD5933-based spectrometer the one that presents lower values for each of the parameters and all three applications.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EBI Application</th>
<th>TBC</th>
<th>AD+AFE</th>
<th>RR</th>
<th>AD+AFE</th>
<th>LC</th>
<th>AD+AFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Value (Ω)</td>
<td>SFB7</td>
<td>917,88</td>
<td>914,15</td>
<td>58,33</td>
<td>57,89</td>
<td>81,37</td>
<td>81,07</td>
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<td>Standard Deviation</td>
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<td>0,0423</td>
<td>0,0177</td>
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<td>0,16%</td>
<td>0,0131</td>
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<tr>
<td>Relative Error</td>
<td>0,4%</td>
<td>0,36%</td>
<td>0,29%</td>
<td>0,10%</td>
<td>0,16%</td>
<td>0,53%</td>
<td>0,53%</td>
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<tr>
<td>Average Value (Ω)</td>
<td>664,49</td>
<td>676,3</td>
<td>25,60</td>
<td>26,00</td>
<td>22,25</td>
<td>22,95</td>
<td>22,95</td>
</tr>
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<td>Standard Deviation</td>
<td>0,5540</td>
<td>0,1280</td>
<td>0,0493</td>
<td>0,0238</td>
<td>0,44%</td>
<td>3,63%</td>
<td>3,63%</td>
</tr>
<tr>
<td>Relative Error</td>
<td>0,14%</td>
<td>1,64%</td>
<td>0,08%</td>
<td>1,63%</td>
<td>0,44%</td>
<td>3,63%</td>
<td>3,63%</td>
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<tr>
<td>Average Value (nF)</td>
<td>3,34</td>
<td>3,37</td>
<td>74,56</td>
<td>74,08</td>
<td>46,67</td>
<td>46,28</td>
<td>46,28</td>
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<tr>
<td>Standard Deviation</td>
<td>0,0009</td>
<td>0,0003</td>
<td>0,0444</td>
<td>0,0181</td>
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<tr>
<td>Relative Error</td>
<td>2,22%</td>
<td>1,47%</td>
<td>1,50%</td>
<td>2,14%</td>
<td>2,16%</td>
<td>2,97%</td>
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</table>

4. Discussion

The spectral plots obtained with both spectrometers show that the AD5933-based spectrometer with the 4-electrode enabling front-end produced complex impedance spectra that are almost exact to the spectra obtained with the SFB7.
The analysis of the error data provided by Table 2 and Figure 3, suggest that the SFB7 presents a better accuracy than the AD5933-based spectrometer. In any case the estimation errors produced with both devices are generally low.

In the other hand according to Table 2, the preciseness shown by the custom-made impedance spectrometer based on the AD5933 is higher than the preciseness obtained with the SFB7. Both dispersions and errors obtained with both equipments are small compared with the high variability of the clinical measurements. E.g. in the measuring of Lungs Circulate Air Volume [5] the error measured with a neumotacometer and with Electrical Impedance Tomography (EIT) is around 20%, compared with the worst case studied in this work for RR the error drops below 4%.

5. Conclusion

The good complex spectroscopy performance exhibited by the AD5933-based spectrometer as well as the high accuracy and precision exhibited for the 2R1C model parameter estimation, which is critical in applications of total body composition assessment [6], strongly supports that EBI spectrometers based in SOC solutions like the AD5933 can be use in typical EBI applications like body composition analysis, respiration rate and pulmonary edema.

The reduced size of the AD5933, its small power consumption [7] together with the availability of off-the-shelf Bluetooth solutions indicate that the implementation of portable applications of EBI is close, even wearable if combined with textile garments [8] and electrodes [2].

6. References


AD5933-Based Electrical Bioimpedance Spectrometer. Towards Textile-Enabled Applications

Abstract

Advances on System-On-Chip and Textile technology allow the development of Textile-enabled measurement instrumentation. Textile Electrodes (Textrodes) have been proven reliable for performing Electrical Bioimpedance Spectroscopy (EBIS) measurements, and the availability of an integrated circuit impedance spectrometer, the AD5933, has allowed the implementation of small size EBIS spectrometers.

In this work an AD5933-based spectrometer has been implemented, and its performance on 2R1C circuits and for tetrapolar total right side EBIS measurements has been compared against the commercially available spectrometer SFB7. The study has been focused on the working upper frequency range and the estimation of the Cole parameters required for assessment of body fluid distribution: R0 and R8. The results indicate that AD5933-based spectrometer implemented in this work can perform accurate impedance measurements well above the upper limits recommended in the datasheet. The AD5933-EBIS presents a good performance compared with the SFB7 on the 2R1C circuit and the total right side measurements, showing a smaller error in the resistance spectrum and small deviation error in the reactance when measuring over 270 kHz. The comparison on the Cole parameters estimation obtained with the SFB7 and the AD5933-based spectrometer exhibit a difference below 1% for the estimation of R0 and R8. Consequently the overall measurement performance shown by the implemented AD5933-based spectrometer suggests its feasible use for EBIS measurements using dry Textrodes. This is of special relevance for the proliferation of EBI-based personalized health monitoring systems for patients that require monitoring the distribution of body fluids, like in dialysis.

AD5933-Based Electrical Bioimpedance Spectrometer. 
Towards Textile-Enabled Applications

J. Ferreira, Student Member IEEE, F. Seoane, Member IEEE, and K. Lindecrantz, Member IEEE.

Abstract— Advances on System-On-Chip and Textile technology allow the development of Textile-enabled measurement instrumentation. Textile Electrodes (Textrodes) have been proven reliable for performing Electrical Bioimpedance Spectroscopy (EBIS) measurements, and the availability of a integrated circuit impedance spectrometer, the AD5933, has allowed the implementation of small size EBIS spectrometers.

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I. INTRODUCTION

Technological improvements in System-on-Chip technology have enabled the integration of complex functional systems into a single integrated circuit. As a result a complete impedance spectrometer is available on a single integrated circuit: AD5933 manufactured by Analog Devices [1]. Its availability in combination with a 4-Electrode Analog Front End (4E-AFE) [2] has allowed the development of a complete Electrical Bioimpedance Spectrometer (EBIS). The performance of the AD5933-based EBIS has been tested on electrical 2R1C-circuits for several Electrical Bioimpedance (EBI) applications [3], validating its potential use on EBI applications like Body Composition Assessment (BCA).

Recent developments in conductive textile fabrics and electrode technology have allowed the implementation of Textile electrodes (Textrodes) garments for EBI-based measurements for BCA [4-5] and cardiovascular monitoring [6].

The BCA parameters indicating the amount of Extra-Cellular (ECF), Intra-Cellular (ICF) and Total Body Fluid (TBF) [7] are obtained from the estimation of the resistance value at DC and infinite frequency, known as Cole parameters R0 and Rg. The broader the frequency range of the obtained EBI measurement spectrum, the better the accuracy of the estimations of the Cole parameters will be. Therefore the frequency limits of the EBI measurement play an important role in the correct estimation of the BCA parameters.

According to the datasheet [1], the AD5933 spectrometer recommended frequency analysis is from 1 to 100 kHz with a system accuracy below 0.5%, but in reality the device allows to perform impedance measurements up to 500 kHz. The availability of such EBI spectrometer together with the proper textrode garment would allow the implementation of BCA monitoring systems for home applications [8].

In this work, the measurement performance of a custom made AD5933-based EBI spectrometer using dry Textrodes is studied, with typical experimental EBI measurements for BCA from the point of view of the estimation of R0 and Rg, and with special attention to the upper frequency limit. The work is based in a comparative study between the AD5933-based EBI spectrometer and a commercially available spectrometer: the ImpediMed SFB7.

II. MATERIALS AND METHODS

A. EBI Spectrometers

Two EBI spectrometers have been used in this work: the ImpediMed SFB7 and a custom made AD5933-EBIS. The SFB7 [9] performs tetrapolar measurements in the frequency range from 4 kHz to 1000 kHz, and it has been used as a golden standard.

The AD5933-EBIS is based the AD5933 Impedance
Network Analyzer as impedance core, and performs also
tetrapolar measurements implementing the 4E-AFE
introduced in [2] . The upper frequency limit was
incremented up to 450 kHz just by programming the
AD5933 registers to do so. The AD5933-based EBIS is
battery driven and uses Bluetooth technology to control and
transfer the measurements to a PC station.

A. Measurement Textrodes

A custom designed Textrode garment, see Fig.1, has been
used to perform Total Right Side EBI measurements [10].
The textrode is based on two pieces: one for the hand-wrist
and other for the foot-ankle both incorporating two separate
conductive textile areas used as electrodes for current
injection and voltage sensing.

The garment has Velcro fasteners and snap-button
collectors. The outer layer is made of synthetic wrap
knitted fabric and an intermediate foam layer assures good
skin-electrode contact. The inner surface is made of
conductive Shieldex® Fabric P130+B. The Shieldex® fabric
is a two dimension stretchable conductive fabric based on
Silver Plated (99% pure silver) and with a raw material
constitution of 78% Polyamide and 22% Elastomer.

B. 2R1C and EBIS Measurements

Using both spectrometers EBIS measurements were taken
on a 2R1C circuit dummy, and Total Right Side (TRS) [11]
on three healthy subjects lying supine in a resting state. The
2R1C circuit model was implemented with a resistor of 1.21
kΩ in series with a 1 nF capacitor, both in parallel with a
resistor of 604 Ω, all components with a 0.1% precision. A
set of 30 complex EBI spectroscopy measurements were
taken for each subject with the textrode garment. In the case
of the 2R1C circuit, 20 measurements were taken.

C. Spectrum Analysis and Cole parameters estimation

The complex impedance spectra have been compared in
the frequency range 5 – 450 kHz, for both circuit and TRS
measurements. In addition the Cole parameters, \( R_0 \), \( R_\infty \), and
\( f_C \), have been estimated from the TRS EBI spectra using the
three frequency ranges: 5-100 kHz, 5-200 kHz and 5-450
kHz. The estimation of the Cole parameters have been
estimated using Impedimed Bioimp Software, the Cole
parameter estimation has been performed with the TD
compensation option disabled.

III. RESULTS

A. 2R1C Circuit Measurements

The average resistance and reactance spectra from the
2R1C circuit measurements are plotted in Fig. 2. Both
devices present a good performance, but the reactance
spectrum obtained with the AD5933-EBIS exhibits a slight
deviation at high frequencies.

The Absolute error for the Resistance and the Reactance
spectra is shown in Fig. 3 with a doted and cross marker line
for the AD5933-EBIS and SFB7 respectively. The AD5933-
EBIS presents a lower error value in the resistance spectra
compared to the SFB7. In the Reactance plot, the AD5933-
EBIS presents an error greater than 5% above 270 kHz
approximately; while SFB7 has an error lower than 4% for
the complete frequency range. In the same figure the Standard Deviation (STD) for the 2R1C measurements is shown for both devices, the SFB7 presents lower STD compared with the AD5933-EBIS. In both cases the STD stays below 0.5 Ω.

B. Spectral Measurement

The complex EBIS measurements obtained with both spectrometers were very similar for the three subjects, exhibiting the same underestimation on the reactance spectrum at high frequencies as observed in the 2R1C circuit measurements. The averaged resistance and reactance spectrum for Subject 1 is shown in the Fig. 4. The resistance spectrum presents a slight difference at frequencies above 200 kHz. In the case of the reactance spectrum the differences is more noticeable and increasing with the frequency.

The impedance plot for EBIS measurements Subject 1 is shown in Fig. 5. The impedance plots obtained with both devices are nearly similar, making difficult to trace some difference between them.

C. Cole Parameter Estimation

The estimated values for the Cole parameters are shown in Table I. This table provides the average values for the Cole parameters estimations obtained with the Bioimp Software from the EBI measurement performed on each subject with both spectrometers. The values estimated from the measurements taken with both spectrometers in the frequencies ranges of 5-100 kHz and 5-200 kHz are very similar. In Table II it is possible to observe the mean difference among the three subjects for each of the parameters, and for each of the three frequency ranges. Notice that for $R_0$ and $R_\infty$ the difference is kept below 1.2%, in the frequency range of 5-450 kHz, the difference on the Cole parameters it is slightly larger but it is still relatively very small

In Table I and Table II it is possible to observe that the deviation produced on the estimation of characteristic frequency, $f_C$, it is slightly larger than in the cases for $R_0$ and $R_\infty$.

Table III shows the Mean Absolute Deviation between the estimation of the Cole parameter obtained with the SFB7 using the 5-450 kHz frequency range and the value for the Cole parameters estimated from the measurements taken with the AD5933-EBIS for the 3 frequency ranges. In the table it is possible to observe that the difference for $R_0$ and $R_\infty$ is smaller than 1%.

IV. DISCUSSION

The close resemblance between the impedance spectra obtained from the 2R1C circuit indicate that the AD5933-EBIS can indeed perform accurate impedance measurement well above other upper limits previously reported, 100 kHz.
Despite the clear deviation observed in the reactance at high frequencies, the Cole parameter estimation performed from EBIS data measured up to 450 kHz produce very similar values for $R_0$ and $R_\infty$ to those estimated from the EBIS measurement performed with the SFB7. This is due to the fact that the semicircular plot produced by the EBIS data in the impedance plane, it is expected that similar impedance plots will produce similar values for $R_0$ and $R_\infty$. The estimation of the Cole parameters depend on the curve fitting approach implemented. Since the resistance spectrum obtained with spectrometers are almost similar, the use of other estimation algorithms based in the resistance spectrum only, such as the one in [13], would also produce precise estimations for $R_0$ and $R_\infty$.

Since the estimation of the body fluid distribution from EBIS data currently depend only on the estimates of $R_0$ and $R_\infty$ [7], it is very likely that the AD5933-EBIS spectrometer in combination with the Textrode garment would be useful for BCA applications. A clinical study comparing the performance of several commercial EBIS meters with the AD5933-EBIS is scheduled to be performed shortly.

V. CONCLUSIONS
The results obtained show the feasibility to obtain accurate TRS EBIS measurements using the custom made AD5933-EBIS with dry Textrodes for Cole parameter and BCA estimation.

The AD5933 EBIS presents a good performance compared with the SFB7 on the 2R1C measurements, showing a smaller error in the resistance spectrum measurement but a noticeable error in the reactance spectrum at frequencies above 270 kHz. On the other hand, the difference observed in the estimation of the Cole parameters, $R_0$ and $R_\infty$ using the AD5933 EBIS is below 1% when compared with the values estimated from a commercial EBIS meter like the SFB7.

The availability of Textrode garments and reduced size spectrometers like the AD5933-EBIS used in this work will enable the implementation of EBI-based personalized health monitoring systems for body fluid distribution. Such systems could play an important role improving the quality of life of chronic kidney disease patients requiring dialysis for example.

REFERENCES