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Bioimpedance and Bone Fracture Detection: A State of the Art

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Abstract. Bioimpedance measurements are used increasingly in health applications because bioelectric parameters have been associated with anatomical and physiological properties, thus enabling to distinguish medical conditions. For bone fracture diagnostics, nevertheless, there is no established non-invasive method. Ex vivo studies and In vivo bioimpedance procedures, both invasive and non-invasive, on mammalians long bones are associated with promising results. In this work, out of a total of 568 papers, we reviewd 59 articles that mention long bone integrity by electric properties, be it Bioimpedance Analysis, Electrical Impedance Spectroscopy or Electrical Impedance Tomography. The papers are described in three sections, "Ex vivo measurements", "In vivo invasive measurements" and "In vivo non-invasive measurements". This review allows to establish the basics to planning the development of new technology to detect bone fracture via bioimpedance measurements.

1. Introduction

Bioimpedance is defined as impedance measurement of a biological system [1]. As impedance is the magnitude opposing current flow in an electrical circuit when voltage is applied to it, all parameters are governed by Ohm´s law [2]. Different from "resistance" which opposes direct current flow, "impedance" results from the application of alternating tension or current. There is thus one "impedance" for every frequency of the stimulating current waveform.

Bioimpedance measurements stem from Ohm´s Law applied to the resulting signal (either voltage or current) in a biological system when energy is applied in the form of a stimulating signal (either current or voltage respectively). If the injected signal is a current, the measurement will be voltage potential and vice versa. Electrodes are used as interfaces between the external measuring unit and the biological system, both to apply and to measure the resulting magnitude. The injected signal has a known amplitude and frequency and the resulting amplitude and phase measurements define the bioimpedance in terms of "modulus" and "phase". This can be expressed as a complex number with a real part known as resistance and an imaginary part for reactance. Resistance and reactance depend of resistivity and permittivity, respectively, and their geometrical size. Resistivity and permittivity are electrical properties of materials and media. In biological systems, the reactance only can be zero or

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negative (capacitive behavior) not positive (inductive behavior). In electrical systems, this is different, the reactance can have capacitive or inductive behavior or zero (purely resistive) [1,3].

We are reviewing in the present paper three techniques as applied to bone fractures, namely Bioimpedance Analysis (BIA), Electrical Impedance Spectroscopy (EIS) as well as in Electrical Impedance Tomography (EIT).

BIA is a method which gives one single biompedance measurement (including modulus and phase), since the stimulating alternating signal is a simple sine wave at a given frequency. EIS yields a set of bioimpedance measurements, called a "spectrum" (hence its denomination), since a set of signals (all of the same amplitude but at different frequencies) is successively injected. Sometimes EIS is described as a signal spectrum being applied since the same signal amplitude is assigned to a succession of either increasing or decreasing frequencies, within the spectrum "band width" [3]. In both BIA and EIS the measurements can be done using either bipolar, tripolar o tetrapolar electrode configurations, i.e. using two, three or four electrodes [1]. For EIT, the spatial resolution of the reconstructed images requires more electrodes or measurement points, usually chosen as a power of two, starting at 16 electrodes. EIT systems typically inject current at two electrodes and measure signals at the remaining electrodes, two by two, following one of a number of possible sequences and configurations [3–5]. In contrast to BIA and EIS, EIT gives a vector of bioimpedance values each associated with its position on a bidimensional mapping. There is a qualitative difference separating BIA and EIS on one side and EIT on the other since the latter is the result of intense mathematical calculations to "create" a slice of bioimpedance values of the body under examination. EIT is usually performed on mixed media volume, such as the thorax, where water and air have very different electrical properties. EIT estimates internal bioimpedance values from external measurements and reconstructs an internal image. This mathematical operation as known as "to solve an inverse problem" because the original electrical properties of each internal point is unknown and only the external consequences of its existence are measurable on the outside, i.e. on the skin of the patient. In much the same way the EKG is the result of skin measurements of internal electrical activity of the heart. The cardiologist in his/her mind reconstructs the cardiovascular function by interpreting EKG signals[6, 7], EIT is used to build imaging estimates of a region confined by the electrodes. Both human anatomical and dynamic function parameters -such as pulmonary ventilation- can be quantified by EIT [3]. Long bone integrity deduced from EIT is an unusual topic of research, since most of EIT applictions deal with chest exploration and regional ventilation.

Since the discovery of X rays, bone fractures are diagnosed by visual interpretation of X ray projections on either a film (XX Century) or electronic arrays (digital radiography, XXI Century) [8,9]. Despite the present trend to reduce the X ray energy involved, there is always an accumulative effect of the ionizing radiation, which increases the statistical likeliness of cellular nucleus damage leading to unwanted mutations [8]. Moreover, X ray equipment is usually large and expensive, even in its mobile versions for Emergency Departments. To overcome these inconveniences -ionizing radiation, size and cost- a few research groups is considering bioimpedance to describe the result of trauma on bone structure.

The present review describes bioimpedance measurements to detect long bones fractures. Research papers on the characterization of different tissues are not included, and neither bone growth electrostimulation.

2. Measurements Methods

The review selected all papers written in English from 1928 to 2018 with the key words bioimpedance, bone, fracture, detection, spectroscopy, analysis, monitoring, electrical impedance tomography, bioresistivy in different combination. The databases used been the digital library of Ministerio de Ciencia y Tecnología de la Republica Argentina (which has access to ACM Digital Library, ACP Scitation, American Chemical Society, American Physics Society, Annual reviews, BioMed Central, IEEE Xplore Digital Library, IOP Science, JSTOR, Knovel, Lyell Collection, Nature Journals, SAGE Premier, SciELO, Science Magazine, Science Direct, Sistema Nacional de

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Respositorios Digitales, SpringerLink, SpringerOpen, Wiley Online Library and Wiley Open Access) and Google Scholar©. The results of these searches were a total of 568 of which only 58 deal with mammalian long bones (femur, tibia, peroneum, humerus, radius and cubitus) AND describe some method or measurement of electrical properties tending ultimately to describe structural bone integrity.

The papers are described in the following three sections, "Ex vivo measurements" reporting 30 papers, "In vivo invasive measurements" 8 papers and "In vivo non-invasive measurements" with 14 papers. All papers described refer to one,- or more- of the BIA, EIS or EIT methods implemented.

2.1. Ex vivo measurements

Hemingway [10] and Burger *et al*. [11,12] are the first authors (1943 and 1961) to describe the electrical properties of bone tissue. Geddes and Baker later write an interdisciplinary compendium with both physiologists and engineers input [13]. The compendium describes several tissues, bioimpedance-wise, showing special interest and deeper analysis for bone tissue. Bone tissue has a large bioelectric variability due to its morphological diversity, evidenced by differences between long bones and compact bones [13]. BIA was used with fixed frequencies of 1.25 MHz and 10 MHz.

A very important contribution was made by C. Gabriel in a series of papers which included conductivity and permittivity of biological tissues of several species (human, bovine, sheep, porcine, among others) using EIS in three different electrode configurations [14–16]. Bioimpedance is given at different frequencies and measured with different electronic equipment: from 10 Hz to 10MHz with HP4182A, from 300kHz to 3GHz with HP8720 and from 130 MHz to 20 GHz with HP8753. The same author had previously developed compensation models to reduce measurement errors due to coaxial cables, and published calibration curves [17].

Bone structure anisotropy was first addressed when bioimpedance was measured in different directions (axial, radial and longitudinal) of long bones [18–21]. Mercato *et al*. [18] measured bone samples applying 500 mV to bipolar electrodes at three frequencies: 100 Hz, 10k Hz and 1 MHz, using an LCR Meter (HP4192A). Casas and Sevostianov [19] perform a tetrapolar measurements with an HP4338B. Saha *et al*. [20,21] report bipolar measurements in three directions taken with an LCR meter (HP4275A) at frequencies of 10 kHz, 100 kHz and 1 MHz. Another set of measurements was limited to axial and longitudinal directions at 120 Hz, 1 kHz, 20 kHz, 40 kHz, 200 kHz, 400 kHz, 2 MHz, 4 MHz and 10 MHz. These results are shown as EIS in Figure 1.

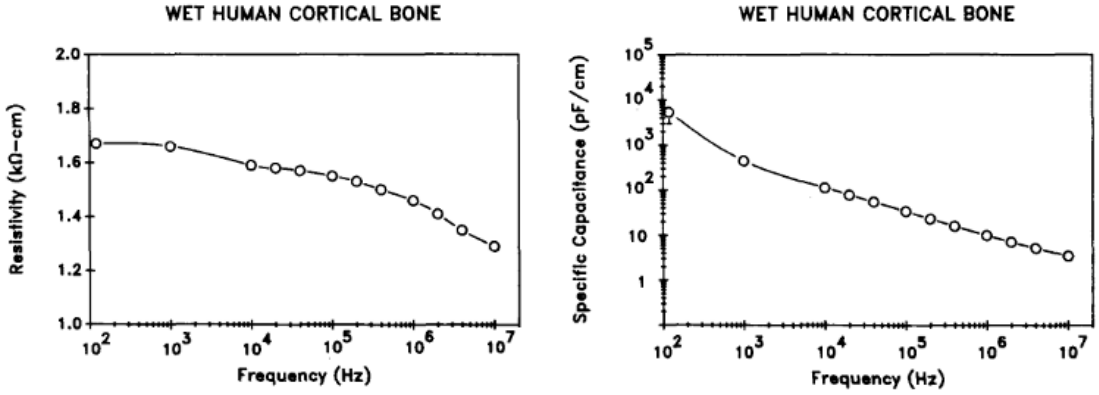

Figure 1. Electrical Impedance Spectroscopy. A. Average resistivity for the axial direction as a function of frequency. B. Average specific capacitance for the axial direction as a function of frequency [21].

Among electro-stimulation reports, there is an interest in biompedance estimations as a means to distinguish osteogenesis stages [22–27]. These papers give BIA and EIS experimental measurements, using function generators, ohmmeters and frequency counters. Since there are no bioimpedance figures for the same bone, intact and broken, these papers are not included in the present review.

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Some authors [28–32] have studied the mechanical properties of the bone, specifically its integrity and porosity. Macromolecular analysis describes the correlation of bone electrical properties with protein structure [33]. This was done using strain gauges and spectroscopy to highlight deformation.

Since the measurements are made 'ex-vivo', bones are exposed to external pollution, some papers [23,34,35] have addressed measurement inaccuracies secondary to ambient conditions.

Electrical properties of bones (conductivity and permittivity) have been estimated to model them with a passive element circuit [36]. For safety reasons [37], measurement only above 20 kHz are taken (20 kHz, 50 kHz and 100 kHz) with an impedance analyzer (Agilent 4294A).

In buco-maxilo-facial surgery, ex-vivo bioimpedance measurements help to verify the correct osteo-integration of implants. EIS measurements are taken on two metallic implants into the bone [38] in the range of 10 Hz to 65 kHz with an impedance analyzer (Solartron 1250) and an electrochemical interface (Solartron 1286). For this application the injected signal is a pure sinusoid of either 10 mV or 100 mV.

Despite the fact that the papers described so far include elements that can be used to distinguish bone lesions, only one author [39] gives ex vivo figures of the same bone, intact and fractured [39]. A current of 400µA at 50kHz is injected in a buffalo tibia using two Ag/AgCl electrodes affixed on the bone surface to measure three conditions: : intact, semi-fractured and fractured. There are differences between the three states, as recorded by a BioPAC system. Figure 2 shows the bone bioimpedance variations as it is partially, then completely broken.

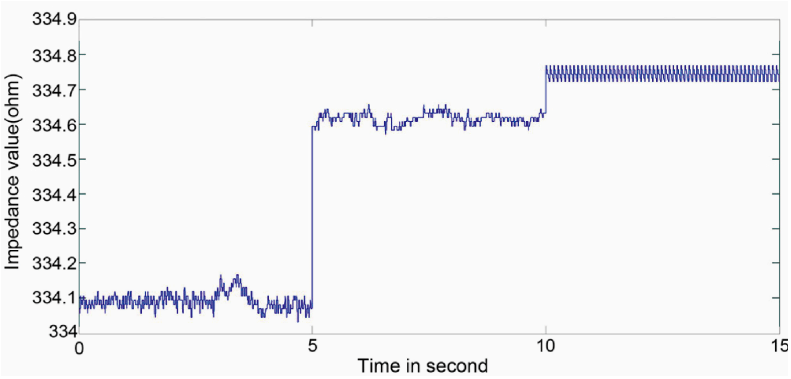

Figure 2. Buffalo tibial bioimpedance from intact to broken condition. From 334.1 ohm for intact, Z increases to 334.7 for fractured bone. After Khan *et al*.[39].

Lin *et al*. [40,41] published cadaveric bone electrical properties before fracture and during the reduction process [40,41]. Every phase of healing is measured by EIS in bipolar mode with embedded electrodes and Keysight Technologies E4980AL-100 Precision LCR device – Sinus tension of 100 mV at frequencies of 20 Hz to 1 MHz.

2.2. In vivo measurements

2.2.1. Animal In-vivo Measurements. In vivo measurements of bone lesions in animals are carried out after fracturing it under controlled conditions. The electrical parameters are then monitored in parallel with X ray imaging. Both the bone lesion and invasive electrode positioning are done under anaesthesia.

Most papers reporting in-vivo procedures include the electrical stimulation to foster bone morphogenesis [42–45]. It was not until 1982 that an in vivo paper reports bone electrical stimulation to record its bioimpedance [46]. Rinaldi and Goodrich verify with five embedded femur electrodes in rabbits what had been published until then. Figure 3 shows electrode positioning and bioimpedance measurement layout. Frequency was 20 Hz to 7000 Hz and applied voltage 0.1 volts to 1.2 volts with

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General Radio Oscillator model 1316 (variable voltage), Keithley 168 Auto-ranging digital multimeter and a Dynascan electronic multimeter Model 290.

Yoshida *et al*. [47] publish BIA at constant frequency (2.0 ± 0.4 Hz) and current (30 ± 6 μA) of rabbit bones surgically implanted external nails. Their aim was to record bioimpedance during the healing process after osteotomy. Different bioimpedance values were found for every bone union phase.

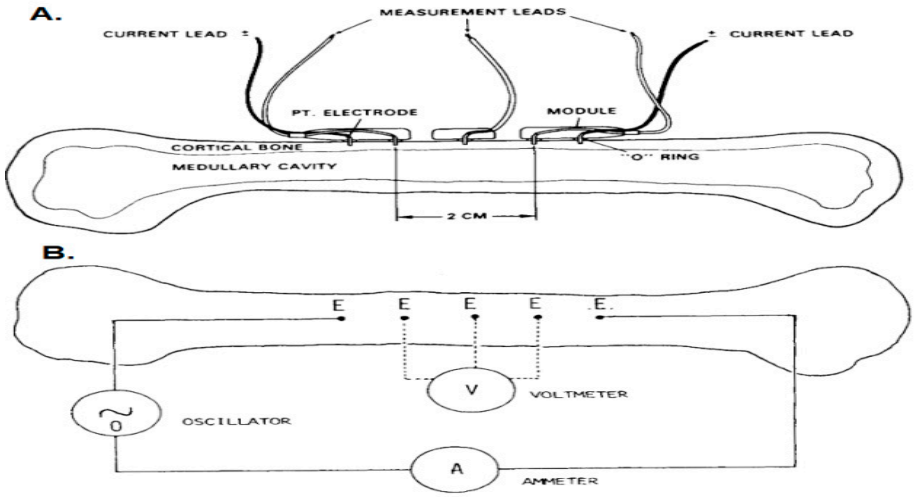

Figure 3. A. Five bone-electrodes affixed onto rabbit femur to measure cortical bioimpedance. B. Circuit diagram with a "current source" to estimate bioimpedance modulus in vivo rabbits. After Rinaldi *et al*.[46].

2.2.2. Invasive Measurements in Humans. Since long bone fracture reduction is treated with externally exposed nails, some authors have published BIA as healing monitoring evidence [48,49]. There is no intention here to detect a fracture, but rather a quantification of a biological process. The nails used for external fixation, are used as "invasive electrodes".

With such settings, Gupta [49] and Kumaravel [48] suggest that bioimpedance measurements could replace X ray images to determine when the bone healing ends, thus avoiding the use of ionizing radiation. They also speculate on the usefulness of BIA in case of bone union failures or delays. Frequency of 100 Hz was used along with a LCR-Q meter [49] while Kuramarel [48] used direct current (DC) with 0.1 to 1.0 volts variable tension, using a Scientech® Model ST4073 voltage generator and an ammeter from EIC Meters Private Limited, Bangalore - 560062, India.

It should be noted in passing that neither research group apparently took care of patient safety, as tensions (not currents) were applied to the electrodes and because the frequency used fell within risky ranges according to standards [37].

2.2.3. Non Invasive Measurements in Humans. In the 1980´s two British groups, one in Sheffield (England) the other in Aberdeen (Scotland) publish Electrical Impedance Tomography (EIT) applications for extremities [50,51]. Within two years, the Sheffield data collection [52] and the Aberdeen Impedance Imaging system [53] are able to produce transversal 2D images from EIT data collected around the skin.

Aberdeen University publishes EIT applications to produce diagnostics and monitoring evidence of human extremities bone lesions: femur [54], humerus [55,56], tibia [54,55] and peroneum [54]. Volunteers offered both intact and fractured extremities at the bones mentioned. In all cases did the authors use their original equipment and methods [53] with 1 mA and 10 kHz current successively

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injected in two out of sixteen skin electrodes to measure voltage from the remaining electrode adjacent pairs.

The Kulkarni group (Aberdeen, Scotland) is generally considered in EIT descriptions [4] as well as reviews [57–59] as the developer of bone fracture applications.

As a test for a new multifrequency broadband equipment [60], an EIT reconstructed human upper extremity section was published [61], but with no apparent clinical consequences in later available literature.

Ohmine *et al*. [62] perform skin electrode measurements on human arms to validate a model. By doing so, they obtain the conductivity of bone as well as other living tissues. There is no attempt here to characterize bone fracture, but it is interesting to mention the fact that they apply a step current to evaluate bioimpedance spectroscopy. Signal analysis theory is employed to obtain the same result as when using classical EIS frequency scanning, but with only one signal [63].

Steihaug *et al*. [64] use traditional BIA for hip fracture and hip replacement surgery characterization with 50 kHz current at 425 μA and tetrapolar array (RJL quantum systems III, RJL systems, USA) and a very similar 50 kHz current at 400 μA (Body impedance analyzer BIA 101 ASE, Akern Srl, Italy). Measurements are taken on affected side as well as contralateral to show differences in fractured and recently operated patients.

3. Discussion

The present revision contains a corpus of knowledge to base upon the development of a method to detect bone fractures using bioimpedance. All ex vivo papers specify the conditions (pH, direction of measurement, temperature, among others) in which the bioimpedance differences were recorded. This ensures reproducibility. The bioimpedance difference is associated with bone structure discontinuity provided there is a standard to compare it to, e.g. contralateral or further along the bone. The usefulness of the available information encompasses EIT, EIS and BIA alike.

Surprisingly, EIT, and not EIS nor BIA, is the only modality to have been used to attempt to characterize bone lesions. But deciding on whether a long bone is fractured based on low resolution sections is difficult and this is why the result has been poor due to date in terms of clinical use. New mathematical tools available after a quarter of a century [65] and increased computational power are available to allow big steps to be taken in the direction of giving reliable EIT images.

Electrical safety has not always been included in the design of experimental set-ups. This aspect must be addressed if bioimpedance is to be used as some substitute for X ray, i.e. broadly and commonly. Accepted safety standards [37] suggest to use frequencies above 10 kHz and to apply controlled current only, since prevalent voltage on unknown impedances may result in such currents that cause harm to patients.

The basics of bioimpedance extremities measurements have been described here. The next step is to address the clinical need for an easy, non-ionizing, low cost and portable instrument to detect bone fractures wherever pre hospital care is called to act: e.g. at a car accident, in the snow or on a boat at sea. Careful planning of experiments based on the present revision should help in the direction of a safe bone fracture bioimpedance detector.

In the Table 1 shows a practical information resume of the present work.

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Table 1. Bone integrity by Electrical Impedance Measurements

Authors	*Aim*	*Method*	*Signal*	*Results*	*Equipment (Model)*
Hemingway *et al.* [10]	Know the distribution of applied currents over human body for the study of diathermy effects.	BIA	1 MHz	High resistance at low frequency is due to superficial fat.	Wheatstone bridge & conductivity cell (Own developments)
Gabriel *et al.* [14–16]	Characterize dielectric properties of different biological tissues.	EIS	10 Hz - 10 MHz	Compendium of dielectric properties of animal & human tissues.	Impedance Analyzer (HP4182A)
Mercato *et al.* [18]	Establish a relationship between the high values of low-frequency permittivity, bone tissue	BIA	10 Hz, 10 kHz & 1 MHz	Correlation between the low-frequency electric conductivity and relative permittivity.	Impedance Analyzer (HP4192A)
Saha *et al.* [20,21]	Electrical and dielectric properties of wet human cancellous bone from distal tibiae	EIS	10 kHz - 10MHz	The variations in the electrical properties for longitudina and transverse directions .	Miliohm Meter (HP4275A)
Arpaia *et al.* [38]	EIS measurements the characterization of the interface between the bone and prosthesis.	EIA	10 Hz - 65 kHz (10 to 100 mV)	capability to detect t a satisfying connective tissue, and its thickness	Impedance Analyzer (Solartron 1250 & Solartron 1286)
Khan *et al.* [39]	Ipedance measurement to detect bone fracture and healing monitoring	BIA	50 kHz (400 µA)	Electrical impedance of a normal bone is less than that of fractured bone	Datalogger (BIOPAC system w MP 45 ADunit)
Lin *et al.* [40,41]	EIS to distinguishtissues involved in bone fracture repair	EIS	20 Hz - 1 MHz (100 mV)	EIS has the feasibility for detecting fracture callus composition, h	Precision LCR device (Keysight E4980AL)
Rinaldi and Goodrich [46]	Measure the conduction properties of rabbit femur with five-point method	EIS	20 Hz - 7 kHz (0.1 to 1.2 V)	Present bioimpedance values of different parts of rabbits femur.	Oscillator (GR1316) & Multimeters (Keithley 168 & Dynasmac 290)
Yoshida *et al.* [47]	Bone electrical impedance using external fixation pins as electrodes,	BIA	2 Hz (30 µA)	The bone remodelling resulted in an increase of Z values post healing.	AC electrical stim BS-1000) Biol. Amp. & Oscil (Kenw DCS8300)
Gupta *et al.* [49]	New tool to diagnose non-union of bones.	BIA	100 Hz	Electrical properties as marker for fracture.	LCR-Q Meter (No information)
Kumarevel *et al.* [48]	Can electrical resistance across the fracture be used as a tool to study fracture healing process ?	BIA	DC (0.1 to 1.0 V)	Resistance versus day graph to predict healing.	V Gen. (Scientech ST4073) & Ammeter (EIC Meters 560062)
Kulkarni *et al.* [57–59]	Generate a new method to clinical monitoring of bone fracture healing process.	EIT	10 kHz (1 mA)	Reconstruct the image of a cross section of different human limbs.	Aberdeen Impedance Imaging System Own development
Brown *et al.* [50]	New method for clinical monitoring	EIT	50 kHz (1 mA)	Image of a cross section of different human body parts	Sheffield Mark 1 (Own development)

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Riu *et al.* [60,61]	Multifrequency EIT measurements in EIT	64 kHz & 125 KHz	Reconstruct the image of a cross section of a human thigh.	(Own development)
Steihaug *et al.* [64]	BIA measurements of hip fracture & repair	BIA 50 kHz (425 μA) & 50 kHz (400 μA)	Resistance was lower on the side of the fractured h	Bioimpedance Analyzer (RJL & Body Impedance Anal BIA 101ASE

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