Electrical Bioimpedance Cerebral Monitoring: Fundamental Steps towards Clinical Application

by

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A
mi padre, mi familia
Y
Anita

ABSTRACT

Neurologically related injuries cause a similar number of deaths as cancer, and brain damage is the second commonest cause of death in the world and probably the leading cause of permanent disability. The devastating effects of most cases of brain damage could be avoided if it were detected and medical treatment initiated in time. The passive electrical properties of biological tissue have been investigated for almost a century and electrical bioimpedance studies in neurology have been performed for more than 50 years. Even considering the extensive efforts dedicated to investigating potential applications of electrical bioimpedance for brain monitoring, especially in the last 20 years, and the specifically acute need for such non-invasive and efficient diagnosis support tools, Electrical Bioimpedance technology has not made the expected breakthrough into clinical application yet. In order to reach this stage in the age of evidence-based medicine, the first essential step is to demonstrate the biophysical basis of the method under study. The present research work confirms that the cell swelling accompanying the hypoxic/ischemic injury mechanism modifies the electrical properties of brain tissue, and shows that by measuring the complex electrical bioimpedance it is possible to detect the changes resulting from brain damage. For the development of a successful monitoring method, after the vital biophysical validation it is critical to have available the proper electrical bioimpedance technology and to implement an efficient protocol of use. Electronic instrumentation is needed for broadband spectroscopy measurements of complex electrical bioimpedance; the selection of the electrode setup is crucial to obtain clinically relevant measurements, and the proper biosignal analysis and processing is the core of the diagnosis support system. This work has focused on all these aspects since they are fundamental for providing the solid medico-technological background necessary to enable the clinical usage of Electrical Bioimpedance for cerebral monitoring.

Keywords: Electrical Bioimpedance Spectroscopy, Hypoxia, Ischemia, Stroke, Brain Monitoring, Impedance Measurements, Biomedical Instrumentation, Non-invasive Monitoring.

PREFACE

This research work has been performed mainly in collaboration between the following research and academic institutions: the School of Engineering at University College of Borås, the Department of Signals and Systems at Chalmers University of Technology, the Sahlgrenska University Hospital, and the Sahlgrenska Academy at Göteborg University.

Specific activities of this research work have been carried out in collaboration with the Department of Electronic Engineering at the Polytechnic University of Catalonia, Spain.

This research work has been mainly funded by the Swedish Research Council (Vetenskapsrådet) through a research grant (No. 2002-5487). The research activity performed has also been part of the following European Network of Excellence: “Computational intelligence for biopattern analysis in support of e-Healthcare”, funded by the European Commission (The BIOPATTERN Project, Contract No. 508803). Funding from the K.G. Eliassons Fond has also been used in this work.

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This thesis work has generated the following publications:

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Spectroscopy Study of the Dynamics of the Transencephalic Electrical Impedance in the Perinatal Brain during Hypoxia.

By Fernando Seoane, Kaj Lindecrantz, Torsten Olsson, Ingemar Kjellmer, Anders Flisberg, and Ralph Bågenholm.

Physiological Measurement, 26 (5) pp. 849-863. ISBN/ISSN: 0967-3334. Aug, 2005.

Current Source for Wideband Multifrequency Electrical Bioimpedance Measurements

By Fernando Seoane, Ramon Bragós, and Kaj Lindecrantz.

Submitted IEEE Transaction on Biomedical Circuit and Systems.

Electrical Impedance Estimation as Total Least Square Problem, Formulation, Analysis and Performance.

By Fernando Seoane, Ramon Bragós, and Kaj Lindecrantz.

Under preparation.

Analysis of the Current Density Distribution in the Human head and its implications for Electrical Bioimpedance Cerebral Monitoring.

By Fernando Seoane, Mai Lu, Mikael Persson, and Kaj Lindecrantz.

Under preparation.

The Current Source for Electrical Impedance Spectroscopy and Electrical Impedance Tomography.

By Fernando Seoane, Ramon Bragós, Kaj Lindecrantz, and Pere J. Riu.

In manuscript.

The Emerging of Electrical Bioimpedance Cerebral Monitoring.

By Fernando Seoane, Kaj Lindecrantz, and Mikael Elam.

In manuscript.

BOOK CHAPTERS

Electrical Bioimpedance Cerebral Monitoring.

By Fernando Seoane and Kaj Lindecrantz.

Encyclopaedia of Healthcare Information Systems. Accepted for Publication.

Current Source Design for Electrical Biomedance Spectroscopy.

By Fernando Seoane, Ramon Bragós, Kaj Lindecrantz, and Pere J. Riu.

Encyclopaedia of Healthcare Information Systems. Accepted for Publication.

INTERNATIONAL CONFERENCES

A Novel Approach for Estimation of Electrical Bioimpedance: Total Least Square.

By Fernando Seoane and Kaj Lindecrantz.

Proceedings of the 13th International Conference on Electrical Bioimpedance. August-Sept, 2007. Graz.

Electrical Bioimpedance Cerebral Monitoring. A Study of the Current Density Distribution and Impedance Sensitivity Maps on a 3D Realistic Head Model.

By Fernando Seoane, Mai Lu, Mikael Persson, and Kaj Lindecrantz.

Proceedings of the 3rd IEEE-EMBS International Conference on Neural Engineering, pp. 256-260. May, 2007. Kohala Coast, Hawai'i.

Current Source for Multifrequency Broadband Electrical Bioimpedance Spectroscopy Systems. A Novel Approach.

By Fernando Seoane, Ramón Bragós, and Kaj Lindecrantz.

Proceedings of the 28th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, vol:1, pp. 5121-5125. Sept, 2006. New York.

Current Source for Wideband Electrical Bioimpedance Spectroscopy Based on a Single Operational Amplifier.

By Fernando Seoane, Ramón Bragós, and Kaj Lindecrantz.

IFMBE Proceedings of the World Congress on Medical Physics and Biomedical Engineering, vol:14, pp. 609-612. Sept, 2006. Seoul.

Extraction of Structural Information from Impedance Spectrum Data. A Step towards the Identification of Cellular Oedema.

By Fernando Seoane and Kaj Lindecrantz.

Proceedings of the 18th EURASIP Biosignal Conference. Analysis of Biomedical Signals and Images, pp. 90-93. June, 2006. Brno.

Influence of the Skull and the Scalp on the Electrical Impedance of the Head and the Implications on Detection of Brain Cellular Edema.

By Fernando Seoane and Kaj Lindecrantz.

IFMBE proceedings of the 12th International Conference on Biomedical Engineering, vol:12. Dec, 2005. Singapore.

The Effect of the Scalp and the Skull Bone in the Total Impedivity of the Neonatal Head and its Implications in the Detection of Brain Cellular Edema.

By Fernando Seoane and Kaj Lindecrantz.

IFMBE proceedings of the the 3rd European Medical and Biological Engineering Conference, EMBEC'05. vol:11. Nov, 2005. Prague.

Evolution of Cerebral Bioelectrical Resistance at Various Frequencies during Hypoxia in Fetal Sheep.

By Fernando Seoane, Kaj Lindecrantz, Torsten Olsson, and Ingemar Kjellmer, and Carina Mallard.

Proceedings of the EPSM 2004 Conference in Australasian Physical & Engineering Science in Medicine Journal, vol:27 (4), pp. 237.

Brain Electrical Impedance at Different Frequencies: The Effect of Hypoxia.

By Fernando Seoane, Kaj Lindecrantz, Torsten Olsson, and Ingemar Kjellmer, Anders Flisberg, and Ralph Bågenholm.

Proceedings of the 26th Annual International Conference oh the IEEE Engineering in Medicine and Biology Society, vol:3, pp. 2322 - 2325. Sept, 2004. San Francisco.

Bioelectrical Impedance during Hypoxic Cell Swelling: Modelling of Tissue as a Suspension of Cells.

By Fernando Seoane, Kaj Lindecrantz, Torsten Olsson, and Ingemar Kjellmer.

Proceedings of the 12th International Conference on Electrical Bioimpedance, vol:1, pp. 73-76. June, 2004. Gdansk.

NATIONAL CONFERENCES & WORKSHOPS.

The Role of the Cerebrospinal Fluid in the Distribution of Electrical Current within the Brain and its Implications for Electrical Bioimpedance Cerebral Monitoring.

By Fernando Seoane, Mai Lu, Mikael Persson, and Kaj Lindecrantz.

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Enhancement of a Voltage Controlled Current Source for Wideband Electrical Bioimpedance Spectroscopy.

By Fernando Seoane and Kaj Lindecrantz.

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The Transcephalic Electrical Impedance Method. Principles for Brain Tissue State Monitoring.

By Fernando Seoane and Kaj Lindecrantz.

EU-Biopattern Project Symposium. Brain Workshop, pp. 11-12. May, 2005. Göteborg.

Electrical Bioimpedance Cerebral Monitoring.

By Fernando Seoane, Kaj Lindecrantz, and Torsten Olsson.

Proceedings of Medicinteknikdagarna 2005. Annual conference of Svensk Förening för Medicinsk Teknik och Fysik. Oct, 2005.

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Fernando Seoane Martinez
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THESIS INTRODUCTION

Research Project Background

The research activity reported in this thesis has been performed under the supervision of Prof. Kaj Lindecrantz as the main task of the research project denominated “Brain damage: Detection and Localisation of Cell Swelling”.

The central hypothesis of this research activity is that non-invasive measurements of electrical bioimpedance provide relevant information regarding the status of the brain tissue, and more specifically regarding underlying physiopathological mechanisms associated with brain cellular swelling as a consequence of hypoxia, ischemia or other potential aetiologies.

Research Goals and Activities

The research goal of this thesis work is twofold: firstly the verification of the hypothesis that physiological changes in brain tissue such as hypoxic cell swelling can be detected by means of measurements of electrical bioimpedance. Secondly, the identification of the fundamental issues for developing an electrical bioimpedance method for early detection of threatening brain damage.

According to the mentioned research goals, this thesis work has been focused in two different areas. To start with and verify the hypothesis under study, the research work done has been focused on the biophysical aspects of hypoxic cell swelling. Secondly, the work has been centred in study of the current status of bioimpedance technology and the fundamental issues, in terms of electronic instrumentation, measurement protocol, biosignal analysis and processing for the development of a non-invasive and clinically feasible method for early detection and monitoring of brain damage based on electrical bioimpedance measurements.

To accomplish the stated research goals, the following different research tasks have been pursued:

- Establish the basic characteristics of the electrical impedance across the brain and its frequency dependence for normal as well as hypoxic brain tissue.
- Verify preliminary results regarding time relation between impedance alterations and the cerebral hypoxia producing cell swelling.
- Design robust instrumentation for multi-frequency bioimpedance measurements extensible to multi-channel applications.
- Investigate the influence of skull bone and other brain tissues on the current flow between the injecting electrodes, a factor that may affect the ability to detect brain cell swelling.
- Study the current density distribution in the brain, its effect on the measurements of electrical bioimpedance, and its dependence on frequency as well as on the measurement setup.

Thesis Contents and Outline.

This PhD. thesis is organized in two main parts. The first part contains an introductory report to research activity performed in the thesis and the second part contains the scientific knowledge and findings obtained as result of the performed research work.

Part I is divided in four chapters that contain a scientific introduction to the main fields and core topics involved in the research activity performed during the thesis work. At the end of part I the cited bibliography is referenced.

Part II includes a selection of scientific publications originated from the performed research activity, containing the core contributions of this thesis.

Summary of Publications

The following six papers are included in part II of this thesis:

Paper A.

Spectroscopy Study of the Dynamics of the Transencephalic Electrical Impedance in the Perinatal Brain during Hypoxia

In this work a piglet model, is used to study of the effect of hypoxia in the electrical impedance of the brain, and a broad spectroscopy study of brain tissue during hypoxia is performed and reported.

The main finding of the work reported in this paper is the confirmation of the suspension of cells model as a valid model to simulated cell swelling. As a result of the validation it is possible to confirm theoretically the relationship between the cell swelling and the corresponding observed changes in electrical bioimpedance.

Other findings are:

- High frequency dependency of the changes in resistance and reactance during cell swelling is shown.
- A close time relationship between the changes in the electrical impedance of the brain and the onset of the hypoxic insult is confirmed.
- The sensitivity to cell swelling of the measured impedance is more stable with respect to frequency in the reactance than in the resistance.
- Reactance increases relatively more than the resistance during cell swelling.
- During cell swelling, the resistance changes the most at low frequencies and the reactance changes the most at medium-high frequencies.

Paper B.

Current Source for Wideband Multifrequency Electrical Bioimpedance Measurements

Through theoretical analysis and empirical test this work demonstrates and suggests circuit solutions suitable for wideband current source for multifrequency impedance measurements.

Paper C

Current Source Design for Electrical Bioimpedance Spectroscopy.

This paper presents the fundamentals as well as the state-of-art of technological and other issues to consider when designing current sources for multifrequency bioimpedance spectroscopy. Focuses is on wideband multifrequency systems, the main challenges for the current source designer.

Paper D

A Novel Approach for Estimation of Electrical Bioimpedance: Total Least Square.

A new way to deal with impedance estimation, the Total Least Square method, is introduced in this work. The main contribution of this paper is to present a new conceptual approach that is free from some constraints that limit the performance of previously used methods like the Fourier analysis and Sine correlation.

Paper E

A Study of the Current Density Distribution and Impedance Sensitivity Maps on a 3D Realistic Head Model.

This paper reports results from a simulation of the distribution of the electrical current through the human head with high anatomical resolution. The results present several findings of relevance for a successful application of measurements of transcephalic electrical bioimpedance:

- The importance of the current draining effect of the high conductive Cerebro Spinal fluid in the total distribution of current density is shown.
- It is shown that the high resistive layer of Skull bone is not as isolating as commonly believed.
- The importance of the appropriate placement electrodes with respect to volume under study it is confirmed.
- It is confirmed that the specific dielectric properties of each tissue and its frequency dependency must be taken into consideration in an application electrical bioimpedance for cerebral monitoring.

There are several other findings obtained from this simulation work, especially for Electrical Impedance Tomography, that will be published elsewhere in an extended version of this paper.

Paper F

Electrical Bioimpedance Cerebral Monitoring.

This paper compiles and introduces to current research activities on brain electrical bioimpedance, highlighting the proliferation of potential clinical applications. It is made clear that despite intensive research on the application of electrical bioimpedance for cerebral monitoring and the advance status of the research, a clinical method has not been put in to practice yet.

PART I

CHAPTER 1

INTRODUCTION TO ELECTRICAL BIOIMPEDANCE CEREBRAL MONITORING

1.1 Introduction

Electrical Bioimpedance (EBI) is a widespread technology within medicine, with more than 60 years of successful applications in clinical investigations, physiological research and medical diagnosis (H. P. Schwan 1999). The first application of bioimpedance techniques for monitoring applications appeared as early as 1940, impedance cardiography (J. Nyboer *et al.* 1940). Since then, bioimpedance measurements have been used in several medical applications; examples from a long list are lung function monitoring (T. Olsson & L. Victorin 1970), body composition (R. F. Kushner & D. A. Schoeller 1986) and skin cancer detection (P. Aberg *et al.* 2004). A complete historical review is available in Malmivuo (J. Malmivuo & R. Plonsey 1995). During the last 20 years even a medical imaging technique has been developed based on measurements of bioimpedance: Bioimpedance Tomography (BT), also known as electrical impedance

tomography (EIT). A complete and recent review is available (R. H. Bayford 2006).

EBI studies have been performed in the neurological area investigating the effect of several aetiologies and physiopathological mechanisms, e.g. spread depression, seizure activity, asphyxia and cardiac arrest (S. Ochs & A. Van Harreveld 1956, A. Van Harreveld & S. Ochs 1957, A. Van Harreveld & J. P. Schade 1962, A. Van Harreveld *et al.* 1963) since the 1950s. But the major activity within electrical bioimpedance cerebral research has been during the last 20 years. Since Holder foresaw the development of electrical bioimpedance-based neurological applications back in 1988 (D. S. Holder & A. R. Gardner-Medwin 1988), several bioimpedance research and clinical studies have been performed in the areas of brain ischaemia (C. E. Williams *et al.* 1991, D. S. Holder 1992a, F. Seoane *et al.* 2004c), spreading depression (D. S. Holder 1992b, T. Olsson *et al.* 2006), epilepsy (G. Cusick *et al.* 1994, A. Rao 2000, T. Olsson *et al.* 2006), brain function monitoring (A. T. Tidswell *et al.* 2001), perinatal asphyxia (B. E. Lingwood *et al.* 2002, B. E. Lingwood *et al.* 2003, F. Seoane *et al.* 2005), monitoring of blood flow (M. Bodo *et al.* 2003, M. Bodo *et al.* 2004, M. Bodo *et al.* 2005) and stroke (G. Bonmassar & S. Iwaki 2004, L. X. Liu *et al.* 2005, L. X. Liu *et al.* 2006).

1.2 Clinical Need

1.2.1 Available Cerebral Monitoring Techniques

Several different imaging techniques are available for diagnosis support or monitoring of the brain, e.g. MRI, CT-scan, etc. These imaging techniques are well established in clinical routine and have shown their critical importance for detection and diagnosis of neurologically related aetiologies. However, none of these modalities are suitable for long-term cerebral monitoring, or applicable in many situations where the brain is particularly at risk, e.g. during an ongoing cardiopulmonary by-pass operation, in the intensive care unit, or for acute stroke assessment in, for instance, ambulances.

There are other monitoring methods routinely used for continuous cerebral monitoring, such as measurements of intracranial pressure. This type of measurement requires invasive techniques that introduce risk of infections and even brain damage. For this reason, invasive methods must be used only in very specific situations and avoided if possible.

The study of the electrical activity of the brain or encephalon, electroencephalography (EEG), is the monitoring technique *par excellence* to detect abnormalities or changes in brain function. It is non-invasive and suitable for real-time as well as for long-term monitoring. EEG monitoring can be used to detect changes and trends in the brain function related to brain damage, but it requires the expertise of a very well trained and skilled

specialist, which in many situations might not be available. However, the analysis of EEG signals has been an area of medical signal processing for many years, and of continuous research to provide artificial intelligence tools for diagnosis support in neurophysiology (N. Löfgren 2005).

1.2.2 Cellular Oedema

Cell swelling, also known as cellular oedema, is part of the physiological adaptations that the cell goes through in response to a threatening stimulus, and it is an early manifestation preceding cellular injury. Cell swelling is part of the cellular adaptation process present in the hypoxic-ischaemic injury mechanism, one of the most common causes of cellular damage, and it is present in aetiologies like perinatal asphyxia and ischaemic brain stroke.

1.2.3 Perinatal background

In the perinatal arena, hypoxia/ischaemia is the most common cause of brain damage in the mature foetus. Up to one of each 250 newborn babies suffers from perinatal asphyxia in fully developed nations. This incidence rate has the result that dozens of thousands of newborns suffer brain damage every year worldwide. The mortality rate can be as high as 50% in severe cases. Many of the infants who survive suffer severe neurological disabilities. The incidence of long-term complications depends on the severity of the hypoxic/ischaemic insult. Among the most frequent consequences are mental retardation, ataxia, epilepsy, and cerebral palsy. Conservative estimates of the yearly cost to society for treatment and care of affected children lie around half a million € per birth (R. Berger & Y. Garnier 1999). A better understanding of the brain and its diseases thus has the potential to generate significant effects, not only on the health of the affected individuals, but also on worldwide economy.

Survival rates of patients with brain damage have increased markedly during the last few decades, but the number of patients with symptoms and handicap from acquired brain damage has not decreased. Society pays for better survival rates with an increased risk of permanent neurological impairment in the survivors. The reduced mortality can be ascribed to a combination of new basic knowledge, improved treatments and improved possibilities for intensive care monitoring of vital functions such as circulation, respiration and metabolism. However, we lack knowledge about the damaging processes and methods to detect, prevent and treat impaired brain function before a permanent lesion develops. There is a strong demand for better understanding of the various processes in the brain, which we can influence today through medication and other means. Functionality and quality of life after impairment of functions can be improved in numerous ways today.

1.2.4 Brain Stroke

Brain stroke, also known as a brain attack, is a cerebrovascular disease and, according to the World Health Organization (J. Mackay & G. A. Mensah 2004), it is the third leading cause of death in the world after coronary heart disease and cancer. Brain stroke is accountable for up to 10% of all the deaths in the world and annually 15 million people suffer from brain stroke, leaving more than 5 million deaths and 5 million with permanent disabilities.

There are two differentiated types of stroke: haemorrhagic and ischaemic. The ischaemic stroke is the most common, being responsible for up to 85% of all brain strokes. One characteristic of the ischaemic brain stroke is that cellular oedema is among its earliest morphological manifestations.

Since the chances of survival from brain stroke decrease rapidly with the time from onset to treatment, an efficient early detection of ischaemic cell swelling would have a major influence on survival rates from brain stroke.

1.3 Motivation for Development

There is a need for efficient methods for continuous monitoring of brain function. Adequate methods may exist for the diagnosis of morphological changes that have already occurred, but there are no techniques to detect clinical situations of impending brain injury.

The features of bioimpedance technology place it as the technology of choice to fill the need for brain monitoring in the medical scenarios mentioned above and several others. Bioimpedance technology is harmless for the patient, portable, and very affordable in comparison with other monitoring techniques already in use.

If it becomes possible to detect efficiently the cellular oedema at its origin we may be able to avoid the consequent cellular and tissue damage, which is brain damage in the case of neuronal cells.

CHAPTER 2

ELECTRICAL PROPERTIES OF TISSUE & BIOIMPEDANCE

2.1 Electrical Conductance of Living Tissue

The electrical conductance of biological tissue is determined by its constituents. In essence, tissue consists of extracellular fluid and cells containing the intracellular fluid inside the cell membrane. The extracellular fluid is the medium surrounding the cells, also denominated the extracellular space. It contains proteins and electrolytes including the plasma and the interstitial fluid. The cell is constituted by a lipid bi-layer plasma membrane containing the protoplasm that contains the cytosol, the organelles and the nucleus of the cell.

Figure 2.1. A living cell and some of its constituents.

A general definition of living tissue is:

“A part of an organism consisting of an aggregate of similar cells and the intercellular substances surrounding them organized into a structure with a specific physiological function.”

2.1.1 Tissue Fluids as Electrolytes

In metals the electrical charge carriers are electrons, but in electrolytes the charge carriers are ions – cations if their charge is positive, and anions if the charge is negative. An electrolyte exhibits ionic DC conductivity, and is defined as:

“A chemical compound that, when dissolved in a solution, dissociates into ions and is able to conduct electric current in the presence of an external electrical field.”

Both intracellular and extracellular fluids are electrolytes because they contain ions, which are free to migrate and transport the electrical charge. Therefore we can consider biological tissue electrically and macroscopically an ionic conductor. The total ionic conductivity of a solution depends on the concentration, activity, charge and mobility of all free ions in the solution. The most important ions contributing to the ionic current in living tissue are K^+ , Na^+ and Ca^{2+} . It should be noted that all three of these are cations. The viscosity and temperature of the solution are also important factors influencing in the ionic conductivity.

Table 2-I. Approximate Concentration of Ions in Living Tissue

Important cellular ionic concentrations		
	Intracellular	Extracellular
Na^+	10-20 mM	150 mM
K^+	100 mM	5 mM
Ca^{2+}	10(-4) mM	1 mM

* Data from Guyton and Hall (2001).

Ionic conductance is a transfer of charges accompanied by movement of a substance, producing changes in the bulk of the electrolyte. As a result, DC ionic conductivity is a linear function of the field only for a limited period of time, and when the strength of the applied external electric field is not high.

For more detailed information about electrolytes and ionic DC conductivity in living tissue, see (S. Grimmes & Ø. G. Martinsen 2000).

2.1.2 The Plasma Membrane

The plasma membrane surrounds the cell completely. It is a thin and elastic structure with a width from 75 to 100 Å and consists primarily of proteins (≈55%) and lipids (≈43%).

Figure 2.2. The lipid bi-layer structure of the plasma membrane.

The Lipid Bi-layer Structure

The elemental structure of the plasma membrane is a double layer formed by only two lipid molecules. The lipid molecules forming the bi-layer have a hydrophilic side and a hydrophobic side; the hydrophobic sides attract each other. This attraction forces the hydrophilic head into the exterior of the structure and the hydrophobic into the interior. This structure is continuously replicated in every direction, creating the plasma membrane. See Figure 2.2.

The intrinsic electrical conductance of this structure is very poor and it is considered as a dielectric. The total structure formed by the intracellular fluid, plasma membrane and extracellular fluid (conductor-dielectric-conductor) behaves as a capacitor, with an approximate capacitance of 0.01 F/m^2 .

The Transmembrane Channels

Intermixed with the lipid bi-layer structure there are proteins of various types. One of them is the integral protein. This type of protein is inserted in the lipid bi-layer crossing through and creating very narrow channels for substances to pass through the plasma membrane, such as ions and water. From an electrical point of view these channels allow current to pass through the insulating membrane in a passive manner.

2.1.3 Tissue and Dielectricity

Any material with the ability to store capacitive energy can be classified as a dielectric, and living tissue has this ability due to its constituents at any level, molecular, subcellular, or cellular.

The compositions of the extracellular and intracellular fluids, especially the organelles, contribute to the overall behaviour of tissue as a dielectric, but the plasma membrane is the cellular structure with the major contribution to the dielectric behaviour of living tissue. The dielectric properties are also influenced by the specific tissue structure.

A number of different dielectric theories have been developed for biological tissue: General relaxation, Structural relaxation and Polar relaxation. But not one of them is able to fully explain all the experimental findings. An extensive review of the dielectric properties of tissues, including developed theories, can be found elsewhere (H. P. Schwan 1957, K. R. Foster & H. P. Schwan 1989).

Dielectricity Theory: Basic Concepts and Definitions

Usually dielectricity theory is explained with the help of the concept of the capacitor. In a capacitor the passive electrical properties of the dielectric material held between the two plane-parallel electrodes are completely characterized by the experimentally measured electrical capacitance C and conductance G . The conductance is defined in equation (2.1) and the capacitance in equation (2.2) when a constant voltage difference is applied between the electrodes:

Here A is the area of the plane electrodes and d is the electrode separation distance; see Figure 2.3.

Figure 2.3. (a) A capacitor: dielectric material between two metallic surfaces. (b) The equivalent circuit with a capacitance in parallel with a conductive element.

$$G = \frac{\sigma A}{d} \quad [\text{S}] \quad \text{Equation (2.1)}$$

$$C = \frac{\epsilon_0 \epsilon A}{d} \quad [\text{F}] \quad \text{Equation (2.2)}$$

σ denotes the electrical conductivity of the material; it represents the current density induced in response to an applied electric field, and it indicates the facility of the charge carriers to move through the material under the influence of the electric field. In the case of living tissue, the conductivity arises mainly from the mobility of the extracellular and intracellular ions.

ϵ_0 denotes the dielectric permittivity of free space, and its constant value is $8.854 \times 10^{-12} \text{ F/m}$, whilst ϵ denotes the permittivity of the material relative to ϵ_0 . The permittivity reflects the extent to which charge distributions within the material can be distorted or polarized in response to an applied electric field. In the case of biological tissue, charges are mainly associated with electrical double layers structures, i.e. plasma membrane, around solvated macromolecules and with polar molecules which, by definition, have a permanent electric dipole moment.

Admittance–Impedance and Conductivity–Resistivity

In the case where the voltage difference is sinusoidal, the electrical characteristics of the circuit in Figure 2.3.(b) vary with frequency and can be specified in several ways. At the natural frequency ω , the complex admittance Y^* can be expressed as follows:

$$Y^* = G + j\omega C = \frac{A}{d} \left(\sigma + j\omega C \epsilon_0 \epsilon \right) \text{ [S]} \quad \text{Equation (2.3)}$$

from which the complex conductivity σ^* , also called admittivity or specific admittance, is defined:

$$\sigma^* = \sigma + j\omega \epsilon \epsilon_0 \quad [\text{Sm}^{-1}] \quad \text{Equation (2.4)}$$

The unit of σ^* according to the International Systems of Units (SI) is Siemens per meter, Sm^{-1} .

Since the impedance is defined as the inverse of the complex admittance, it can be written as

$$Z^* = 1/Y^* = R + jX = \frac{G - j\omega C}{G^2 + (\omega C)^2} \text{ [}\Omega\text{]} \quad \text{Equation (2.5)}$$

from which the complex specific impedance z^* , also denominated impedivity, of the material is defined:

$$z^* = 1/\sigma^* = \frac{\sigma - j\omega \epsilon_0 \epsilon}{\sigma^2 + (\omega \epsilon_0 \epsilon)^2} = \rho^* \text{ [}\Omega\text{m]} \quad \text{Equation (2.6)}$$

Notice that the complex specific impedance z^* can also be denominated complex resistivity, and in such a case it is denoted by ρ^* . In either case, as expressed in equation (2.6) both are the inverse of the complex conductivity σ^* . Since a Siemens is the inverse of an Ohm, $\text{S}=1/\Omega$, the SI units of z^* and ρ^* are Ωm .

2.1.4 Frequency Dependency. The Dispersion Windows

Living tissue is considered as a dispersive medium: both permittivity and conductivity are functions of frequency; see Figure 2.4. This observed frequency dependence is denominated dispersion and it arises from several mechanisms (K. R. Foster & H. P. Schwan 1989). (H. P. Schwan 1957) identified and named three major dispersions: α -, β -, and γ -dispersions. Another subsidiary dispersion was noted at first in 1948 (B. Rajewsky & H. P. Schwan 1948) and later identified and termed δ -dispersion (H. P. Schwan 1994); see Figure 2.4.

α -dispersion

The understanding of the α -dispersion remains incomplete (H. P. Schwan 1994). A multitude of various mechanisms and elements contribute to this frequency dependence, three well-established ones being (H. P. Schwan & S. Takashima 1993):

Figure 2.4. Frequency dependence of the conductivity (a) and permittivity (b) in the brain grey matter.

- The frequency-dependent conductance of the channel proteins present in the cell membrane.
- The frequency dependence of the surface conductance and capacitance largely caused by the effect of the counter-ion atmosphere existing near charged cell surfaces.
- The effect of the endoplasmic reticulum, when it exists.

Table 2-II. Electrical Dispersions of Biological Matter[□].

Contributing Biomaterial Element		Dispersion			
		α	β	γ	δ
Water and Electrolytes				●	
Biological Macromolecules	Amino acids		●	●	●
	Proteins		●	●	●
	Nucleic acids	●	●	●	●
Vesicles	Surface Charged	●	●		
	Non-Surface Charged		●		
Cells with Membrane	+ Fluids free of protein		●		
	+ Tubular system	●	●		
	+ Surface charge	●	●		
	+ Membrane relaxation	●	●		
	+ Organelles		●	●	●
	+ Protein		●	●	●

[□] Table contents from (H. P. Schwan 1994)

β -dispersion

The β -dispersion is caused mostly by the cellular structures of tissue, due to the low conductivity of the plasma membrane of the cells forming the tissue. It takes time to charge the membranes through the conducting mediums, the extracellular and intracellular fluids. The introduced time constant is determined by the plasma membrane capacitance, cell radius and the fluid conductivities (H. P. Schwan 1957).

Contributing to the β -dispersion caused by the cell structure, there are other tissue constituents (K. R. Foster & H. P. Schwan 1989): proteins, amino acid residues and organelles. For a more detailed description of the contributions of the different tissue constituents to the different dispersions, the author suggests reading the article review by Pethig (R. Pethig & B. D. Kell 1987).

γ -dispersion

This frequency dependence is caused by the high content of water in cell and tissue. Tissue water is identical to normal water, which relaxes at 20 GHz, except for the presence of proteins and amino acids, etc. Tissue water displays a broad spectrum of dispersion from hundreds of MHz to some GHz.

δ -dispersion

This is a weak subsidiary dispersion effect observed around 100 MHz caused by proteins bonded to water.

2.2 Cell Electrical Conductance

The electrical characteristics of biological tissues are, to simplify, a composite of the characteristics of the constitutive cells. It is useful to depict equivalent electric circuit models of the cells and tissue, because they help us to understand the conductance phenomenon and to attribute a physical meaning to the impedance parameters in biological material.

2.2.1 Electrical circuit of the cell

Considering the main constituents of the cell, introduced in the previous chapter, applying theory of electric circuits and simplifying makes it possible to deduce a basic electrical model for the cell; see Figure 2.5.

Figure 2.5. Equivalent electrical circuit of a cell. The circuit in (b) is the equivalent of the model in (a) after performing some circuit simplifications and considering the large value of R_m . The circuit in (c) is the equivalent circuit of the cell, neglecting the effect of R_m . Note that C_m^* is equal to $C_m/2$.

If current is injected into the extracellular medium, it can:

- Flow around the cell through the extracellular fluid; this is equivalent to circulating through R_e in the equivalent circuit.
- Flow through the cell across the plasma membrane; C_m represents this possibility in the equivalent circuit.
- Or flow across the transmembrane ionic channel; this is equivalent to circulating through R_m in the equivalent circuit.

Once the current is in the cell, it flows through the intracellular medium, circulating through R_i , and leaves the cell flowing across the plasma membrane through the parallel bridge $R_m || C_m$, the same way it flowed into the cell.

Considering the extremely low conductivity of the plasma membrane, the value of R_m is very high. At low frequencies, near DC, the plasma membrane acts as an insulator and the current is not able to penetrate the cell, and most of the current flows around the cell. The insulating effect of the cell membrane decreases with increasing frequency, and a portion of the current is able to flow through the cell. At frequencies above 1 MHz the membrane capacitance is not an impediment to the current and it flows indiscriminately through the intra and extracellular medium.

Usually, as the membrane conductance is very low, the effect of R_m is neglected and the equivalent electric circuit is very simple. In this case only a single dispersion exists, the frequency dependence introduced by the capacitor C_m ; see Figure 2.5.c. The use of this simplified model is widespread and it is appropriately used to explain the impedance measurements in a broad range from DC to a few tens of MHz.

Figure 2.6. Current paths in a suspension of cells at various frequencies.

2.3 Tissue Electrical Conductivity, Resistivity & Impedance

Biological tissue is built up by cells; therefore, from an electrical point of view, it can be considered as an aggregation of conductive cells, suspended in a conductive fluid. This conceptual consideration leads us to the model for a suspension of cells.

2.3.1 Suspension of Spherical Cells

The consideration of biological tissue as a suspension of spherical cells is an old established practice in biophysics studies. At first, this model was believed to be valid only when the volume fraction of concentration of cells was considered to be small (J. C. Maxwell 1891), usually $< 30\%$, but experimental measurements suggest that the model is valid for high concentration as well, near 80% (K. S. Cole *et al.* 1969, M. Pavlin *et al.* 2002).

Electrical Resistivity of a Spherical Cell

Consider a cell as a sphere of radius a_2 containing a conductive medium of resistivity r_2 surrounding a spherical and centered core of radius a_1 and resistivity r_1 . The set of the two concentric spheres can be replaced by a single sphere of radius a_2 and uniform resistivity, r , as given in equation (3) from article 313 of Maxwell's treatise (J. C. Maxwell 1891).

Figure 2.7. The conductance of a stratified sphere of radius a_2 containing a conductive medium of resistivity r_2 and a centered solid sphere of radius a_1 and resistivity r_1 is equivalent to a single sphere of radius a_2 containing a conductive medium of resistivity r , given by equation (2.7).

$$r = \frac{(2r_1 + r_2) a_2^3 + (r_1 - r_2) a_1^3}{(2r_1 + r_2) a_2^3 - 2(r_1 - r_2) a_1^3} r_2 \quad [\Omega\text{m}] \quad \text{Equation (2.7)}$$

In the case of cells, the plasma membrane is very thin ($a_2 \cong a_1 = a$ and $a_2 - a_1 = \delta$), and the resistivity of the membrane is very high compared with the resistivity of the intracellular fluid, $r_2 \gg r_1$. The equivalent resistivity r can be simplified (K. S. Cole 1928)

First simplification, using $a_2 \cong a_1 = a$, $a_2 - a_1 = \delta$ and $a \gg \delta$:

$$r = \frac{r_1 + \frac{\delta r_2}{a} \left(1 - \frac{r_1}{r_2} \right)}{1 - \frac{2\delta}{a} \left(1 - \frac{r_1}{r_2} \right)} r_2 \quad [\Omega\text{m}] \quad \text{Equation (2.8)}$$

Second simplification, $r_2 \gg r_1 \rightarrow 1 \gg \frac{r_1}{r_2}$:

$$r = r_1 + \frac{\delta r_2}{a} \quad [\Omega\text{m}] \quad \text{Equation (2.9)}$$

Considering that the plasma membrane introduces a capacitive effect, δr_2 is substituted by z_m^* denoting the impedivity of the membrane for a unit area in Ωm^2 , including the reactive component (J. C. Maxwell 1891).

$$r = r_i + \frac{z_m^*}{a} \quad [\Omega m] \quad \text{Equation (2.10)}$$

(K. S. Cole 1928, 1932) assumed a constant phase angle φ_m for z_m^* , in such a way that $\tan(\varphi_m) = x_m / r_m$. This means that with $z_m^* = r_m + jx_m$ then r_m complies with $r_m = x_m \cot(\varphi_m)$, where $\cot(\varphi_m)$ is constant. This assumption fits the empirical data, but it has lacked a theoretical demonstration for almost 80 years, and continues without one.

$$\tan(\varphi_m) = \frac{x_m}{r_m} \rightarrow z_m^* = r_m + jx_m \Leftrightarrow z_m^* = |z_m| \angle \varphi_m \quad \text{Equation (2.11)}$$

2.3.2 Electrical Resistivity of a Suspension of Spherical Cells

The electrical equivalent resistivity of a sphere containing a uniform suspension of spheres of radius a , and resistivity r_i , in a medium with a resistivity r_e and radius a_2 , as depicted in Figure 2.8, was calculated by Maxwell in his article 314 (J. C. Maxwell 1891).

$$r = r_e \frac{(1-f) r_e + (2+f) r_i}{(1+2f) r_e + 2(1-f) r_i} \quad [\Omega m] \quad \text{Equation (2.12)}$$

Figure 2.8. The conductance of a sphere of radius a_2 containing a conductive fluid of resistivity r_e in which there are uniformly disseminated solid spheres of radius a and resistivity r_i is equivalent to a single sphere of radius a_2 containing a conductive medium of resistivity r , given by equation (2.12).

In equation (2.12) r is the equivalent resistivity of the suspension, r_e is the resistivity of medium surrounding the spheres, r_i is the resistivity of the contained spheres and f is the volume factor of concentration of cells. The units of the resistivities r , r_e and r_i are in Ωm and the volume factor f is dimensionless. Equation (12) is re-arranged as done by Cole (K. S. Cole 1928).

Considering each of the suspended cells in Figure 2.9 as its equivalent single spherical cell, r_i in equation (2.12) is replaced by r from equation (2.10). In this way the obtained suspension is equivalent to the original suspension in Figure 2.8. The equivalent complex impedance z^* of the suspension containing concentric spherical cells is given by equation (2.13)

(J. C. Maxwell 1891). Notice that the notation changes in equation (2.13) from r_i in equation (10) to r_i , and from r in equation (2.10) to z^* .

Figure 2.9. A sphere containing conductive spherical cells of radius a disseminated in a conductive fluid.

$$z^* = r_e \frac{(1-f)r_e + (2+f) \left(r_i + \frac{z_m^*}{a} \right)}{(1+2f)r_e + 2(1-f) \left(r_i + \frac{z_m^*}{a} \right)} \quad [\Omega m] \quad \text{Equation (2.13)}$$

Usually the resistivity effect of the plasma membrane is neglected and the membrane is considered as an ideal capacitor. Thus the specific impedance of the membrane is only imaginary, $z_m^* = jx_m$ with reactive part

$$x_m = -\frac{1}{\omega c_m} \quad [\Omega m] \quad \text{Equation (2.14)}$$

The impedivity is an intrinsic parameter of a material independent of the shape. Therefore the impedivity given by equation (2.13) is the impedivity of any compound medium consisting of a substance of resistivity r_e in which there are disseminated spheres of radius a and resistivity r_i with a shell of impedivity z_m^* .

2.3.3 Tissue Impedance

The electrical impedance of a material is given by its impedivity or specific impedance, $z^*(\omega)$, times a shape factor, k , as indicated in equation (2.15). Such a shape factor depends on the length of the volume conductor, L , and the available surface, S , for the electric current to flow through towards the electric field gradient. This surface is normal to the direction of the gradient. See Figure 2.10.

Figure 2.10. Volume conductor with impedivity z^* , length L and cross-sectional area S . Notice that S changes along the X -axis.

Figure 2.11. Cylindrical conductor with resistivity ρ , length L and cross-sectional area S , normal to the electric field $\vec{E}$.

$$\mathbf{Z}(\omega) = \mathbf{z}^*(\omega) k = \mathbf{z}^*(\omega) \int_0^L \frac{dx}{S(x)} \quad [\Omega] \quad \text{Equation (2.15)}$$

In the simple case of a pure resistive medium with resistivity constant along the frequency with the shape of a cylindrical conductor (see Figure 2.11), the total resistance $\mathbf{R}$ of the conductor along the X-axis is given by

$$\mathbf{R} = \rho \frac{L}{S} \quad [\Omega] \quad \text{Equation (2.16)}$$

where L is the length of the cylinder, S is the cross-sectional area of the conductor and ρ is the resistivity of the material. **N.B.** the cross-sectional area normal to the electrical field is constant along X.

CHAPTER 3

BRAIN DAMAGE & ELECTRICAL BIOIMPEDANCE

3.1 Introduction to Cellular Damage

The cell is usually confined to a narrow range of functions[⊗]. This function specificity of the cell is due partly to its genetic program and partly to the surrounding environment, the availability of energy sources and the capacity of its metabolic pathways. The state of the cell when it is able to handle normal physiological demands is denominated homeostatic steady state.

In the presence of a pathological stimulus or excessive physiologic stress, the cell has the capacity to adapt itself, achieving a new but altered steady state to preserve the viability of the cell. This process is denominated cellular adaptation, and when the limits of the adaptability of the cell are overcome, cell injury occurs. Depending on the severity and the duration of the stimuli, cell injury is reversible up to a certain point – after which irreversible cell injury occurs, leading to cell death. The capacity of the cellular adaptation varies among different type of tissues, and brain tissue exhibits a very high sensitivity to hypoxic insults (A. C. Guyton & J. E. Hall 2001, T. Acker & H. Acker 2004, V. Kumar 2005).

⊗ The information presented in this chapter is mainly extracted from (V. Kumar 2005).

3.2 Hypoxic/Ischaemic Cellular Damage

Among the most important and common causes of cell injury is hypoxia; it strikes at one of the most vulnerable intracellular systems, namely the aerobic oxidative respiration mechanism of the cell, involving oxidative phosphorylation and production of ATP. Among the causes of hypoxia the most common is ischaemia, i.e. loss of blood supply. Other common causes of hypoxia are inadequate oxygenation of the blood after a cardiorespiratory failure or loss of the oxygen-carrying capacity of the blood as in anemia.

Figure 3.1. Response of the cell in presence of a pathological insult. Relationship among normal, adapted, reversible cell injury and cell death.

3.2.1 Ischaemic/Hypoxic injury mechanism

In the cell, the structural and biochemical elements are strongly linked and a strike against one system leads to a widespread and quick chain of events affecting other systems in the cell. The duration and severity of the pathological stimulus are important factors for the severity of cell injury, but the type of cell and its current state and adaptability also strongly influence the final outcome; e.g. a similar hypoxic insult injures brain tissue more severely than muscle tissue.

Hypoxia is simply a reduction in the availability of oxygen, while ischaemia is a reduction in the blood flow. In ischaemia, additionally to the lack of oxygen, there is a reduction in the delivery of metabolic nutrients and an excessive accumulation of catabolites, otherwise removed by the blood flow. Therefore, ischaemia usually leads to injury of tissues faster than hypoxia.

Cellular Adaptation

In a hypoxic/ischaemic situation, the cell adapts itself to the lack of available oxygen. The cell stops the generation of ATP with the use of oxygen and changes from aerobic to anaerobic metabolism, producing ATP from glycogen and creatine phosphate instead. Anaerobic metabolism results in the accumulation of osmotic active products like lactic acid and inorganic phosphates, causing a reduction in the intracellular pH value and influencing the intracellular osmotic pressure.

The availability of ATP is severely reduced and the energy-dependent Na^+/K^+ pump in the plasma membrane reduces its transport activity or loses it completely. The cell is then no longer able to keep the ionic gradients across the membrane. The failure of this active transport results in alteration of the intracellular ionic contents, (A. J. Hansen 1984, H. H. De Haan & T. H. M. Hasaart 1995, R. Berger & Y. Garnier 1999, C.-S. Yi *et al.* 2003, V. Kumar 2005). Na^+ increases and K^+ decreases, resulting in a membrane depolarization (A. J. Hansen 1985). In the absence of a membrane potential, Cl^- ions (R. Berger & Y. Garnier 1999) and large amounts of Ca^{2+} (A. J. Hansen 1984, H. H. De Haan & T. H. M. Hasaart 1995) flow through the voltage-dependent ion channel into the cell.

Figure 3.2. Biochemical and physiological processes during hypoxia in the cell.

The combined effect of the process above mentioned, the failure of the active transport, the opening of the voltage-dependent channels and the anaerobic metabolism, produces an abnormally high intracellular concentration of catabolites and ions. The net gain of solute induces an influx of water following the osmotic gradient, aiming to establish an isosmotic pressure on both sides of the plasma membrane. Consequently, the cell swells, causing cellular oedema (H. H. De Haan & T. H. M.

Hasaart 1995, K. H. Kimelberg 1995), one of the earliest and most common histological manifestations of hypoxic injury (V. Kumar 2005), also denominated cellular oedema or acute cell swelling.

At the same time as the water influx, the endoplasmic reticulum suffers an early dilation followed by a detachment of the ribosomes from the granular endoplasmic reticulum. If hypoxia persists, other alterations take place like blebs formation on the surface of the cell and mitochondrial swelling.

Reversible and Irreversible Cell Injury

All the previously mentioned cellular alterations are reversible if normoxia is re-established; the cell is in a state of reversible cell injury. If the insult continues, the cell reaches “the point of no return” and irreversible cell injury ensues. There is no generally accepted explanation for the key biochemical mechanisms behind transition from reversible to irreversible cell injury. However, in certain ischaemic tissues, certain structural and functional changes indicate that the cells have been irreversibly injured (V. Kumar 2005).

Figure 3.3. Structural changes in the cell during hypoxia/ischaemia.

Types of Cell Death: Necrosis and Apoptosis

There are two identified types of cell death: necrosis and apoptosis. Necrosis is always a pathological process, while apoptosis need not be associated with cell injury. Cell death in the hypoxic/ischaemic injury mechanism occurs mainly by necrosis during the acute phase, but mainly by apoptosis during the phase of reperfusion/reoxygenation. In brief, the above-mentioned changes in intracellular pH value and ionic concentration damage the membranes of the lysosomes. Hydrolytic enzymes are released into the cytoplasm and trigger a chain of events, resulting in necrosis. The cell is eventually dissolved in the extracellular fluid (H. H. De Haan & T. H. M. Hasaart 1995, R. Berger & Y. Garnier 1999). For a more detailed description of the cell death mechanisms see (V. Kumar 2005).

3.2.2 Ischaemia-Reperfusion Injury Mechanism

There is one injury mechanism closely related to the hypoxic/ischaemic injury mechanism, the ischaemia-reperfusion mechanism. When the normal oxygen level and blood flow are restored, the cells will recover from the injury, provided that the cells were reversibly injured. If the cells were irreversibly injured, new injurious processes start during reperfusion, resulting in cell death through necrosis, as well as apoptosis, of cells that otherwise could have recovered. This mechanism is of special interest to us for two main reasons:

- It occurs in most of the hypoxic/ischaemic injury cases.
- It can be medically treated, thereby reducing its damaging effects.

3.3 Hypoxia in the brain

As has been mentioned before, different types of cells and tissues react in a different way to hypoxia; brain tissue is especially vulnerable to lack of oxygen (H. M. Bramlett & W. D. Dietrich 2004). For normal functioning, the brain needs oxygen but it particularly needs sufficient glucose (R. Berger & Y. Garnier 1999). The transmission of electric impulses and biosynthetic reaction within the neurons continuously require an intracellular source of energy. This energy is usually produced by the breakdown of glucose during the aerobic glycolysis. When the cell resorts to anaerobic glycolysis during hypoxia, the availability of intracellular glucose is drastically reduced. Thus neurons are much more susceptible to hypoxia than most types of cells (T. Acker & H. Acker 2004, V. Kumar 2005), suffering ischaemic necrosis after a few minutes from the hypoxic insult.

When hypoxia/ischaemia strikes the brain a further mechanism of injury comes into play, the release of an excess of excitatory amino acids, in particular glutamate. Glutamate is an important and abundant excitatory transmitter substance that acts by promoting calcium ion influx into nerve cells, especially in basal ganglia of the brain. When hypoxia/ischaemia prevails, glutamate accumulates in the interstitial fluid and creates an overexcitation of the neurons leading to cell death (Johnston, 2001).

3.3.1 Hypoxia and Perinatal Asphyxia

It has been observed that the perinatal brain exhibits a higher robustness against hypoxic/ischaemic insults than the adult brain. There are several reasons for this special robustness. To begin with, the amount of synapses in the perinatal brain is much smaller than in the adult brain; consequently the oxygen demand is much lower. Also, due to the particular risk associated with birth, the perinatal brain has a special protection mechanism against hypoxia/ischaemia. Before the oxygen supply has been reduced too much, the blood flow is redistributed to maintain enough oxygen available to maintain the aerobic cerebral

metabolism. The augmentation of cerebral blood flow is done at the expense of the perfusion to other organs and systems like muscles, skin, and kidneys. If blood flow redistribution does not satisfy the oxygen requirements, the brain cells resort to anaerobic metabolism and the chain of events will develop as explained above (H. H. De Haan & T. H. M. Hasaart 1995).

It has also been observed that the developing brain exhibits a relatively higher sensitivity towards the injurious effects of free radicals derived from oxygen and nitrous oxide during reperfusion/reoxygenation than the adult brain (Blomgren & Hagberg 2006).

3.3.2 Brain Stroke and Hypoxia

Ischaemic stroke is caused by arterial embolism or thrombosis; in both cases the arterial blood flow to the brain or a region of the brain is reduced or completely interrupted. Since oxygen is transported by the blood stream, a reduction of the cerebral blood flow directly compromises the oxygen supply, ultimately causing hypoxia.

3.4 Brain Damage and Impedance

As we have seen in previous sections, the electrical properties of biological tissue depend on the biochemical composition and its structure. During hypoxia/ischaemia, the cells and the tissue they build up adapt and suffer modification in their composition, size and shape.

3.4.1 Hypoxic Damage

During the cellular adaptation and the reversible injury phase, the ionic redistribution in the cellular environment, the accumulation of catabolites in the intracellular space, the cell swelling and the consequent shrinking of the extracellular space modify the conductivity of the intracellular and extracellular fluids, affecting the total impedance of the tissue. During the irreversible injury and cell death phase, the destruction of the membranes of the organelles and ultimately the plasma membrane changes completely the electrical properties of the tissue.

From the suspension of cells model in Figure 2.9, there are three main effects on the tissue impedance expected as a consequence of cell swelling:

- The shrinking of the extracellular space will reduce the surface available for the charges to flow through, increasing the value of the tissue impedance, according to equation (2.15). This effect is more remarkable for decreasing frequency. Note that at DC the natural frequency ω is 0, leaving the impedivity depending only on the resistivity of the extracellular fluid. Equation (3.1) contains the resulting expression for the impedance of a suspension of cells at DC:

$$z^* = r_e \frac{(1-f)}{(1+2f)} \quad [\Omega m] \quad \text{Equation (3.1)}$$

N.B. Equation (3.1) is the resulting expression of equation (2.13) for $\omega = 0$.

- Since the capacitance of the cell membrane depends on the cell radius, equation (10), an increment in the cell radius will change the capacitance effect of the cell and consequently the reactance of the tissue. Since at DC and high frequencies the reactance of tissue is very small, this change will be more noticeable at medium frequencies. Note that the reactive part of equation (2.13) is zero for both DC, equation (3.1), and for very high frequency, $\omega = \infty$. Equation (3.2) contains the resulting expression:

$$z^* = r_e \frac{(1-f) r_e + (2+f) r_i}{(1+2f) r_e + 2(1-f) r_i} \quad [\Omega m] \quad \text{Equation (3.2)}$$

- As we can deduce from equation (3.2), at high frequency the impedance of tissue does not depend on the capacitance properties of the membrane, but depends only on the resistivity of the intra- and extracellular spaces. Since cell swelling implies a volume shift from the extracellular space to the intracellular in favor of the latter, and the cytoplasm is usually more conductive than the extracellular fluid, cell swelling will cause the resistance at high frequencies to decrease.

These three effects have been confirmed in (F. Seoane *et al.* 2004a, F. Seoane *et al.* 2004b, F. Seoane *et al.* 2005).

3.4.2 Ischaemic Damage

During ischaemia, on top of the effect on the impedance associated with the accompanying hypoxic cell swelling, there is also the effect of the reduction or even complete lack of blood in the ischaemic region. Since the conductivity of the blood is larger than the conductivity of many of the intracranial brain tissues, see Table 3-III, the ischaemic effect will contribute to increasing the resistance of the ischaemic brain tissue.

3.4.3 Haemorrhagic Damage

Brain haemorrhage may occur as a consequence of severe ischaemia and hypoxia as well as trauma or a number of other causes. In this case, blood from the cerebrovascular system leaves the brain arteries and veins to invade the intercellular space, causing a haematoma. Since blood exhibits a dielectric conductivity much larger than white and grey matter tissues, the resistance of the haematoma region decreases. Note that the same damage to the cerebrovascular system which causes an intracranial haemorrhage may impair the blood supply to other regions of the brain, causing ischaemia and the corresponding changes in impedance in the ischaemic region.

TABLE 3-III. Dielectric Conductivity of Intracranial and Scalp Tissues

Tissue	Conductivity σ [S/m]		
	50 Hz	50 kHz	500 kHz
Blood	0.70	0.70	0.75
Blood Vessel	0.26	0.32	0.32
Body Fluid	1.5	1.5	1.5
Bone Cancellous	0.08	0.08	0.087
Bone Cortical	0.02	0.021	0.022
Bone Marrow	0.0016	0.0031	0.0038
Cartilage	0.17	0.18	0.21
Cerebellum	0.095	0.15	0.17
Cerebro-Spinal Fluid	2	2	2
Fat	0.02	0.024	0.025
Glands	0.52	0.53	0.56
Gray Matter	0.075	0.13	0.15
Ligaments	0.27	0.39	0.39
Lymph	0.52	0.53	0.56
Muscle	0.23	0.35	0.45
Nerve Spine	0.027	0.069	0.11
Skin Dermis (Dry)	0.0002	0.00027	0.044
White Matter	0.053	0.078	0.095

CHAPTER 4

TRANSCEPHALIC MEASUREMENTS OF ELECTRICAL BIOIMPEDANCE

4.1 Introduction

A transcephalic measurement of electrical bioimpedance (EBI) is a measurement of the electrical impedance of the whole head as the volume conductor. The impedance is measured from the surface of the head, i.e. a non-invasive measurement.

Impedance does not produce measurable energy by itself and a change in impedance is not a signal. Hence, to measure the impedance of an object, electrical energy is fed to the object and the impedance is estimated by using Ohm's law (4.1), directly or indirectly:

$$Z = \frac{V}{I} \quad [\Omega] \quad \text{Equation (4.1)}$$

The basic principle behind EBI measurements is to feed the biological tissue with a known voltage or current and measure the resulting complementary magnitude, current or voltage respectively. Since the input voltage or current is known and the output current or voltage is measured, Ohm's law can be used to estimate the impedance of the object.

Since the EBI measurements are performed in biological tissue – animal or human and often alive – for safety reasons the applied energy must fulfil several requirements. For instance, current as well as current density through the tissue must be limited below a threshold to avoid tissue damage or patient discomfort, and accumulation of charges within the tissue must be avoided; i.e. one should never stimulate with D.C. voltage or current.

4.2 Impedance Instrumentation

Usually an EBI measurement is performed by measuring the voltage drop caused by a known current that is injected into the tissue. But an EBI measurement can also be obtained by measuring the current generated by a known voltage applied on the tissue. The second approach is more appropriate to measure bioadmittance, which is the mathematical inverse of the bioimpedance. Note that all of these methods are classified as deflection methods, and electrical impedance can also be measured by null methods (R. Pallàs-Areny & J. G. Webster 2001), e.g. zero crossing

Figure 4.1. Two different instrumentation setups for an electrical bioimpedance measurement based on the V/I approach. (a) A two-electrode setup and (b) a four-electrode setup.

bridges.

The electronic instrumentation for impedance measurements is basically configured by a current source which generates the known current to be injected into the tissue and a differential amplifier to measure the corresponding voltage drop; see Figure 4.1. In the case of EBI a very important element of the measurement setup is the electrodes, which are the interface between the electronic circuit and the tissue.

The electrodes have their own polarization impedance, Z_{ep} , and it may be added to the measured impedance, Z_m , depending on the selected measurement approach. Note in Figure 4.1 how by using the four-electrode Technique (4-ET) the effect of the electrodes is avoided and Z_m is equal to Z_{TUS} , the impedance of the tissue under study.

4.2.1 The Four-Electrode Technique

In principle at least, the 4-ET eliminates the contribution of the electrode polarization impedance to the voltage measurement on the input

of the differential amplifier (H. P. Schwan 1963, J. J. Ackmann *et al.* 1984). This is one of the reasons why the 4-ET is among the most common techniques to perform EBI measurements (J. J. Ackmann 1993).

From Figure 4.1 it is apparent that the current source and the differential amplifier are the most important electronic devices for this type of deflection measurement.

The Current Source

A large enough output impedance Z_{out} of the current source ensures that the current flowing through the injecting leads is the same current as the one being generated by the current source. Ideally, the Z_{out} is infinite and the injecting current would then always be the same as the generated current, independently of the value of the load.

Since in practice Z_{out} is not infinite and its value varies with frequency, usually decreasing with increasing frequency, the value of Z_{out} is a very important parameter of the current source. It may define the frequency range of operation of the current source, and even limit the range of application of the measurement system. Therefore, in an impedance measurement system the output impedance of the current source must be kept large enough over the whole frequency range of operation.

Voltage Measurements

The whole principle of neglecting the effect of the electrode polarization impedance from the voltage measurement by using the 4-ET (see Figure 4.1) is based on the fact that, due to the large input impedance Z_{in} of the differential amplifier, ideally infinite in operational amplifiers and instrumentation amplifiers, the current through the measurement electrode is zero, causing a null voltage drop i.e. the voltage sensed by the measurement amplifier corresponds to the voltage drop on the tissue.

As electronic amplifiers are not ideal and have finite input impedances and capacitances, and also have parasitic capacitances associated with the input and ground, the current through the measurement electrodes may suddenly be different than zero. Such a non-ideal effect is also frequency-dependent; therefore the amplifiers used for the voltage pick-up must have an input impedance as large as possible over the measurement frequency range. Sometimes the use of buffer amplifiers with high input impedances, usually with J-FET input, are used to ensure the null flow of current through the measuring leads (J. J. Ackmann 1993).

The Two-Reading Method

Even if we could consider the current source and the voltage sensing amplifier as ideal, it happens that, due to electromagnetic coupling between conductors, parasitic capacitances arise in a EBI measurement setup – e.g. between the leads and ground, the injecting electrodes and the sensing

electrodes, the patient and ground, as well as the measurement leads and ground, etc. See Figure 4.2.

Figure 4.2. Four-electrode measurement setup including non-ideal parameters of the current source and parasitic capacitances associated with the different elements of the system.

As can be seen in Figure 4.2, there are several paths for the current to flow through and avoid flowing through the Tissue Under Study (TUS). Therefore, in EBI measurements, assuming that the current through the tissue is the same as the current generated by the current source is not a reliable practice, especially at high frequencies when the effect of the parasitic capacitances is most influential.

To increase the reliability of the impedance measurement, the value through the tissue cannot be just assumed, but should be measured; in this way the impedance can be obtained with the actual current value. Usually this is done by measuring the voltage drop in a resistor connected in series with the TUS, as in Figure 4.3. This type of impedance measurement is called the two-reading method (R. Pallàs-Areny & J. G. Webster 2001). Notice that in this measurement setup, as well as in the case of the use of buffer amplifiers, both measurement amplifiers must have an identical frequency response.

Figure 4.3. Schematic diagram of an impedance measurement setup using the Four-Electrode Technique and implementing the two-reading method.

The measured impedance, Z_m , is obtained by multiplying the value of the reference resistor with the quotient of the two voltage readings as follows in (4.2)

$$Z_m = R_{ref} \frac{V_{TUS}}{V_{REF}} = Z_{TUS} \quad [\Omega] \quad \text{Equation (4.2)}$$

Note that R_{ref} can be used not only as a reference resistor to calculate the current injected into the tissue, but also as a safety resistor to limit the current flowing through the tissue.

4.3 Impedance Sensitivity Maps

In an impedance measurement the impedance is obtained through the relationship of measured voltage and injected current according to Ohm's law. In a volume conductor, the number of pairs of points to inject a current is infinite, and the same applies for the number of pairs of points to measure a potential difference caused by the injected current. Since in most cases the voltage difference between two points in a volume conductor obviously depends on the selected points, measurements of impedance in a volume conductor depend on the arrangement of the injecting and sensing electrodes.

The relationship between the pair of electrodes depends on the electrode placement and electrical properties of the volume conductor. This relationship is crucial for continuous electrical impedance monitoring, since such a relationship is needed for the appropriate interpretation of a voltage change and the consequent impedance change.

4.3.1 The Lead Vector

Considering a linear, finite and homogeneous conductor, the potential at a point M, Φ_M , in the surface caused by a unit dipole $\vec{i}$ fixed at the point Q and oriented in the x direction is given by

$$\Phi_M = L_{Mx} |\vec{i}| = L_{Mx} \quad [V] \quad \text{Equation (4.3)}$$

Since the volume conductor is linear, the potential at M caused by a dipole $p_x \vec{i}$ will be p times L_M :

$$\Phi_M = L_{Mx} p_x |\vec{i}| = L_{Mx} p_x \quad [V] \quad \text{Equation (4.4)}$$

This expression holds for dipoles in the y and z directions as well. Since any dipole $\vec{p}$ can be decomposed into three orthogonal components $p_x \vec{i}, p_y \vec{j}, p_z \vec{k}$ and the linearity assumption ensures superposition, the potential created by each of the components can be superposed, and thus the potential at any point M can be expressed as the dot product between the source dipole $\vec{p}$ and the vector $\vec{L}_M$:

$$L_{Mx} p_x + L_{My} p_y + L_{Mz} p_z = \vec{L}_M \bullet \vec{p} = |\vec{L}_M| |\vec{p}| \cos(\widehat{\vec{L}_M \vec{p}}) = \Phi_M \quad [V] \quad \text{Equation (4.5)}$$

The expression in equation 4.5 is valid even for inhomogeneous volume conductors of infinite extent (J. Malmivuo & R. Plonsey 1995).

Figure 4.4. The formation of the lead vector in a linear, finite and homogeneous volume conductor. The figures have been modified from (J. Malmivuo & R. Plonsey 1995), online version Chapter 11, Figure 11.5.

The lead vector $\vec{L}_M$ is a set of transfer coefficients that, multiplied by the dipole source, yields the potential at the point M. The lead vector describes how a dipole source at a certain fixed point O in a volume conductor influences the potential at a point within or on the surface of the volume conductor relative to the potential at a reference location, often considered as zero. The value of the lead vector depends on:

- The location O of the dipole $\vec{p}$.
- The location of the field point M.
- The shape of the volume conductor.
- The distribution of the conductivity of the volume conductor.

The lead vector transfers the electric energy created by a dipole source to the volume conductor. In the case of a voltage dipole with units of Volts times metres, Vm, the units of the orthogonal components of the lead vector will be purely geometrical m^{-1} . But when the source is a current dipole with units of Amperes times metres, Am, then the lead vector has geometrical and electrical units: Ohms per meter, Ωm^{-1} .

Since the potential at the points M and Q due to a dipole $\vec{p}$ can be stated as $\vec{L}_M \bullet \vec{p}$ and $\vec{L}_Q \bullet \vec{p}$, respectively, the difference of potential between M and Q can be calculated as follows:

$$\Phi_M - \Phi_Q = \Delta\Phi_{MQ} = V_{MQ} \quad [\text{V}] \quad \text{Equation (4.6)}$$

Substituting in equation (4.6) the expressions for Φ_M and Φ_Q and developing the expression with vector algebra, we obtain

$$\begin{aligned} V_{MQ} = \Phi_M - \Phi_Q &= \vec{L}_M \bullet \vec{p} - \vec{L}_Q \bullet \vec{p} \Rightarrow \\ &= (\vec{L}_M - \vec{L}_Q) \bullet \vec{p} = \vec{L}_{MQ} \bullet \vec{p} \end{aligned} \quad [\text{V}] \quad \text{Equation (4.7)}$$

Transfer Impedance and Lead Vector

If we consider the dipole $\vec{p}$ as a current dipole $\vec{I}_{\phi AB}$ caused by the current I_ϕ through port AB, according to Figure 4.5(A), then applying equation (4.7), the potential difference between the points C and D is established by

$$\Phi_{CD} = \vec{L}_{CD} \bullet \vec{I}_{\phi AB} \quad [\text{V}] \quad \text{Equation (4.8)}$$

I Therefore, applying the definition of lead vector to a volume conductor defining a two-port system as depicted in Figure 4.5(A), we find that that the lead vector for a current source, as obtained in (4.8), is the transfer impedance vector, exactly as defined by Schmitt in 1957 and 1959:

Notice that the ratio is that of a voltage to a current. This makes the name "impedance" appropriate for, according to the general form of Ohm's law, impedance $Z = E/I$ and, because voltage difference is produced at points other than those at which current is introduced, transfer rather than simple impedance is implied.

...It now becomes apparent why we must use current dipole moment, which is the product of current with the distance between entrance and exit points of current, rather than current itself in computing transfer impedance,...

...Consider a tiny current-dipole source of moment M at some position within the body causing a potential to be picked up at external electrodes P...

...Normally this product is called a scalar product because the result is always a scalar quantity (voltage) that results from this kind of multiplication of two vectors (current and transfer impedance). Because the operation is sometimes symbolized by a dot, for example, $P = \mathbf{M} \bullet \mathbf{Z}$, it is also called a dot product...

Otto H. Schmitt (O. H. Schmitt 1957)

Thus, the dipole can be thought of as projecting itself, to a constant scale, on an effective axis not necessarily going through the recording points. In the diagram (Fig. 4.5(b)), lead-off points c and d may be thought of as effectively represented by a vector on an axis $c'd'$ at the source. The magnitude of potential realized at the lead-off electrodes will be proportional to the magnitude of the current source times its distance of separation (i.e., its current dipole moment) multiplied by the cosine of the spatial angle between it and a reference line $c'd'$.

It is seen at once that this has become a vector dot product system and that the $c'd'$ reference has become a reference vector characteristic of a particular lead system. One, therefore, vectorializes $\mathbf{Z}$ in the alternating current version of the Ohm's law relationship $\mathbf{E} = \mathbf{I}\mathbf{Z}$. $\mathbf{I}$ becomes a dipole current moment (amperes times separation in centimeters). $\mathbf{Z}$ becomes a transfer impedance which is dimensionally ohms per centimeter in magnitude, but assumes the spatial attributes of a vector. Voltage, of course, remains a scalar quantity which is consistent with its representation as the scalar product of the transfer impedance with the current dipole moment. $V = \mathbf{I}_m \cdot \mathbf{Z}_t$.

Otto H. Schmitt (O. H. Schmitt 1959)

N.B. Expressions $P = \mathbf{M} \cdot \mathbf{Z}_y$, $V = \mathbf{I}_m \cdot \mathbf{Z}_t$ and equation (4.8) are the same.

Note that the expression for the scalar voltage from the lead vector in equation (4.8) is equivalent to Ohm's law in three dimensions for the transfer impedance. This is a natural consequence of the vectorial representation of Ohm's law, which holds for a uniform and anisotropic volume conductor (M. Mason & W. Warren 1932).

4.3.2 Mutual Impedance & Transfer Impedance

A voltage lead is a particular terminal pair in which a voltage drop is developed. In Figure 4.5(B), the voltage lead C-D measures the voltage drop Φ_{CD} caused by the current I_ϕ through port AB, and the voltage lead A-B measures the voltage drop Ψ_{AB} caused by the current I_ψ through port CD (D. B. Geselowitz 1971).

Figure 4.5. (A) Four-electrode system for measurements of mutual impedance. The selected terminology is the same as that used in (D. B. Geselowitz 1971). (B) Lead vector and transfer impedance vector in a volume conductor, Fig.7 in (Schmitt, 1959).

Considering the system in Figure 4.5(A) as a two-port system, linear and passive, by applying the reciprocity theorem of Helmholtz a relationship between the ports AB and CD can be established through the mutual impedance as follows:

$$\frac{\Psi_{AB}}{I_{\psi}} = Z_{AB\psi} = Z_{CD\phi} = \frac{\Phi_{CD}}{I_{\phi}} \quad [\Omega] \quad \text{Equation (4.9)}$$

Note that in the case where $I_{\phi} = I_{\psi} = I$, since $Z_{AB\psi} = Z_{CD\phi} = Z_{mutual}$ then $\Phi_{AB} = \Phi_{CD} = \Phi$ and we can write Ohm's law for the mutual impedance Z_{mutual} as in (4.10a)

$$\Phi = Z_{mutual} I \quad [V] \quad \text{Equation (4.10a)}$$

When the current is caused by a current dipole such that $\vec{I}_{\phi} = \vec{I}_{\psi} = \vec{I}$ through the corresponding ports, the mutual impedance Z_{mutual} is related to the lead vector $\vec{L}$ and the transfer impedance vector $\vec{Z}_t$ as in (4.10b).

$$\begin{aligned} \Phi_{CD} = \vec{L}_{CD} \bullet \vec{I}_{\phi} = \Phi_{AB} = \vec{L}_{AB} \bullet \vec{I}_{\psi} = \Phi = \vec{Z}_t \bullet \vec{I} \\ \vec{Z}_t \bullet \vec{I} = \Phi = Z_{mutual} I \end{aligned} \quad [V] \quad \text{Equation (4.10b)}$$

As shown in (4.10b) the voltage drop between two points, a scalar value, caused by a current element, a dipole or the current as such, is obtained by using the concept of mutual impedance in the case of current and using the transfer impedance vector in the case of a current dipole.

The mutual impedance Z_{mutual} is impedance as we know it directly from Ohm's law, but the transfer impedance vector $\vec{Z}_t$ is an impedance element with geometrical information, given by the vectorial form.

Reducing the volume conductor to a cylinder of finite length as in Figure 2.11, if current is injected through the circular edges, applying Ohm's law as in (4.1) we obtain $V = ZI$, similar to (4.10).

Since the total impedance of the cylinder is $Z = z^* k$, from (2.15), with units $(\Omega) = (\Omega m)(m^{-1})$, and the cell factor k in a cylinder is $k = LS^{-1}$ from (2.15), then we can rewrite V as $V = z^* \frac{L}{S} I$. Considering the dimensions

of the expression V , $(V) = (\Omega m) \frac{(m)}{(m^{-2})} (A) = (\Omega m^{-1})(A)(m)$ and comparing

them with the lead vector and the transfer impedance vector equation (4.10b) and its corresponding units, it is seen at once that in any volume conductor, the spatial information introduced by the cell factor k in the calculation of the impedance, mutual or not, is included in the vectorial

components of the transfer impedance vector $\vec{Z}_t$ or lead vector $\vec{L}$ and the current dipole $\vec{I}$, as expected from the vectorialized Ohm's law.

4.3.3 The Lead Field

It follows from the reciprocity theorem that the vector transfer impedance function $\vec{L}_{CD}(x,y,z)$ as defined by Schmitt is identical at each point to the electric field $\vec{E}$ which would exist at that point (x,y,z) if a unit current I were injected into the lead CD (R. Mc Fee & F. D. Johnston 1953). This field is called the lead field (D. B. Geselowitz 1971).

Since the electric field and the current density field are linearly related through Ohm's law, the lead field can be defined as electric field $\vec{E}$ per reciprocal unit current, as done by Geselowitz, or as current field $\vec{J}$ per reciprocal current as done by (J. Malmivuo & R. Plonsey 1995), or in both ways as done by McFee & Johnston.

4.3.4 Sensitivity Distribution

The sensitivity of a voxel gives an idea of the contribution of the conductivity of each voxel to the measured impedance (S. Grimnes & Ø. G. Martinsen 2007). In other words:

the sensitivity distribution of an impedance measurement gives a relation between the measured impedance, Z (and change in it), caused by a given conductivity distribution (and its change).

Pasi Kauppinen (P. Kauppinen et al. 2005)

The expressions for the impedance measurement sensitivity are given by equation (4.11), in current-lead field form in the left part, and in voltage-lead field form in the right part. Note that both forms are related by Ohm's law.

$$S_{VmJ} = \frac{\vec{J}_\phi \bullet \vec{J}_\psi}{I_\phi I_\psi} = \frac{\vec{E}_\phi \bullet \vec{E}_\psi}{I_\phi I_\psi} \sigma^2 = S_{VmE} \sigma^2 \quad [\text{m}^{-4}] \quad \text{Equation (4.11)}$$

Here S_{Vm} is the sensitivity at a point in the space for an impedance measurement of the volume conductor V , with the 2-port measurement setup m from Figure 4.5; the symbol $\bullet$ is the dot product, I_ϕ and I_ψ are the electrical currents used to energize the volume conductor; $\vec{J}_\phi$ and $\vec{J}_\psi$ are the current density fields, and $\vec{E}_\phi$ and $\vec{E}_\psi$ are the electric fields, i.e. impedance lead fields associated with the current and voltage leads for the impedance measurement setup m . Note that $\vec{J}_\phi$ and $\vec{J}_\psi$ must be obtained with reciprocal energization, i.e. $I_\phi = I_\psi$. The same holds for $\vec{E}_\phi$ and $\vec{E}_\psi$. **N.B.** Since both current and voltage lead fields are defined

$\vec{E}_\phi$ and $\vec{E}_\psi$. **N.B.** Since both current and voltage lead fields are defined per unit current, the dimensions of the impedance measurement sensitivity in current form $\mathbf{S}_{VmJ}$ are m^{-4} , while in voltage form $\mathbf{S}_{VmE}$ are $\Omega^2\text{m}^{-2}$.

Figure 4.6. (a) Current density fields generated by a current dipole at AB and CD, red and blue respectively. (b) Corresponding sensitivity map for the measurement setup from Figure 4.5, with current density field as in Figure 4.6(a).

Applying equation (4.11) to the current density fields in Figure 4.6(a) associated with the measurement setup depicted in Figure 4.5, the corresponding sensitivity map is obtained in Figure 4.6(b), where the volume conductor has been reduced to two dimensions for the sake of clarity.

Observe that the sensitivity $\mathbf{S}_{Vm}$ may be positive, negative or null, depending on the orientation of the two lead fields. In this way a change in the conductivity of a specific voxel may cause an increment or a decrement in the measured impedance – or it may be entirely unaffected by the conductivity change, as in the case when the lead fields in the voxel are perpendicular to each other.

4.3.5 Sensitivity Distribution and Impedance Measurements

Equation (4.11) expresses the sensitivity to conductivity changes in the volume conductor V with the measurement setup m and how a change in the conductivity contributes to a change in the total measured impedance. Such a relationship can be expressed as follows:

$$\Delta Z = \Delta\sigma \int_V \mathbf{S}_{VmE} dv = \Delta(\sigma^{-1}) \int_V \mathbf{S}_{VmJ} dv = \Delta\rho \int_V \mathbf{S}_{VmJ} dv \quad [\Omega] \quad \text{Equation (4.12)}$$

Observe the transformation from the voltage-lead field form and the change in conductivity, $\Delta\sigma$, as defined by Geselovitz (D. B. Geselovitz 1971) to the current-lead form and the change in resistivity $\Delta\rho$ as expressed in (S. Grimnes & Ø. G. Martinsen 2007).

The total measured impedance, the sensitivity distribution, and the change in the dielectric properties of the volume elements are related as follows:

$$\mathbf{Z}_{Vm}(\omega) = \int_V \frac{1}{\sigma_{vx}^*(\omega)} S_{VmJ}(\omega) d\mathbf{v} = \int_V \rho_{vx}^*(\omega) S_{VmJ}(\omega) d\mathbf{v} \quad [\Omega] \quad \text{Equation (4.13)}$$

Here V is the total volume conductor containing a certain number of unitary elements of volume v_x , and $\mathbf{Z}_{Vm}$ is the measured impedance; σ^* is the complex conductivity of a voxel, ρ^* is the complex resistivity or impedivity, and S_{VmJ} is the impedance measurement sensitivity, defined as current-lead fields. Note that in biological tissue the dielectric properties are frequency-dependent; therefore the sensitivity and the impedance will be as well.

There are two important inferences from equations (4.12) and (4.13) (S. Grimnes & Ø. G. Martinsen 2007):

- (1) The larger the absolute value of sensitivity in one voxel, the larger its contribution to the total measured impedance.
- (2) A negative value of sensitivity in one voxel means that an increment in the resistivity of that voxel will cause a decrease in the total measured impedance.

4.4 Impedance Estimation

Several approaches exist for estimating an impedance value from a reading of voltage and electrical current. The most well known and used is the sine correlation technique. The Fourier transform is also a common tool used for impedance measurements.

4.4.1 Sine Correlation

The sine correlation technique is an impedance estimation method based on the trigonometric identities for the double angle:

$$\begin{aligned} \cos(2\alpha) &= 1 - 2\sin^2(\alpha) = 2\cos^2(\alpha) - 1 \\ \sin(2\alpha) &= 2\sin(\alpha)\cos(\alpha) \end{aligned} \quad \text{Equation (4.14)}$$

A sine wave $\sin(\omega_m t)$ is generated at a certain frequency ω_m with known amplitude I and it is injected as current signal on the tissue. Then the voltage caused in the tissue by the current is measured by obtaining $V_m(t)$ as follows:

$$\begin{aligned} V_m(t) &= I \sin(\omega_m t) |Z_{TUS}| \angle \theta \Rightarrow \\ &= I |Z| \sin(\omega_m t + \theta) = V_m \sin(\omega_m t + \theta) \Rightarrow [V] \quad \text{Equation (4.15)} \\ &= V_{ip} \sin(\omega_m t) + V_{iq} \cos(\omega_m t) \end{aligned}$$

Note that the measured voltage $V_m(t)$ can be decomposed in two components: a signal in phase with the injected current, corresponding to the voltage drop in a pure resistor, $V_{ip}(t)$, and a signal in quadrature with

Figure 4.7. Block schematic diagram representing the application of the sine correlation technique in an impedance measurement using the Four-Electrode method.

the injected current corresponding to the typical voltage drop in a pure reactance component, $V_{iq}(t)$.

By generating with the same signal source two reference signals of unitary current amplitude uA , one of the reference signals being in phase and another in quadrature with the injected current by multiplying each of the reference signals with the measured voltage $V_m(t)$, as in Figure 4.7, the signals $ip(t)$ and $iq(t)$ are obtained as follows:

$$\begin{aligned}
 ip(t) &= uA \sin(\omega_m t) \times V_m(t) \Rightarrow \\
 &= uA \sin(\omega_m t) (V_{ip} \sin(\omega_m t) + V_{iq} \cos(\omega_m t)) \Rightarrow \\
 &= uA V_{ip} \sin^2(\omega_m t) + uA V_{iq} \sin(\omega_m t) \cos(\omega_m t) \Rightarrow \quad [A^2\Omega] \text{ Equation (4.16)} \\
 &= uA V_{ip} \left(\frac{1 - \cos(2\omega_m t)}{2} \right) + uA V_{iq} \left(\frac{\sin(2\omega_m t)}{2} \right) \Rightarrow \\
 ip(t) &= \frac{uA V_{ip}}{2} + \frac{uA V_{iq}}{2} (\sin(2\omega_m t) - \cos(2\omega_m t))
 \end{aligned}$$

$$\begin{aligned}
 iq(t) &= uA \cos(\omega_m t) \times V_m(t) \Rightarrow \\
 &= uA \cos(\omega_m t) (V_{ip} \sin(\omega_m t) + V_{iq} \cos(\omega_m t)) \Rightarrow \\
 &= uA V_{iq} \cos^2(\omega_m t) + uA V_{ip} \sin(\omega_m t) \cos(\omega_m t) \Rightarrow \quad [A^2\Omega] \text{ Equation (4.17)} \\
 &= uA V_{iq} \left(\frac{1 + \cos(2\omega_m t)}{2} \right) + uA V_{ip} \left(\frac{\sin(2\omega_m t)}{2} \right) \Rightarrow \\
 iq(t) &= \frac{uA V_{iq}}{2} + \frac{uA V_{ip}}{2} (\cos(2\omega_m t) + \sin(2\omega_m t))
 \end{aligned}$$

Observe that both the $ip(t)$ and $iq(t)$ signals are periodic with mean value ip_0 and iq_0 respectively, of

$$ip_0 = \int_T ip(t) dt = \frac{uA V_{ip}}{2} \quad [A^2\Omega] \text{ Equation (4.18)}$$

$$iq_0 = \int_T iq(t) dt = \frac{uA V_{iq}}{2} \quad [A^2\Omega] \text{ Equation (4.19)}$$

Considering that V_{ip} and V_{iq} were the voltage drop caused in the resistance and in the reactance by the current flow of known amplitude I , and remembering that the amplitude uA of the reference signals was the unit, then using the identities in equations (4.16) and (4.17) both the resistance and the reactance can be estimated from $ip(t)$ and $iq(t)$ respectively as follows:

$$R = \frac{V_{ip}}{I} = \frac{2 ip_0 / uA}{I} = \frac{2}{I} \int_T ip(t) dt \quad [\Omega] \quad \text{Equation (4.20)}$$

$$X = \frac{V_{iq}}{I} = \frac{2 iq_0 / uA}{I} = \frac{2}{I} \int_T iq(t) dt \quad [\Omega] \quad \text{Equation (4.21)}$$

This V/I voltage measurement and decomposition approach implicitly selects an impedance measurement $R + jX$. If the current was the measured and decomposed signal in an I/V approach, then the selected measurement is an admittance $G + jB$. **N.B.** The period of the modulated signal T is half of the period of the stimulating frequency $T_m = 1/2\pi\omega_m$, and it is the minimum time to obtain a correct impedance estimation.

4.4.2 Fourier Analysis

In this case the impedance estimation is done in the frequency domain by using the Fourier transform of the measured time signals. This approach only supports digital implementation, and cannot be implemented with analog electronics as in the case of the sine correlation technique.

The basic principle is to measure the voltage drop $V_m(t)$ in the tissue caused by a known current $I(t)$ and apply the Fourier transform in both current and voltage time signals, to obtain the corresponding expressions in the frequency domain $I(j\omega)$ and $V_m(j\omega)$, see Figure 4.8. Then one applies Ohm's law to the frequency domain signal to obtain the quotient between the voltage and current, and consequently the impedance in polar form:

$$\begin{aligned} \frac{V_m(j\omega)}{I(j\omega)} &= Z(j\omega) \Rightarrow \\ Z(j\omega) \Big|_{\omega \rightarrow \omega_m} &= |Z| \angle \theta \end{aligned} \quad [\Omega, \angle \text{radian}] \quad \text{Equation (4.22)}$$

Figure 4.8. Block schematic diagram representing an application of the Fourier transform for impedance estimation in Four-Electrode impedance measurement.

In the case where the injected current $I(t)$ is a pure tone with fundamental frequency ω_m , the spectral information of the current and voltage signals and consequently the impedance will be zero at any other frequency than ω_m .

With the Fourier approach, by using a single stimulation signal containing all frequencies, it would be possible to obtain the whole spectrum of the tissue impedance at once. For this reason the Fourier technique is quite appropriate for multifrequency measurements.

In the case of the use of the sine correlation technique for multifrequency measurements, it is not only necessary to generate a pair of reference signals at each of the frequencies to estimate the impedance, but also more signal processing needs to be done, such as filtering before correlation to avoid undesired effects e.g. from signal harmonics.

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PART II

SPECTROSCOPY STUDY OF THE DYNAMICS
OF THE TRANSENCEPHALIC ELECTRICAL
IMPEDANCE IN THE PERINATAL BRAIN
DURING HYPOXIA

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Spectroscopy study of the dynamics of the transencephalic electrical impedance in the perinatal brain during hypoxia

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Abstract

Hypoxia/ischaemia is the most common cause of brain damage in neonates. Thousands of newborn children suffer from perinatal asphyxia every year. The cells go through a response mechanism during hypoxia/ischaemia, to maintain the cellular viability and, as a response to the hypoxic/ischaemic insult, the composition and the structure of the cellular environment are altered. The alterations in the ionic concentration of the intra- and extracellular and the consequent cytotoxic oedema, cell swelling, modify the electrical properties of the constituted tissue. The changes produced can be easily measured using electrical impedance instrumentation. In this paper, we report the results from an impedance spectroscopy study on the effects of the hypoxia on the perinatal brain. The transencephalic impedance, both resistance and reactance, was measured in newborn piglets using the four-electrode method in the frequency range from 20 kHz to 750 kHz and the experimental results were compared with numerical results from a simulation of a suspension of cells during cell swelling. The experimental results make clear the frequency dependence of the bioelectrical impedance, confirm that the variation of resistance is more sensitive at low than at high frequencies and show that the reactance changes substantially during hypoxia. The resemblance between the experimental and numerical results proves the validity of modelling tissue as a suspension of cells and confirms the importance of the cellular oedema process in the alterations of the electrical properties of biological tissue. The study of the effects of hypoxia/ischaemia in the bioelectrical properties of tissue may lead to the development of useful clinical tools based on the application of bioelectrical impedance technology.

Keywords: bioimpedance, brain damage, cellular oedema, cerebral monitoring, perinatal asphyxia

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

1. Introduction

Hypoxia/ischaemia is responsible for many disorders, disabilities and deaths related to the nervous system as a result of severe lack of oxygen and/or cerebral circulation failure. For instance, up to 48% of all patients suffer from cognitive dysfunction after cardiac surgery with imposed cardiac arrest (Toner *et al* 1998) and up to 1.5% of newborns suffer from perinatal asphyxia (Legido *et al* 2000). This high incidence rate of hypoxic/ischaemic brain damage not only influences dramatically the life of thousands of affected people and their families, but also entails a huge economic burden for society, billions of euros every year worldwide.

Perinatal asphyxia is one of the diseases related to hypoxic/ischaemic brain damage and it is the most significant cause of mortality, neuro-developmental disability and long-term neurological morbidity in newborn infants. Neural rescue therapies have been tested on animals with satisfactory results (Gunn *et al* 1998) and clinical trials of hypothermia therapy are in progress on humans. Even when a successful therapy may allow the recovery of the affected patients as a requirement prior to therapy initiation, the hypoxic situation needs to be clearly and efficiently detected. Moreover, the time window between insult and start of therapy appears to be narrow (Vannucci and Perlman 1997, Roelfsema *et al* 2004).

1.1. Hypoxia and cellular oedema

Hypoxia/ischaemia is an important and common cause of cell injury. It affects the cellular metabolism, impinging on the aerobic oxidative respiration of the cell (Cotran *et al* 1989). Lack of oxygen in the cell forces the cell to resort to anaerobic metabolism with glycogen–glucose breakdown halted at the lactate level. The reduced capability of the cell to produce energy forces the cell membrane to lose some of its regulation and active transport functions. This leads to a rapid accumulation of osmotic active products in the intracellular space, an accumulation accompanied by an isosmotic increment in water and resulting in an inevitable intracellular swelling. This intracellular swelling is denominated cellular or cytotoxic oedema (Klatzo 1994) and it characterizes the early phase of hypoxia/ischaemia.

1.2. Electrical bioimpedance

Biological tissue is a dielectric conductive material and electrical current passes through the tissue when a difference of electric potential is applied to the tissue in a closed electric circuit. Biological tissue is often considered as an aggregation of cells, with a semi-permeable membrane containing the intracellular fluid, surrounded by the extracellular fluid. Both intracellular and extracellular fluids are conductive, therefore exhibiting a certain resistance, and the cellular membrane acts as a capacitor, figure 1.

1.3. Effects of cell swelling on the bioelectrical impedance of the tissue

Cell swelling causes cellular oedema, which implies a redistribution of fluids between the intracellular and extracellular spaces. This fluid redistribution causes changes in the structure

Figure 1. (A) and (B) show the pathways of the electrical current through biological tissue; (A) low frequency, (B) high frequency. (C) shows the electrical circuit model equivalent of biological tissue; three elements 2R-1C parallel type.

of the tissue, resulting in changes in the electrical bioimpedance (Van Harreveld 1957). The electrical impedance consists of two components: resistance and reactance, and both depend on the shape of the cells, tissue structure and tissue composition. Therefore, our working hypothesis is that during cell swelling both of them may be modified notably and in theory substantial changes are expected, especially in the reactive part.

Previous experimental studies, focused on hypoxic/ischemic brain damage, have successfully confirmed the association between hypoxic/ischemic events and changes of the electrical bioimpedance in the brain (Van Harreveld 1957, Williams *et al* 1991, Holder 1992, Lingwood *et al* 2002).

1.4. Multi-frequency measurements in brain hypoxia/ischaemia

Multi-frequency analysis of brain electrical impedance during hypoxia/ischaemia has been used only once before, to our knowledge, in Lingwood *et al* (2002). In such study, multi-frequency measurements of resistance and reactance were performed and using the Cole analysis the resistance at zero frequency (R_0) was estimated. The dynamics of the estimated R_0 value were reported but no multi-frequency impedance data were included in the results.

In agreement with our working hypothesis, in this study we take the step of studying the dynamics of the impedance during normoxia followed by an induced hypoxic event and further during a phase of reoxygenation. We study the measured complex impedance, both resistance and reactance, and the observed frequency dependence on the measurements' frequency range.

In order to verify that the measured variations in impedance are in fact related to hypoxic cell swelling, the variations are interpreted in relation to the model of biological tissue as a suspension of spherical cells, figure 2 and equation (1) from Cole (1928).

$$Z = r_e \frac{(1-f)r_e + (2+f)(r_i + \frac{z_m}{a})}{(1+2f)r_e + 2(1-f)(r_i + \frac{z_m}{a})} \quad (1)$$

where Z is the specific impedance of tissue in Ω cm, r_e is the resistivity of extracellular fluid in Ω cm, r_i is the resistivity of cytoplasm in Ω cm, z_m is the surface membrane impedivity in Ω cm², a is the cell radius in cm and f is the volume factor of concentration of cells.

2. Methodology

A bioimpedance spectroscopy study of biological tissue during cell swelling has been performed. An experiment with live animals was performed to invasively measure

Figure 2. Suspension of spherical cells in a conductive fluid. Equation (1) shows the equivalent electrical impedivity (specific impedance) of a suspension of spherical cells.

Figure 3. The four-electrode method and the placement of electrodes following the standard 10–20 system on the head of a piglet. Two electrodes inject the current while the resulting voltage through the tissue is measured with the other two. Current injecting electrodes are placed on C3 and C4 and potential-sensing electrodes are placed on P3 and P4.

transencephalic electrical impedance on piglets before, during and after hypoxia. Numerical calculations based on the model of tissue as a suspension of cells were performed to calculate the effective behaviour of the electrical bioimpedance of tissue regarding the frequency, tissue structure and radius of the cells.

The performed animal experimentation was approved by the Ethics Committee for Animal Research of Göteborg University.

2.1. Animal preparation and induced hypoxia

Newborn pigs, 1–4 days old, were anaesthetized with ketamine for induction and chloral hydrate for maintenance and then ventilated to maintain normal blood gases. Transencephalic impedance was recorded together with arterial blood pressure, heart rate and electroencephalic activity (EEG). After a 1 h long control period, 45 min of severe hypoxia was instituted by decreasing oxygen in the inhaled gas mixture to 6% to induce loss of EEG activity. Then oxygen was added to the gas mixture and normal oxygenation was maintained for the following 16 h. The subjects were killed immediately at the end of the experiments by a lethal overdose of pentothal.

2.2. Measurement of transencephalic impedance

Four burr holes were drilled through the scalp in positions P3, P4, C3 and C4; see figure 3. Silver rod electrodes of 2.5 mm diameter with rough surface were screwed into the holes with the surface resting on the dura. The electrical bioimpedance was measured using a frequency selectable custom-made impedance meter (Jakobsson 2000), based on the four-electrode current-injection/voltage-measurement method (Ackmann *et al* 1984). The impedance meter was calibrated with resistive loads and Cole phantoms, 2R1C parallel type, obtaining a margin error of $\pm 0.5 \Omega$ up to 650 kHz and $+1.5/-0.7 \Omega$ to 1300 kHz.

A symmetric sinusoidal current of 500 μA peak value was applied for continuous electric stimulation. The current was injected through the current electrodes placed on C3 and C4. The complex electrical bioimpedance, resistance and reactance, was measured from potential-sensing electrodes placed on P3 and P4.

The dynamics of the resistance was studied in seven subjects at the frequencies 50 kHz and 200 kHz. A more elaborate study was performed in two subjects where the measurements were made in the frequency range from 20 to 750 kHz. In these two subjects the impedance, resistance and reactance, was measured and the results were compared with the suspension of cells model.

2.3. Numeric calculations on the suspension of cells model

The impedivity of a suspension of spherical cells was calculated using the expression derived by Cole (1928) applying the articles 313 and 314 of Maxwell's treatise (Maxwell 1873). The impedivity obtained was used to calculate the impedance of a cylindrical conductor. The limits and accuracy in the calculation of the electrical bioimpedance of tissue modelled as a suspension of cells have been studied and reported by Cole (Cole *et al* 1969, Cole 1976).

$$f = \frac{N_c \times 4 \times \pi \times a^3}{3 \times V_t} \quad (2)$$

where, f is the volume factor, N_c is the number of cells, V_t is the total volume of the suspension and a is the radius of the cells.

Equation (1) was fitted to geometrically satisfy three dimensions using equation (2) to define the volume factor, f , with respect to the radius of the cells a . Both real and imaginary components were calculated with equation (1) and the resulting values were represented using complex impedance plots for different values of cell radii. The model represented a cylindrical portion of tissue of radius 20 mm and length 20 mm containing 10^9 cells. The plasma membrane was considered an ideal capacitor. Thus, z_m in equation (1) is substituted by $(j\omega c_m)^{-1}$, where j is the imaginary operator $\sqrt{-1}$, ω is the angular frequency in radians s^{-1} and c_m is the surface membrane capacity in farads cm^{-2} . The resistivity values used in the numerical calculation are electrical properties of myelinated nerve fibres extracted from Malmivuo and Plonsey (1995).

3. Results

The measurements performed showed that the electrical bioimpedance of the brain changes notably during and after hypoxia with respect to the normoxic baseline value.

3.1. Dynamics of resistance—normoxic phase

During normoxia, before the hypoxic insult was induced, the subjects ($n = 7$) presented a stable brain electrical resistance baseline for each subject, though at significantly different

Table 1. Statistics of the measured resistance baseline prior to hypoxia. Measurements performed at 50 kHz and 200 kHz over a set of seven subjects.

Subject	Frequency 50 kHz		Frequency 200 kHz	
	Mean (Ω)	SD (Ω)	Mean (Ω)	SD (Ω)
1	56.3	0.047	52.1	0.037
2	50.0	0.050	45.2	0.051
3	50.5	0.058	44.1	0.062
4	50.4	0.259	47.3	0.221
5	33.0	0.061	20.7	0.067
6	85.0	0.462	75.8	0.495
7	68.4	0.459	58.8	0.203
Average at 50 kHz				
Mean	56.2 Ω		49.1 Ω	
Standard deviation	16.4 Ω		16.7 Ω	

Table 2. Statistics of the maximum variation in the resistance during hypoxia. Measurements performed at 50 kHz over a set of seven subjects.

Subject	Frequency 50 kHz	
	Maximum (Ω)	Ratio (%)
1	15.4	27.0
2	19.1	38.3
3	38.4	76.1
4	22.7	45.0
5	7.5	22.6
6	22.1	26.0
7	81.0	118.4

values. The average resistance measured at 50 kHz was 56.2 Ω with a 16.4 Ω standard deviation (SD) and 49.1 Ω with a 16.7 Ω SD measured at 200 kHz. As it is possible to observe in table 1, most of the subjects presented baseline values close to the average value, but one subject showed a very high baseline value, 85.0 Ω at 50 kHz and 75.8 at 200 kHz, and another subject showed a noticeably low baseline, 33.0 Ω at 50 kHz and 20.7 at 200 kHz.

3.2. Dynamics of resistance—hypoxic phase

During hypoxia, the transencephalic resistance increased remarkably over the established baseline. The same individual specificity observed for the value of the baseline was observed for the time evolution of the resistance measured during hypoxia.

Figure 4 shows the evolution of the resistance measured at 50 kHz during hypoxia in each of the seven subjects. The resistance increases in every subject but with different slopes reaching different maximum values. The resistance began to increase right after hypoxia was initiated. The maximum observed variation was 81.0 Ω corresponding to a relative increment of 118.4% over the normoxic baseline. The minimum observed variation was 7.5 Ω corresponding to 22.6%. See table 2 containing the maximum observed variation in the resistance for all the piglets.

Figure 4. Time evolution of the cerebral electrical resistance in the asphyxiated piglet measured at 50 kHz in seven different subjects. The 45 min hypoxic period is marked within the vertical discontinuous lines.

After the normal oxygenation was re-instituted, the resistance kept increasing for a short period of time before decreasing back to lower values. The length of such a period varies for each of the subjects; see figure 4.

The evolution of the resistance measured at 200 kHz was identical to the evolution of the resistance at 50 kHz for every piglet. The only difference was that the values of the magnitude and the proportional changes were slightly smaller.

3.3. Dynamics of resistance—post-hypoxic phase

At low frequencies, during the post-hypoxic phase three different dynamics were observed in the resistance. In the first group of piglets, the resistance decreased towards the baseline and after the baseline value was restored, the resistance value remained stable for the remaining part of the experiment. In the second group, the resistance after reaching the baseline value and keeping stable for a certain period, started increasing again. In the third group, after decreasing for a short period, the resistance started increasing again, before the baseline value was reached.

3.4. Complex electrical bioimpedance during hypoxia

In both piglets, the complex bioimpedance, both reactance and resistance, across the brain tissue exhibited similar changes during hypoxia and after hypoxia was instituted. Figure 5

Figure 5. Plot of transencephalic electrical bioimpedance on the brain of a piglet at three different moments during hypoxic cell swelling. The complex impedance is plotted in the frequency range from 20 kHz to 750 kHz and from the right to the left.

shows the time evolution of the cerebral electrical impedance in one of the subjects before, during and after hypoxia. The behaviour of the cerebral impedance in the other piglets followed a similar evolution. The plots contained in figure 6 are calculated complex impedance plots, illustrating absolute reactance versus resistance over the frequency range from 20 kHz to 750 kHz obtained from the numerical calculations.

We observed that during hypoxia the radius of the impedance plot increased and the centre was shifted to higher values of the resistance. After oxygenation was re-instituted, the radius of the plot decreased and the centre shifted back towards the normoxic value.

The numerical results obtained from the calculations based on the suspension of cells and the experimentally measured values matched well at any frequency. Both sets of bioimpedance plots, experimental in figure 5 and numerical in figure 6, show an analogous behaviour. The radius of the locus increases with the radius/swelling of the cells; an increase followed by a shift of the centre of the impedance locus to high values over the resistance axis.

3.5. Effect of the frequency

Results from the measurements showed that, during deprivation of oxygen, the reactance and the resistance changed in a different and independent manner from each other and both showed a certain frequency dependence.

The reactance increased during hypoxia at every measured frequency in the range of 20 kHz–750 kHz; see figure 7(a). The maximum proportional increment in the reactance over the baseline increased with the frequency until it reached a maximum value at 300 kHz; after that it decreased with the frequency, see figure 8.

Figure 6. The complex impedance plot of a suspension of spherical cells for three different radii of cells. The suspension shape is a cylinder of radius 0.02 m and length 0.02 m. According to equation (1) $r_e = 3 \Omega \text{ m}$, $r_i = 1.1 \Omega \text{ m}$, $r_m = \infty$, $C_m = 0.01 \text{ F m}^{-2}$. Cells' radii $a_1 = 7.11 \mu\text{m}$, $a_2 = 7.49 \mu\text{m}$, $a_3 = 7.63 \mu\text{m}$. The volume factor of cell concentration, f , is 0.60, 0.70 and 0.74, respectively. The total number of cells in the suspension is 10^9 . The impedance is calculated in the frequency range from 20 kHz to 750 kHz and plotted from the right to the left.

The behaviour of the resistance during hypoxia showed a higher frequency dependence, increasing the most at low frequencies. The maximum proportional increment over the baseline decreased with increasing frequency and at the highest measured frequency, 750 kHz, the resistance decreased instead of increasing; see figures 7(b) and 8.

The measurements show that during hypoxia the changes in the reactance were proportionally larger than those in the resistance for the complete frequency range of the measurements, especially at high frequencies; see the comparison chart in figure 8.

4. Discussion

This study confirms that cell swelling in the brain following hypoxia modifies considerably the complex electrical impedance of the brain. This is consistent with previous studies performed in different species; fetal sheep (Williams *et al* 1991), rats (Holder 1992) and newborn piglets (Lingwood *et al* 2002). These changes in the electrical bioimpedance during hypoxia occur in both resistance and reactance, real and imaginary parts of the impedance and they are approximately in concordance with numerical simulations based on tissue modelled as a suspension of cells.

4.1. Resistance and reactance

The reactance during the hypoxic insult changes the most and exhibits a higher sensitivity than the resistance at any measured frequency in the range of 20 kHz–750 kHz. This fact is in obvious contradiction to the widely spread idea that during cell swelling alterations mainly occur in the resistance (Somjen 2001) but it is in accordance with the expected and calculated behaviour of the impedance of a suspension of spherical cells during cell swelling, increasing radius.

Figure 7. Evolution of transencephalic electrical impedance, reactance in (A) and resistance in (B), in a neonatal piglet during hypoxia. Measurements performed at seven frequencies in the frequency range of 20 kHz–750 kHz. Hypoxia was instituted in the period between vertical markers.

4.2. Effect of the frequency

The reactance not only exhibits a higher sensitivity than the sensitivity observed for the resistance during hypoxia, but the sensitivity of the reactance is also much more stable than the sensitivity of the resistance over the complete frequency range. The sensitivity

Figure 8. The comparison chart of the maximum proportional variation over the frequency of the reactance and the resistance during hypoxia in the brain tissue of the neonatal piglet.

of the reactance is also positive at any frequency and the maximum values are obtained at intermediate frequencies.

The sensitivity exhibited by the resistance changed a lot with increasing frequency. At low frequencies, the resistance changes and increases the most, as was expected from the suspension of cells model. With increasing frequency the sensitivity gradually decreases, reaching a point when the resistance decreases instead of increasing during hypoxia, resulting in a negative value of the sensitivity at high frequencies. The experimentally observed behaviour is also in accordance with the calculated behaviour of the electrical resistance of a suspension of spherical cells during cell swelling. The agreement between the theoretically expected behaviour and the experimentally obtained results is evidence to support the statement that the observed changes in the resistance at high frequencies are due to cell swelling and not as a result of measurement artefacts.

The decrease of the resistance at high frequencies during global cell swelling is probably best explained by the facts that at high frequencies the electrical current uses both intracellular and extracellular fluids to travel through the tissue and the intracellular fluid is more conductive than the extracellular fluid (Malmivuo and Plonsey 1995).

Therefore, the redistribution between extracellular and intracellular fluids in favour of the latter, occurring during cell swelling, increases the proportion of the more conductive fluid in detriment of the less conductive leaving an overall more conductive, less resistive material.

4.3. High subject specificity

The results obtained indicate that transencephalic electrical bioimpedance is subject specific to a very great extent. The value of the resistance, measured before hypoxia was induced, varied

significantly between specimens. These observations are in accordance with the work reported by Lingwood *et al* (2003). Geometrical variations in the electrode placement between the different subjects, especially considering the small head of the piglet, may cause significant differences in the measured impedance values. Even if the placement of the four electrodes was identical between subjects, each piglet may have a slightly individual brain size that modifies in a specific way the current distribution within the conducting volume influencing the sensed measurement. Therefore, such geometric effects of the conducting volume between subjects should be considered as an important contributor to the variability of the observed baseline together with other subject specific factors, e.g., tissue morphological differences between subjects, different degrees of maturation and individual variations in the amount of cerebrospinal fluid.

The subject specificity was not only observed in the variability of the normoxic baseline value, but it was observed that, even when the cerebral impedance exhibited the same general evolution during hypoxia, the time course of the changes was highly specific to each specimen. The comparatively large variability in the individual response was also demonstrated by the different reactions of the animals during the period of re-oxygenation. Some animals recovered their normoxic impedance baseline while other animals had a secondary rise of impedance after the initial recovery. This behaviour corresponds to the previously described phases of primary and secondary energy losses (Penrice *et al* 1997). This should be due to the fact that the physiological system of each piglet responds in a slightly different way to the hypoxic insult and thus affects the timing of the physiological mechanism following hypoxia.

4.4. The model of suspension of cells

The consideration of biological tissue as a suspension of spherical cells in a conductive fluid is an approximation far from reality and to develop the numerical calculations considering the resistivity of the intracellular and extracellular space as real and frequency independent only moves the model even further away from reality. In spite of this, the model has been used for almost a century, since Fricke (1924, 1925), with acceptable results, and the limitations and accuracy of the different approaches have been studied and reported for many years by Cole (Cole *et al* 1969, Cole 1976).

It is known that the electrical conductivity of the brain tissue is anisotropic (Geddes and Baker 1967), but we have neglected that anisotropy and used an electrical isotropic model, as it has been reported by Haueisen that the anisotropy of the white and grey matter of the brain does not affect the measurements of EEG (Haueisen *et al* 2002).

In the simulation of the hypoxic insult on the suspension of cells model, the cell swelling effect has been considered only as an increment in the radius.

The alterations in the biochemical composition of the intra- and extracellular fluids have been neglected, considering the respective conductivities constant. Obviously, calculations based on a model considering the time alterations of local conductivities during hypoxia would be a more realistic approximation, but a study on how those conductivities change with the evolution of hypoxia has to be performed beforehand.

The morphology of the brain with the neurons and the axons forming networks in any direction is very different from a suspension of cells and it is quite unlikely that the paths that the electrical current follows through the brain tissue are similar to the paths through a suspension of spherical cells, especially in terms of homogeneities. The effect of the orientation of the biological structures on the effective impedance is clearly observed in muscular tissue, and it probably plays an important role in the impedance of brain tissue as well. Work with suspension of non-spherical cells reported by Kanai *et al* (2004) shows, as expected, that the

orientation affects the total impedance of the suspension. However, the effect is significantly minimized with the increase of the volume factor of concentration of cells.

However, with the mentioned and known limitations of this simple model the reasonable agreement between the experimental data and the numerical results is remarkable and allowed us to verify that in fact the observed change of the impedance was related to hypoxic cell swelling.

4.5. Invasive measurements

The measurements performed in this experiment are invasive, avoiding the effect of the scalp and the skull. In non-invasive measurements, the impedance of the scalp and especially the high resistivity of the skull would reduce the effect of the alterations of internal cell swelling in the total effective transencephalic impedance. Authors (Holder 1992, Lingwood *et al* 2002) have reported that changes in the resistance during hypoxia are around 10–20 times smaller when measured non-invasively than when done invasively. Regarding the reactance no previous work has been found in this respect.

4.6. About the impedance plots

The impedance plots used in some of the figures in the results section are just regular parametric plots of reactance–resistance along the frequency; they are neither Cole plots nor Cole–Cole plots, terminology commonly misused among different authors.

A ‘Cole plot’ presents the evolution of the complex electrical impedance, reactance versus resistance, along the frequency as a part of a semicircular locus with the depressed centre. In the plot, the arc is segmented by the resistance axis and the impedance data are drawn along the arc from R_0 to R_∞ . The impedance data plotted are given by the equation for the impedance proposed by Cole (1940). For the application of the Cole equation a constant phase angle must be assumed for the membrane impedivity; the angle is also well indicated in the plot directly as the intersection angle between the radius from the depressed centre of the semicircle and the resistance axis (Cole 1968) or indirectly as the angle between the tangent line to the arc at the intersection point with the resistance axis (Martinsen *et al* 2002). A ‘Cole–Cole plot’ is similar to the ‘Cole plot’ but it contains information about complex permittivity and not about impedance (Cole and Cole 1941).

5. Conclusion

The consequent cell swelling following hypoxia causes measurable alterations in the electric impedance of the tissue. These alterations affect both the real and the imaginary parts, resistance and reactance, and can be measured with the four-electrode method.

Bioelectrical impedance technology is quick, affordable, portable and harmless when used non-invasively. All these characteristics make this type of technology very suitable for use in a clinical scenario.

There are some uncertainties about the evolution of the complex bioimpedance during cell swelling and the effect of the frequency on the sensitivity of the resistance and reactance is one of those issues that should be investigated further. The effect of the skull on the non-invasive measurements of the complex bioimpedance, mainly the reactance, should also be addressed.

A clear fact is that, in order to apply the monitoring of changes of complex bioimpedance to detect threatening episodes of hypoxia, multi-frequency measurements have to be performed. But how to perform these measurements, simultaneously or sweeping between certain selected

frequencies, how many and which frequencies should be monitored, are issues to be approached in order to improve the efficacy of the application of measurement of bioelectrical impedance for the detection of cell swelling.

Independently of these uncertainties, the combination of the monitoring of the electrical bioimpedance of the brain with other monitoring modalities currently in practice, such as EEG activity and cerebral function monitoring (CFM), may improve the effectiveness of current detection methods.

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CURRENT SOURCE FOR WIDEBAND MULTIFREQUENCY ELECTRICAL BIOIMPEDANCE MEASUREMENTS

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Abstract – New research and clinical applications of broadband electrical bioimpedance spectroscopy have arisen, increasing the upper limit frequency used in the measurement systems. The current source is an essential block in any electrical bioimpedance analyzer and must provide an output current virtually constant regarding the working load and the frequency of measurement. To comply with such requirements, the output impedance of the source must be much larger than the working load at any frequency of operation. Originally, single Op-Amp based current sources were used with good performance, but this approach was abandoned when the upper frequency of operation increased. Several approaches have been proposed over the years and, despite the increasing complexity of the designs, the performance of them all degrades markedly near or below 1 MHz – for example, mirrored transconductance amplifiers, current conveyors, floating mirrors etc. In recent years the development of electronic technology has made available devices that allow us to obtain a current source based on a simple, single Op-Amp circuit topology with large output impedance, higher than 100 k Ω , at 1 MHz and above. In this paper the traditional approach of the voltage-controlled current source based on an inverting Op-Amp configuration with the load in the loop is extensively studied, implemented and tested. The experimental and simulation results from such a study have allowed us to propose, implement and test certain enhancements of the basic design. The overall results confirm our idea that the current electronic technology allows us to revisit simple structures for voltage-controlled current sources in multifrequency broadband applications of electrical bioimpedance. The results also highlight the important effect of circuit parasitic capacitances, especially at high frequencies in the order of MHz.

Index Terms: Electrical Bioimpedance, EIT, Bioimpedance Tomography, Current Source, Impedance Spectroscopy.

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1 Introduction

Measurements of Electrical Bioimpedance (EBI) are a well-established method for the study of various properties of body tissues. It is used for patient monitoring of e.g. *respiratory rate* (T. Olsson & L. Victorin 1970) and *tissue states* such as ischemia (M. Genesca *et al.* 2005) in organ transplantation. It is also used for different types of clinical studies, such as assessment of body composition using the BIA method (R. F. Kushner 1992).

Along with technical developments, EBI methods have gained increasing interest among physicians and researchers, and new methods based on spectral analysis of impedance are emerging. Examples of this are *skin cancer screening* (D. G. Beetner *et al.* 2003, P. Aberg *et al.* 2004) and methods for detection of *tumours* (C. Skourou *et al.* 2004, C. Skourou *et al.* 2007), *meningitis* (B. K. Van Kreel 2001), *brain cellular edema* (B. E. Lingwood *et al.* 2002, F. Seoane *et al.* 2005), and *breast cancer* (M. Assenheimer *et al.* 2001). All these applications depend on the EBI recorded over a wide frequency range. The goal is often to obtain an impedance spectrum corresponding to the β -dispersion, *i.e. between a few kHz and up to some MHz*. Thus, EBI measurement systems with characteristics in terms of accuracy, stability and robustness at frequencies above 1 MHz as well as at the traditionally used 50 kHz are required.

A common way of measuring EBI is to inject a constant current and record the resulting voltage across the tissue of interest; see Figure 1. For this method the current source is an important component and its performance will influence the performance of the entire system, particularly with respect to sensitivity, frequency stability and frequency range of operation.

A key parameter of a current source is the output impedance, Z_{out} , as it determines both the operational frequency range and the range of load impedance in which the current source is able to maintain the constant current, I_{out} .

Figure 1. An ideal representation of a 4-terminal voltage over current EBI measurement system.

Over the years different EBI measurement system designs have been proposed and investigated (K. G. Boone & D. S. Holder 1996), including their high-frequency performance. Consequently several designs and approaches in the design of current sources have been implemented and studied, *e.g. current conveyors* (R. Bragos *et al.* 1994), *floating-mirrored transconductance amplifiers* (J. J. Ackmann 1993), *Howland-based topologies* (J.

Jossinet *et al.* 1994) and Negative Impedance Converters (NICs) (A. S. Ross *et al.* 2003, K. H. Lee *et al.* 2006).

All these current sources operate very well at frequencies in the order of kHz, and even at a few hundred kHz. But with the exception of NIC-based sources, the performance degrades significantly with increasing frequency, especially the output impedance. In the NIC-based current sources, the impedance Z_{out} is high at a single discrete frequency but it is unable to keep a large enough Z_{out} in a continuous frequency range. Therefore, NIC-based sources fit well for stepwise frequency sweep systems but are completely unsuitable for true multifrequency measurements.

Advances in the development of integrated circuits have provided electronic circuit designers with reliable new wide-bandwidth Op-Amps allowing us to revisit basic structures, like the Voltage-Controlled Current Source (VCCS) based on a simple, single Op-Amp topology in an inverter configuration; see Figure 2. In this work we study the performance of the VCCS together with two different ways to improve it. We focus specifically on the performance of the output impedance in relationship to both the discrete circuit elements and the Op-Amp intrinsic specifications, *e.g.* the feedback loop resistance, the Op-Amp's differential gain, CMRR and input impedance.

Figure 2. Load-in-the-Loop current source, a traditional implementation of a VCCS based on a single Op-Amp circuit. N.B. $V_{control}$ is DC-free.

The remainder of this paper is organized as follows. In Section II, the general specifications of a VCCS are introduced, and the specific concerns when designing VCCS for biomedical applications are described. In section III, the methods applied in the present study are explained as well as the materials used in the experimental setups. In section IV, the basic single Op-Amp with negative feedback topology as VCCS is studied. In section V, the method to drive the original VCCS circuit is investigated; and in section VI, the approach to decrease the bias current through the load is analyzed. Sections VII and VIII conclude the paper with a general discussion regarding the three studied VCCS circuits and the conclusions drawn from the performed investigation, respectively.

2 Voltage Controlled Current Source

2.1 General Specifications

In general terms, several parameters can be defined as linear specifications for a VCCS: input and output impedances, transconductance, *i.e.* the I_{out}/V_{in} ratio, the transconductance's frequency response, and DC parameters like the input bias current and output DC current for zero input voltage. Input and output ranges and linearity can also be defined.

Some of these parameters, however, are non-critical in the design of a complex circuit which includes system-level calibration. The accuracy of the transconductance value and even its frequency response are systematic and could be calibrated. The input parameters will also produce systematic effects, and the adequacy of the input and output ranges should be ensured by design. The key specification of a current source connected to a variable load Z_L is the output impedance Z_{out} , which also has a frequency response. The ratio between Z_L and Z_{out} gives the systematic error in the current injected to the load at each frequency. If Z_L is unknown and variable, this error is not systematic and should be minimized by forcing $Z_{out} \gg Z_L$ by design.

2.2 Special Considerations for Biomedical Applications

EBI is one of the applications in which the load impedance is unknown and variable. Z_L is composed by the tissue impedance to be measured, and mainly by the electrode impedances, which would present a variation that in some cases could be larger than the impedance under measurement. Thus, Z_{out} should be much higher than these impedance values or, at least, than their variations. This condition could easily be achieved at low frequency but not above 100 kHz, where Z_{out} is dominated by the output capacitance.

The alternative of applying voltage instead of injecting current has several drawbacks. The current is not intrinsically limited, and then the safety is not ensured. The limitation imposed by the standard IEC-60601 is defined in terms of current. The current measurement circuits, which are mandatory in this case, could have the same load-dependent errors as current sources, and the use of a variable current could induce nonlinear effects.

Another condition that arises when applying a current source to a living tissue is the need of decoupling the residual DC-currents by using series capacitors. A DC path should be provided to these currents. The easiest method is the use of a resistor in parallel with the current source, but this will result in a reduction of Z_{out} . The alternative of using a DC-feedback circuit involves a circuit complexity that can be avoided by ensuring a very low value for this DC current.

Figure 3. Equivalent models. (A) Equivalent model of a non-ideal operational amplifier and (B) the equivalent model of the AD844 current conveyor.

3 Material and Methods

3.1 Circuit Analysis

The current source circuits studied in this work have been analyzed by using the equivalent models of a non-ideal Op-Amp and the current feedback amplifier AD844 used as a current conveyor; see Figure 3. For each circuit, an equivalent model of the VCCS has been created and the expression for Z_{out} of the model has been found.

Following (R. C. Jaeger & T. N. Blalock 2004), the circuit input has been analyzed and Z_{ic} , the common-mode input impedance in (1), and Z_{id} , the differential-mode input impedance (2), have been calculated, using the values provided by the manufacturer of the Op-Amp circuits, selected for each of the studied circuit topologies.

$$Z_{ic} = R_{ic} \parallel C_{ic} \quad (1) \quad Z_{id} = R_{id} \parallel C_{id} \quad (2)$$

The resulting expressions for the equivalent Z_{in} and Z_{out} have been developed, and their values have been calculated for the same set of values of the discrete components and the integrated circuit specifications of the Op-Amps that were used in each implementation, as described below.

In the analysis of Z_{out} we have considered the gain of the Op-Amp as the relationship between its output and input:

$$V_{out}(s) = A_d(s) \times V_d(s) + A_{cm}(s) \times V_{cm}(s) \quad (3)$$

where A_d is the differential mode gain, A_{cm} is the common mode gain of the Op-Amp, and V_d and V_{cm} are the differential and common mode input voltages of the Op-Amp.

Since the Common Mode Reject Ratio (CMRR) is defined as

$$CMRR(s) = A_d(s) / A_{cm}(s) \quad (4)$$

$G(s)$ can be rewritten as follows:

$$G(s) = A_d(s) \times \left(V_d(s) + V_{cm}(s) / CMRR(s) \right) \quad (5)$$

3.2 Physical Implementation

To compare the model results with results from physical realizations, the current sources were implemented on a single-sided eurocard prototyping board using the following active components:

The Op-Amp integrated circuit LMH6655 in a SOIC package for the implementation of the single Op-Amp VCCS; see section IV.

The current feedback Op-Amp Integrated circuit AD844 in a PDIP8 and the Op-Amp integrated circuit LMH6655 in a SOIC package for the implementation of the current-driven VCCS; see section V.

The VCCS with added DC-path circuit in section VI has not been physically implemented.

3.3 Output Impedance Analysis

Equivalent models for the output of each VCCS circuit have been obtained together with an analytical expression for the corresponding output impedance, Z_{out} . The dependence of Z_{out} with respect to the values of the discrete components and the intrinsic parameters of the active components has been studied by using the obtained model and the expression for Z_{out} .

3.4 Output Impedance Measurements

The output impedance of the implemented current sources has been measured with the impedance analyzer LCR HP4192A in Gain/Phase measurement mode, applying the technique used by Bertemes-Filho in (P. Bertemes-Filho *et al.* 2000). The obtained measurement results have been compared with the calculated values resulting from the output impedance analysis.

4 Single Op-Amp VCCS

4.1 General Considerations

Figure 4 illustrates one of the first examples of a single Op-Amp circuit VCCS with floating load (D. Sheingold 1966), known as *load-in-the-loop* current source. With an ideal Op-Amp the characteristics of the VCCS are determined solely by the passive components, but in real implementations the performance of the source at higher frequencies will depend largely on the non-ideal properties and specifications of the Op-Amp.

Figure 4. The circuit under study, the Load-in-the-Loop Current Source.

4.2 Circuit Analysis Results

Output Current

The VCCS's output current, I_{out} , is given by the ratio between V_{in} and R_{in} ; see (6). R_{in} is then the transconductance of the current source.

$$I_{out} \approx I_{in} = \frac{V_{in}}{R_{in}} \quad (6)$$

Figure 5. Equivalent circuit used to calculate the output impedance of the VCCS.

Output impedance

The output impedance Z_{out} of the VCCS is found from the equivalent circuit in Figure 5. The analytical expression for the Op-Amp's and the overall VCCS's input impedance is written in (7) and (8) respectively as:

$$Z_i = 2Z_{ic} \parallel Z_{id} \quad (7) \quad \text{and} \quad Z_{in} = R_{in} \parallel Z_i \quad (8)$$

The output impedance of the VCCS, Z_{out} , is written in (9), with the corresponding equivalent circuit shown in Figure 6:

$$Z_{out} = R_{safe} + R_f \parallel \left(Z_o + (R_{in} \parallel Z_i) opz(s) \right) \quad (9)$$

Figure 6. Equivalent circuit for the output impedance of the VCCS circuit. Note that R_{ic} in parallel with C_{ic} and R_{id} in parallel with C_{id} define Z_{ic} and Z_{id} respectively as indicated in (1) and (2).

where the Operational Amplifier Impedance factor opz is defined as:

$$opz(s) = (A_d(s) + 1) \left(1 - \frac{1}{2CMRR(s)} \right) \quad (10)$$

Table 1. Values & Expressions used in the Calculations.

Symbol	VALUE/EXPRESSION	Frequency Dependence & Notes
R_f	390 kOhms	
R_{safe}	390 Ohms	
R_{in}	6.2 kOhms	
R_{id}	20 kOhms	
C_{id}	0.55 pF	
R_{ic}	4 MOhms	
C_{ic}	0.9 pF	
$A_d(j\omega)$	$A_{d0} / \left(1 + j\omega / \omega_0 \right)$	$A_{d0} = 67\text{dB}$ $\omega_0 = 2\pi 125000 \text{ radxs}^{-1}$
$CMRR(j\omega)$	$CMRR_o / \left(1 + j\omega / \omega_0 \right)$	$CMRR_o = 90\text{dB}$ $\omega_0 = 2\pi 9000 \text{ radxs}^{-1}$

Only values related to Z_{out} .

The magnitude of the output impedance has been calculated with the values from Table 1, and the frequency dependence is plotted in Figure 7.

4.3 Output Impedance

The measured output impedance values from the experimental tests are shown in the following figures, Figs. 7-9.

For validation of the obtained analytical expression for Z_{out} , the measurements and the calculation results are plotted together in Figure 7. The dotted trace corresponds to the measured values, and the continuous to the calculated Z_{out} .

Fig. 7. Plotted output impedance, measured and calculated.

Figure 8. Plotted output impedance, for different values of $R_{in} = 1 \text{ k}\Omega$, $2.2 \text{ k}\Omega$, $3.9 \text{ k}\Omega$ and $6.2 \text{ k}\Omega$. **N.B.** $R_f = 390 \text{ k}\Omega$. The continuous trace is the fitted sigmoid curve for each of the measurements

The measured and calculated impedances agree well. Both the impedance at 1 MHz and the frequency for impedance 100k Ω are indicated. **N.B.:** the values used in calculations as well as the values selected for the physical implementation are the same, and they are indicated in Table I.

The influence of the resistance R_i at the input of the VCCS, and the feedback resistor R_f on the output impedance Z_{out} , is shown in Figure 8 and Figure 9 respectively.

Figure 9. Plotted output impedance for different values of R_f . $R_f = 160$ k Ω , 390 k Ω , and open circuit. **N.B.** $R_{in} = 3.9$ k Ω . Fitted sigmoid curves in continuous trace.

4.4 Discussion

Output Impedance Equivalent Circuit

There is good agreement between calculated and measured impedances in the entire frequency range of application, from a few kHz to some MHz. The opz factor contains the contribution to Z_{out} of the Op-Amp's parameters, dominated by the differential gain of the Op-Amp, $A_d(s)$, making the frequency of the dominant pole of $A_d(s)$ the key to obtaining a large output impedance at high frequencies.

Regarding R_{in}

Increasing the value of R_{in} increases the value of Z_{out} . The main role of R_{in} is to set the value of the most important parameter of a current source: the output current. Increasing the value of R_{in} requires a higher voltage of the source driving the current source, and this provides a design criterion for the choice of value for R_{in} .

Regarding R_f

The feedback resistor is in parallel connection to the output of the current source, acting as current divider of the output current. Therefore, the smaller the value of R_f the smaller the output impedance becomes. The main function of R_f is to provide a path for the bias current of the Op-Amp, because usually in a bioimpedance measurement system the

capacitance of the electrodes and the DC-uncoupling capacitor in series with the driving voltage source eliminate any path to ground for the Op-Amp bias currents, as mentioned in section 2.2.

5 Current-Driven VCCS

5.1 General Considerations

The influence of the VCCS's equivalent input impedance, Z_{in} , on the overall output impedance of the VCCS circuit, Z_{out} , is clearly realized from (8) and (9) in section IV.B. Since at high frequencies Z_{out} is essentially proportional to Z_{in} , we have modified the original load-in-the-loop VCCS topology from Figure 4, replacing the Thevenin source V_{in} by a Norton source, thereby increasing R_{in} to $R_{in} + Z_{out_I}$, where Z_{out_I} is the output impedance of the Norton source; see Figure 10.

Figure 10. Proposed design. A current source based on a single Op-Amp circuit in inverting configuration driven by current. Note that the new R_{in} equivalent is R_{in} in series with Z_{out_I} .

The implemented current source is driven by a primary VCCS using the current conveyor AD844 in a previous stage; see Figure 11.

Figure 11. Current source proposed. A Load-in-the-Loop VCCS circuit driven by a current conveyor.

5.2 Circuit Analysis Results

Output current.

The transconductance of the circuit proposed in Figure 11 is determined by the relationship between V_{in} and R_{iref} at the input of the AD844. In this way, the output current is generated independently of any element related to the output impedance.

$$I_{out} \approx I_{in} = \frac{V_{in}}{R_{iref} + R_{IN844}} \quad (11)$$

Figure 12. Equivalent circuit model used to calculate the output impedance of the proposed current source in Figure 11.

Output impedance

To obtain an analytical expression for the output impedance in (12) the equivalent model depicted in Figure 12 was analyzed.

$$Z_{out} = R_{safe} + R_f \parallel \left(Z_o + \left((R_{in_b} + R_t \parallel C_t) \parallel Z_i \right) opz(s) \right) \quad (12)$$

$$Z_i = 2Z_{ic} \parallel Z_{id} \quad (13)$$

As expected (12), resembles the expression in (9) with the difference that the term R_{in} is now replaced by the term $R_{in_b} + R_t \parallel C_t$. In the original *load-in-the-loop* circuit according to (8), the input impedance Z_{in} was set by the value of R_{in} , because typically the value of R_{in} is smaller than Z_i in the operational frequency range. Whereas in the proposed circuit, the term limiting the value of Z_{in} at high frequencies is Z_i .

All the values used in the calculations and in the circuit implementation are found in Table II. Z_{id} is the differential input impedance, $R_{id} \parallel C_{id}$ as in (2), and Z_{ic} is the common mode input

TABLE II. Values and Expressions for the Electrical Parameters

Symbol	VALUE/EXPRESSIO N	Frequency Dependence & Notes
R_f	390 kOhms	
R_{safe}	390 Ohms	
R_{in}	6.2 kOHMS	
Z_o	0.08 Ohms	<i>Imaginary part discarded</i>
R_{id}	20 kOhms	
C_{id}	0.55 pF	
R_{ic}	4 MOhms	
C_{ic}	0.9 pF	
R_{in_b}	6.2 kOHMS	
R_t	3 MOhms	
C_t	4.5 pF	
C_{i_p}	10 pF	<i>Parasitic</i>
C_{t_p}	10 pF	<i>Parasitic</i>
C_{f_p}	0.25 pF	<i>Parasitic</i>
$A_d(j\omega)$	$A_{d0} / \left(1 + j\omega / \omega_0 \right)$	$A_{d0} = 67\text{dB}$ $\omega_0 = 2\pi 125000 \text{ radxs}^{-1}$
$CMRR(j\omega)$	$CMRR_0 / \left(1 + j\omega / \omega_0 \right)$	$CMRR_0 = 90\text{dB}$ $\omega_0 = 2\pi 9000 \text{ radxs}^{-1}$

Figure 13. Plots of the output impedance, measurements and calculations, for each of the circuits.

impedance, $R_{ic} \parallel C_{ic}$ as in (1), of the LMH6655 Op-Amp circuit, building up Z_i as in (13), while $R_t \parallel C_t$ is the output impedance of the terminal T_z of the AD844 current conveyor circuit. These values are obtained from the respective datasheets.

5.3 Impedance Measurements

Figure 14. Plots of the output impedance, measurements and calculations, for the proposed circuit, including parasitic capacitances.

Figure 13 illustrates the calculated Z_{out} of the original VCCS and the current-driven VCCS. As expected, the output impedance of the current conveyor-driven circuit is larger than the output impedance of the original circuit. The experimental measurements revealed a certain increment; at 1 MHz, for instance, the measured Z_{out} of the improved circuit is 16% larger than the output impedance of the original VCCS. Note in Figure 13 that the observed increment is not as large as expected from the calculations.

Figure 14 shows again the measured Z_{out} and the calculated Z_{out} for the enhanced circuit, but this time the effect of parasitic capacitances is accounted for: C_{i-p} is the parasitic capacitance associated with the input of the LMH6655, C_{t-p} is associated with the output of the AD844 and C_{f-p}

is associated with the feedback loop of the Op-Amp circuit. Now there is good agreement between the measured and the calculated impedance values. As can be observed in the figure, both plots fit relatively well, especially at high frequencies. Thus, around 1 MHz and above, the Z_{out} is highly influenced by parasitic capacitances.

5.4 Discussion

Output Impedance

Judging from the calculations, Z_{out} has indeed increased with the increase in Z_{in} that results from the introduction of the current drive. The Op-Amp impedance factor, opz (10), plays the same role in the current-driven VCCS as in the pure VCCS. As is seen in (9), opz is a crucial factor that links the value of Z_{in} directly to the output impedance Z_{out} . As the factor opz is frequency-dependent, decreasing with increasing frequency, opz is one key factor behind the decreasing output impedance Z_{out} at higher frequencies.

Parasitic Capacitances

At higher frequencies (1 MHz and above), the effects of the circuit and parasitic capacitances are no longer negligible. In the case of the current-driven VCCS, connecting the T_z output of the AD844 to the input of the original VCCS introduces a new parasitic capacitance. This capacitance not only cancels the high input impedance effect obtained by introducing the current conveyor; it also increases the effect of the already

Figure 15. Equivalent circuits for the output impedance of the proposed current source circuit. (a) The equivalent circuit of the ideal VCCS, (b) including parasitic capacitances, indicated with discontinuous trace, and (c) simplified circuit equivalent. **N.B.** R_{safe} and Z_o are very small and can be neglected.

present input capacitance at the inverter input of the Op-Amp. The resulting input capacitance, which is approximately $>90\%$ parasitic, attenuated by the factor opz , is an important contributor to the output capacitance of the current source; see the equivalent circuit for the output impedance in Figure 15.

A careful circuit implementation, *i.e.* use of only SMD components, short connections, avoiding parallel tracks, etc, would probably reduce the effect of the parasitic capacitances significantly. It is evident that a microelectronic implementation as integrated circuit will provide the best performance and will be the most robust option to avoid parasitic capacitances, especially $C_{t,p}$.

6 VCCS with Additional DC Path to Ground

6.1 General Considerations

As the load does not necessarily provide a DC path for the current, R_f , the resistance in the feedback loop is necessary, as connected in Figure 4 and Figure 11. Without a DC feedback, the gain of the circuit would be the same as that of the Op-Amp, *i.e.* extremely high, and the circuit would get saturated. As R_f is in parallel with the VCCS output, it will clearly contribute to the circuit's output impedance, decreasing its value and setting the upper limit of the total output impedance at low frequencies.

An increase or removal of R_f would increase the total Z_{out} considerably, as experimental measurements showed in Figure 9 (dotted line with empty circle markers), but any of them cannot be considered without providing an alternative path to ground for the Op-Amp's bias current. Following the prior idea, the original VCCS circuit has been modified as in Figure 16, by adding a new resistor R_b between both the Op-Amp's inputs and ground, creating a new DC path to ground. Note that R_f has not been removed but its value has been increased significantly.

Figure 16. VCCS circuit under study. Proposed modification inside the dotted area.

6.2 Circuit Analysis Results

Output Current

As in the original circuit, the VCCS's output current, I_{out} , is defined by the relationship between V_{in} and R_{in} as defined in (14), the same as (6).

Therefore, once again the main role of R_{in} is to define the transconductance of the current source, while the role of R_b is to provide a path to ground for most of the DC current.

$$I_{out} \approx I_{in} = \frac{V_{in}}{R_{in}} \quad (14)$$

Output impedance

The circuit shown in Figure 17 is the equivalent circuit for the output impedance for the overall VCCS, and the corresponding analytical form of Z_{out} is written in (15). Note that it is the same general expression as in the two previous cases, with the difference that the term Z_i has changed from

Figure 17. Equivalent circuit for the output impedance of the VCCS circuit.

(7) and (13) to (16). Due to the connection of both R_b s, Z_i has increased and such an increment of Z_i will contribute as well as the increment of R_f to increase the total value of Z_{out} .

$$Z_{out} = R_{safe} + R_f \parallel \left(Z_o + \left(R_{in} \parallel Z_i \right) opz(s) \right) \quad (15)$$

$$Z_i = R_b \parallel 2Z_{ic} \parallel \left(Z_{id} + R_b \parallel 2Z_{ic} \right) \quad (16)$$

6.3 Resulting Output Impedance

The obtained output impedance with the bias resistors connected at the Op-Amp's input is much larger than the output impedance of the original VCCS; see Figure 18.

Figure 18. Calculated impedance for both VCCS circuits. Original VCCS: $R_{in} = 8k\Omega$, $R_{safe} = 390\Omega$, $R_f = 390k\Omega$. Modified: $R_b = 100k\Omega$, $R_f = 3.9M\Omega$. R_{in} and R_{safe} are the same in both VCCS circuits and the rest of the values used are from Table I.

As is easy to observe in Figure 18, the modified VCCS provides a very large output impedance at low and medium frequencies, in the order of $M\Omega$, keeping Z_{out} 's value above $100\text{ k}\Omega$ up to 3 MHz .

6.4 Discussion

Output Impedance:

The value of R_f predominates at low and medium frequencies, as was expected and was shown before in the two previous cases. This confirms our original hypothesis that, by using a R_f larger than in the original circuit from Figure 4, the VCCS will obtain a larger Z_{out} . But the obtained increment in the value of Z_{out} is not only due to the use of a larger resistance in the feedback loop. The insertion of R_b between ground and the non-inverting input of the Op-Amp increases the value of Z_i from (7) to (16); therefore R_b plays an important role in the expression for Z_{out} as well, especially at high frequencies. For instance at 1 MHz , just by increasing from $390\text{ k}\Omega$ to $3.9\text{ M}\Omega$ the value of R_f in the original circuit, the obtained output impedance would be smaller than $200\text{ k}\Omega$ while in this case the value is 282 , almost 50% larger.

Bias Current

The added DC path to ground created by the connection of R_b to the inverting input of the Op-Amp circuit creates a current divider for the bias current from the inverting input, and due to the large value of R_f only a small portion, approximately R_b/R_f , of the bias current will flow through R_f . Most of the bias current flows through R_b .

R_f Removal and Offset Voltage

As long as R_f is present in the circuit, its value will limit the DC gain of the circuit, so as long as the input voltage offset is kept below $V_{cc}/(1+R_f/R_b)$ the Op-Amp will be free from saturation; but if R_f is removed, the DC gain of the Op-Amp will be the gain in open loop configuration, and the input voltage offset must be kept below V_{cc}/A_{d0} , where A_{d0} is the differential gain at DC of the Op-Amp.

7 General Discussion

Considering the simplicity of the Op-Amp equivalent model used for the circuit analysis, it is surprising to observe that the analysis results have been so accurate and shown such a concordance with the experimental measurements.

The more important parameters of the Op-Amp circuit for the total output impedance of this type of VCCS circuits are: the input impedance Z_i , the differential gain $A_d(s)$ and the Common-Mode Rejection Ratio $CMRR(s)$. The combination of the last two defines the opz factor; see (10).

The multiplication of Z_i with the opz factor provides the major contribution of the Op-Amp to the total output impedance of the VCCS.

The opz factor not only multiplies and propagates to Z_{out} the Op-Amp's input impedance, but any impedance at the input. The main contributing parameter is the differential gain $A_d(s)$; therefore its maximum value, A_{d0} in a single pole system, as well as its frequency response, the frequency of the dominant pole, are critical for the output impedance of the VCCS circuit.

For high-frequency applications, in order to keep a large value of Z_{out} the value of the differential gain at the frequency of interest must be large enough. This situation usually can be guaranteed when the frequency of the dominant pole is very high. Wideband Op-Amps are a good choice for this type of VCCS because, even when they have a relatively low open loop gain, they keep the gain up to high frequencies since the dominant pole is at very high frequencies.

We have observed that the VCCS's output impedance depends not only on the Op-Amps parameter, but also on external elements of the VCCS circuit: R_f and R_{in} . These two elements have an important impact on the total impedance, and both are subjected to critical interrelationships with the Op-Amp parameters and the VCCS specifications.

The transconductance in a VCCS is one characteristic of the greatest importance, and it must be as robust and constant as possible. Therefore, at first, it should be completely independent of any element that contributes to the output impedance.

When using VCCS in biomedical applications, the controlling voltage normally is DC-free, due to using a DC-blocking filter at the input of the VCCS, and the load is also kept DC-free by the electrode capacitances. In this case, the bias currents of the Op-Amp gain a certain importance, and for the correct functioning of the Op-Amp they have to be taken care of properly, setting limits for other VCCS elements like R_f . The proposed VCCS circuit implementation deals with the bias currents' effect to a certain extent. Another way to minimize such an effect would be using Op-Amps with J-FET inputs, which generally have extremely small bias currents.

Taking all these factors and issues into consideration, we could say that the best implementation of this type of VCCS is a mixture of the topologies tested in this work: a current conveyor circuit driving a single J-FET Op-Amp-based VCCS topology with a DC path to ground for the bias current at the inputs of the Op-Amp.

Even with the perfect current source design for high frequencies, its performance can be disastrous due to the effect of parasitic capacitances. Parasitic capacitances are always of high importance in any type of AC circuit, but they become critical at high frequencies. Considering that in a biomedical application there will be always parasitic capacitances associated with the patient and other elements of the measurement set-up, when implementing the circuitry special attention must be paid to avoiding parasitic capacitances which are intrinsic to design and manufacturing processes.

8 Conclusions

Current sources for electrical bioimpedance measurements with appropriate performance for wideband multifrequency applications can be implemented by using a single Op-Amp circuit. The presented circuit analysis, which relates the VCCS main parameter Z_{out} to the Op-Amp parameters, allows us to select the most adequate commercial Op-Amp for a given VCCS specification.

The Op-Amp equivalent circuit employed is very simple, but its use for the analysis of this type of VCCS circuits is appropriate and it has been very useful in this work. The total output impedance for this type of VCCS can be approximated by a general equivalent circuit modeled as three impedances building up a parallel bridge; see Figure 19, where Z_{in} is the input impedance of the VCCS considering the Op-Amp ideal, Z_i is the equivalent input impedance of the Op-Amp from the inverting input to ground, Z_f is the impedance in the feedback loop, and $opz(s)$ is the Op-Amp impedance factor as defined in (10).

Figure 19. General equivalent circuit for the output impedance of a Load-in-the-Loop VCCS. N.B. the values of Z_o and R_{safe} are considered negligible.

The requirements for such Op-Amp circuits are basically three: large differential input impedance, low bias currents and, most importantly, an open-loop gain with the first pole in its frequency response as high in frequency as possible.

In this frequency range, in the order of 1 MHz, the effect of parasitic capacitances is decisive for the performance of the current source. In order to minimize their destructive effects, parasitic capacitances must be taken into account at the earliest stage of the circuit design, avoiding their existence if possible or at least minimizing their value.

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CURRENT SOURCE DESIGN FOR ELECTRICAL BIOIMPEDANCE SPECTROSCOPY

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Introduction

The passive electrical properties of biological tissue have been studied since the 1920s, and with time the use of Electrical Bioimpedance (EBI) in medicine has successfully spread (H. P. Schwan 1999). Since the electrical properties of tissue are frequency-dependent (H. P. Schwan 1957), observations of the bioimpedance spectrum have created the discipline of Electrical Impedance Spectroscopy (EIS), a discipline that has experienced a development closely related to the progress of electronic instrumentation and the dissemination of EBI technology through medicine.

Historically, the main developments in EIS related to electronic instrumentation have been two: firstly, the progressive shift from ‘real studies’, where only resistance is measured, to ‘complex studies’ where the reactance is also measured. Secondly, the increasing upper limit of the measurement frequency makes it possible to perform studies in the whole β -dispersion range (H. P. Schwan 1957).

Basically, an EBI measurement system obtains the relationship between voltage and current in an object, obtaining the impedance or the admittance according to (1) and (2). In EBI most of the systems measure the impedance of the tissue, therefore injecting a known current and measuring the corresponding voltage drop in the biological sample. See Figure 1(A).

$$Z = \frac{V}{I} \quad (1)$$

$$Y = \frac{I}{V} \quad (2)$$

In an EBI measurement system the current source plays a very important role, and its features are critical for the overall performance of the measurement system – especially for the frequency range of operation and the load range that the system is able to measure. The use of current driving instead of voltage driving is the most extended approach (J. P. Morucci & B. Rigaud 1996), which applies an intrinsically safe current-limiting mechanism and reduces the possible nonlinearities. Given that the signal generator usually provides a voltage at its output, the current driver often is a Voltage Controlled Current Source (VCCS).

Figure 1. (A) An ideal representation of a 4-terminal voltage over current EBI measurement system.

Background

The functional purpose of a current source is to generate an electric current signal with a specific magnitude. Therefore, the output current is the most important characteristic of a current source, and parameters related to the output current define the performance of the source.

An ideal current source will provide exactly the same current to any load independently of its value at any frequency. To fulfil this aim, the output impedance Z_{out} must be very large, ideally ∞ , at all frequencies. See Figure 1(B).

In practice the frequency range is limited to an operational frequency range at which the value of the output impedance of the source is very large in comparison with the value of the load. In bioimpedance applications, a commonly accepted value is at least 100 k Ω .

As a safety measure in biomedical applications, when current is injected into the body, the accumulation of electrical charges is avoided as much as possible. Therefore the DC component of the stimulating current should be zero.

Over the years there have been two main approaches in current source design: voltage-based structures and current-based structures. In voltage-based structures, what is responsible for the generation of the output current is the voltage in one or more nodes of the active circuit, *e.g. the virtual ground in the case of Op-Amps*. In a current-based structure, the output current is generated by an active device with intrinsic current-mode operation, *e.g. Transconductance Amplifiers and Current Conveyors*.

Voltage-Based Structures

Howland-based circuits and Load-in-the-Loop structures are the most common approaches to implement VCCS, and both are based on a single Op-Amp circuit. Another family of VCCS is based on a differential amplifier with unity gain and positive feedback.

Load-in-the-Loop

This current source design is one of the approaches first used to implement current sources with floating load (D. Sheingold 1966). In Fig. 2(A) it is possible to observe the principle of operation for the output current generation and the importance of the Op-Amp circuit. Note that as long as the Op-Amp provides a virtual ground and infinite input impedance, the output current is independent of the value of the load, *i.e. the output impedance is infinite*. Since the characteristics of an Op-Amp circuit are frequency-dependent, the output impedance of the current source exhibits a similar dependence. Equation (3) shows the analytical expression for the output impedance, Z_{out} , of the current source circuit in Fig. 2(A),

Figure 2. (A) A Voltage Controlled Current Source implementation with Load-in-the-Loop. (B) A Voltage Controlled Current Source implemented with the original Howland current circuit. (C) VCCS based on a differential amplifier with positive feedback.

considering the frequency dependence of the differential gain (F. Seoane *et al.* 2007a). Z_o and Z_{in} are the output and input Op-Amp impedances, and Z_1 is the impedance which determines the transconductance of the VCCS.

$$Z_{out} = \left(Z_o + (Z_{in} \parallel Z_1) (A_d(s) + 1) \left(1 - \frac{1}{2CMRR(s)} \right) \right) \quad (3)$$

Howland Source

This circuit topology (D. Sheingold 1964) is probably the structure most used as a current source in EBI. Figure 2(B) shows the original circuit for the Howland source. When the impedance bridge is balanced, *i.e.* $Z_1 \times Z_3 = Z_4 \times Z_2$, the output current is proportional to V_{in} and only dependent on the value of Z_2 (4). Regarding the output impedance, as long as the bridge is balanced the output impedance of the current source is infinite; see (5).

$$I_{out} = \frac{V_{in}}{Z_2} \quad (4) \quad Z_{out} = \frac{Z_1 \times Z_2 \times Z_4}{Z_2 \times Z_4 - Z_1 \times Z_3} \quad (5)$$

The expression in (6) is the output impedance of the Howland source, considering the frequency dependence of the differential gain of the Op-Amp circuit.

$$Z_{out}(s) = \left(1 + \frac{A_d(s)}{1 + \frac{Z_3}{Z_1}} \right) \times (Z_1 \parallel Z_3) \quad (6)$$

Even using perfectly matched resistors, there is a degradation of Z_{out} due to the Op-Amp frequency response. In addition, resistors' tolerance imposes a finite Z_{out} even at low frequencies. Note that, for the sake of simplification of the final expression, it is assumed that $Z_2 = Z_1$ and $Z_4 = Z_3$, which also balance the bridge.

The Howland circuit has been studied for many years and enhancements on this topology have been implemented and tested (P. Bertemes-Filho *et al.* 2000).

Structures Based on a Differential Amplifier

Several VCCS structures can be reduced to a differential amplifier with unity gain and positive feedback, as depicted in Figure 2(C). As shown in (7), in the case where the amplifier differential gain A_d is equal to 1, the output current I_{out} is load-independent, *i.e. the output impedance of the current source is infinite*.

$$I_L = \frac{(A_d - 1) \times V_L - A_d \times V_{in}}{Z} \Rightarrow I_L \Big|_{A_d=1} = -\frac{V_{in}}{Z} \quad (7)$$

The differential amplifier admits several implementations, monolithic or with discrete Op-Amps, and typically with classical structures having one, two or three devices. The output impedance of the resulting VCCS is not ideal and depends on the accuracy of the condition $A_d = 1$, as shown in (8).

$$Z_{out}(s) = \frac{Z}{1 - A_d(s)} = \frac{Z}{\varepsilon} \frac{1 + \frac{s}{\omega_o}}{1 + \frac{s}{\omega_o \varepsilon}} \quad (8)$$

At very low frequency its value is $Z_0 = Z/\varepsilon$, with ε being the relative error in A_d . The first pole of Z_0 depends on the first pole of A_d and again on ε . Both this error and its frequency behaviour will depend on the structure used to build the differential amplifier, on the tolerance of devices, and on the frequency response and the Common Mode Rejection Ratio (CMRR) of the Op-Amps.

Current-Based Structures

Current sources based on current-mode structures (C. Toumazou *et al.* 1989) involve a transconductor at device level, *e.g. transistor*, or at circuit level. The resulting VCCS circuits normally use less passive components and are simpler than those based on Op-Amps, making them more suitable for integrated implementations. Their frequency bandwidth is higher than that obtained with Op-Amps based on the same technology.

Figure 3. (A) Current conveyor: symbol. (B) Current conveyor simplified schematic. (C) OTA, schematic symbol for an Operational Transconductance Amplifier.

Most circuits based on current-mode devices are open-loop structures, which limits their accuracy. The core of circuit-level current-mode structures is usually a Current-Conveyor (CCII) or an Operational Transconductance Amplifier (OTA). Both could be directly used to build VCCS circuits.

Current Conveyors

The Current Conveyor (CCII) (A. S. Sedra *et al.* 1990) is a current-mode building block whose acronym stands for Second Generation Current Conveyor. CCII is a three-port device with two inputs (X, Y) and an output (Z). Figure 3(A) displays its symbol and Figure 3(B) the simplified diagram of the usual implementation. The Y input is a high-impedance node whose voltage is copied to X, the low-impedance node. The input current at X node is copied to the Z high-impedance output node. To implement a VCCS with a CCII, a voltage generator V_i is connected to the Y node and a resistor R between ground and the X node. Thus, node Z generates the current replicated at node X, providing a large output impedance. Note that, since $i_x = V_i/R = i_{out}$, R is the VCCS transconductance. The main limitation on its use is the lack of commercial availability, e.g. *Analog Devices AD844*, *TI-Burr-Brown OPA660*. There are several EBI and EIT instruments that include CCII in their structure (O. Casas *et al.* 1996, R. J. Yerworth *et al.* 2002).

Transconductance Amplifiers

In essence, an Operational Transconductance Amplifier (OTA) is an amplifier that generates an output current linearly proportional to its voltage differential inputs, as expressed in (9). The gain of an OTA is not just gain, but transconductance, denoted by g_m and adjustable by the value of input currents I_{abc} and I_{bias} . See Figure 3(C).

$$I_{out} = (V_{in+} - V_{in-}) \times g_m \quad (9)$$

Since the OTA is a current output device, its output impedance should be very large. Therefore, considering its ideal features of output current controlled by voltage with a linear relationship and high output impedance, the OTA circuit is the perfect VCCS.

The Effect of Parasitic Capacitances

Parasitic capacitances can be found associated with many elements of an impedance measurement system. They may be associated with the output of the current source, C_o , the stimulating leads, C_m , and the sensing leads, C_{in} , as well as between the electrodes, C_{ie} , the system's ground and earth, C_{is} and even the patient and earth, C_{bg} .

All these parasitic capacitances create pathways for the current to leak away from the tissue for measurement, e.g. *the patient*. The origin of such capacitances and their effects have been studied in detail by several authors, e.g. *Scharfetter* (H. Scharfetter *et al.* 1998).

The main effect of parasitic impedances associated with the current source is to reduce the output impedance of the source with frequency. This effect may be negligible in the frequency range of operation of the measurement system, but otherwise the parasitic capacitances set the frequency limit of operation of the impedance meter, especially in those without a reference current measurement. The output impedance can be affected severely by parasitic capacitances associated with the output, C_o (F. Seoane *et al.* 2007a), but also by parasitic capacitances intrinsic to the current source circuitry (*ibid.*). In practice, circuits without active capacitance compensation exhibit a certain output capacitance, including CCII and OTA, typically of 3–5 pF. This fact limits the output impedance to 50 k Ω at 100 kHz.

Challenges & Design Trends for Current Sources in EIS Systems

The selection of a specific approach for the design of the current source reduces, in most of the cases, the versatility of the measurement instrument. Therefore, current source design usually is application-specific. Currently, electronic instrumentation for wideband multifrequency measurements is an important research area within electrical bioimpedance spectroscopy, pursuing the goal to widen the frequency band of operation of the EIS measurement systems.

Multifrequency Measurements

Biological tissue, due to its structure and the electrical properties of its constituents, presents an electrical impedance that varies with frequency (H. P. Schwan 1957). Therefore the impedance at a certain frequency is often different from that at another frequency, and for the same reason the impedance spectrum of a tissue or subject may provide information regarding the status of the tissue or its composition, for *e.g.* *Body composition and skin cancer screening*.

Currently, there are two methods to obtain the impedance spectrum of a tissue: using true multifrequency systems or sweeping frequency systems. The latter uses an excitation signal containing just one tone, sometimes two or even three, at a specific frequency. The spectrum impedance is obtained after several excitations by sweeping the frequency of the applied tone to cover the frequency range of measurement. In contrast, multifrequency systems use an excitation signal containing several tones, often a multisine (R. Bragos *et al.* 2001), obtaining the impedance spectrum of the sample after only a single excitation.

These two methods impose different requirements on the current source. Multifrequency systems need a current source able to provide a large output impedance simultaneously in the complete frequency range of measurement, while current sources for sweeping systems only need to

provide a large output impedance at the frequency of the tone or tones contained in the excitation signal.

Enhancing Design Approaches

There are many factors that influence the performance of an impedance measurement system, and each type of current source exhibits an intrinsic robustness to different sources of errors. For instance, in previous paragraphs we have introduced the effect of parasitic capacitances that shunt the stimulating current away from the measurement tissue or patient. Just by selecting one type of current source, the robustness against certain parasitic effect can be improved; *e.g. load-on-the-loop structures are more robust against leads' parasitic capacitance than grounded-load structures, like Howland*. Such improvement is often slight, although in some cases it is enough to obtain a suitable current source for a specific application.

In most cases, circuit design approaches for current sources are used to specifically minimize or even eliminate sources of error in EBI systems, such as parasitic capacitances.

Symmetrical Current Sources

The use of symmetrical current sources allows us to minimize the common mode voltage at the load, thereby reducing the errors due to limited CMRR of the voltage measuring differential amplifier. The previously described current sources are referred to ground, except the load-in-the-loop source, which is floating but not symmetrical. Symmetrical current sources are presently implemented by connecting the load between the outputs of two complementary current sources as in Figure 4. The current at a given moment is injected by one of the sources and drained by the other one. The unavoidable impairment between both sources creates a differential current which finds a path to ground through

Figure 4. (A) Floating current source. (B) Implementation based on two equal sources referred to ground.

the common mode output impedance Z_{Ocm} of the current sources. This fact would generate again a large common mode voltage at the load, unless a common mode feedback (CMFB) circuit is used (O. Casas *et al.* 1996, H. G. Goovaerts *et al.* 1999).

Negative Impedance Converters

There are several different circuit topologies to implement: Negative Impedance Converters (NICs). Figure 5(A) shows a well-known NIC topology (A. S. Sedra & P. O. Brackett 1979), widely used in EIS and EIT (A. S. Ross *et al.* 2003, K. H. Lee *et al.* 2006). Such topology is able to synthesize an inductance between the points *a* and *b* with the value given by (10).

$$L = \frac{R_1 \times R_3 \times Z_4 \times C_1}{Z_2} \quad (10)$$

Therefore, by connecting the NIC circuit in parallel to the output of the current source as in Figure 5(B), it is possible to obtain an equivalent output impedance that is only resistive, eliminating any capacitance associated with the output Z_{eq} , independently of its origin. Tuning the discrete components of the NIC to make L comply with (11), the capacitive part of Z_{eq} in Figure 5(B) can be cancelled at any specific frequency, ω_s . This yields at ω_s an output impedance only real and significantly large, in the order of $G\Omega$ (Ross 2003).

Figure 5. (A) Circuit schematic for a Generalized Impedance Converter for Inductances. (B) Equivalent circuit for the connection of the NIC circuit to the output of the current source.

$$L \Big|_{IM\{Z_{eq}\} \rightarrow 0} = \frac{I}{\omega^2 (C_o + C_{par})} \quad (11)$$

Despite the possibility to obtain a current source with virtually no reactive component, the use of NICs is limited for several reasons:

- An NIC increases the instability of the system.
- NIC circuits need to be trimmed for each frequency before each measurement, limiting the use of the VCCS to only sweeping systems.
- The trimming process introduces unpractical time delays between measurements, and when the measurement system incorporates an automatic trimming block, such a block may be as complex as the rest of the measurement system.

Single Op-Amp Basis

Some of the sophisticated alternatives in the VCCS design appeared to overcome the drawbacks of single Op-Amp circuits implemented with the available Op-Amps at that time. Modern voltage and current-feedback amplifiers, with gain-bandwidth products of hundreds of MHz, allow us to retrieve these structures with good results for not highly demanding applications.

Current Conveyor + Load-in-the-Loop

Combining basic structures in cascade, where the CCII feeds current to a secondary current source, it is possible to obtain a VCCS circuit that is simple and has extraordinary performance, exhibiting large output impedance values at frequencies higher than 1 MHz (F. Seoane *et al.* 2007a). The simplicity of this approach allows an easy microelectronic implementation avoiding any parasitic capacitance associated with internal connections and discrete components of the VCCS. The drawback of this design is that it does not allow the implementation of a symmetric current source; thus it requires an external CMFB circuit to minimize the common voltage at the load.

Differential Difference Amplifier

A modern approach to the implementation of the VCCS based on a differential amplifier with unity gain is that which uses a Differential Difference Amplifier (DDA) to implement the differential amplifier. This structure allows high bandwidth and the unity gain is not compromised by resistors matching. (J. Ramos-Castro *et al.* 2004) describe an isolated front-end for cardiac applications whose current source is built with the AD830. (P. Riu *et al.* 2006) describe a symmetrical current source based on differential amplifiers with unity gain built around AD8130 with intrinsically high pass response, which ensures lower transconductance at low frequencies to improve safety.

Future Development Trends

Modern mixed-mode ICs, *e.g.* *A/D and D/A converters, DDS, programmable gain amplifiers*, usually have differential inputs and outputs, including current outputs in some cases. Differential floating architectures can then be more easily implemented at whole system level. Integrated implementations (N. Terzopoulos *et al.* 2005) will help to reduce parasitic capacitances, but not the intrinsic output capacitance related to devices' loop-gain falling at high frequency. Only active capacitance compensation could allow a further improvement of output impedance. Proposed structures are, however, useful at only a single or a discrete set of frequencies, when using a parallel array of NIC circuits (K. H. Lee *et al.* 2006).

Conclusion

The incessant developments in electronic technology, especially in circuit integration and bandwidth of operation, together with the increasing numbers of applications making use of electrical bioimpedance spectroscopy, guarantee continuous improvement in the performance of electronic instrumentation for electrical bioimpedance measurements, including the current source. Classical structures can be retrieved with enhanced performance, and new building blocks allow wide operational bandwidths and large output resistances. Parasitic output capacitance is still a bottleneck unless active capacitance compensation is used, but the reduced bandwidth of this technique limits its application in multifrequency EIS.

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Terms and Definitions

Current Source: A two-terminal analog electronic building block which generates an electrical signal with constant current amplitude independently of the load connected at the terminals.

Differential Amplifier: An amplifier whose output depends on the difference between two inputs through a gain (differential gain), and residually on the mean voltage between both inputs.

Electrical Bioimpedance: The physical magnitude that indicates the total impediment that a biomaterial offers to the flow of free electrical charges and the orientation of bounded electrical charges towards an existing electrical field.

Negative Impedance Converter: Type of electric circuit that can generate any impedance between two points – capacitances or inductances.

Operational Amplifier: Differential amplifier with a high open-loop gain which allows the implementation of accurate circuits by using voltage feedback.

Parasitic Capacitance: A capacitance usually defined between a node and ground due to wires, tracks, pads, and p-n junctions in the signal path.

Transconductance: A contraction of *transfer conductance*, the relation between the voltage at the input of an electric system and the current at the output. It is denoted by g_m and measured in Siemens units.

A NOVEL APPROACH FOR ESTIMATION OF ELECTRICAL BIOIMPEDANCE: TOTAL LEAST SQUARE

Fernando Seoane and Kaj Lindecrantz

Abstract— There are several methods used for AC-impedance estimation in Electrical Bioimpedance measurements. In this paper we propose a novel method for digital estimation of electrical impedance based in the Total Least Square (TLS) technique and we carry out a performance comparison between the proposed method and the typical Digital Sine Correlation (DSC) method. The TLS method has been implemented using the Singular Value Decomposition approach and the performance of both methods have been compared in terms of robustness against noise and size of the data set. The results indicate that the TLS method shows a better performance for impedance estimation than the DSC with reduced set of measurement samples and high SNR levels, while its performance worsen for increasing number of samples and decreasing SNR. The DSC method exhibits a better robustness against noise, especially for increasing the number of data samples. The main observed advantage of the TLS method is that it suffers from less mathematical constraints than the DSC method, and since the noise levels in bioimpedance applications are not expected to be very high we conclude that the TLS method is a good choice as impedance estimator.

Keywords— Digital Impedance Estimation, Bioimpedance, Sine Correlation, Total Least Square.

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Introduction

The use of Electrical Bioimpedance Spectroscopy (EBS) in biomedical applications has grown in the past years *e.g. skin cancer* (P. Aberg *et al.* 2004), *organ transplantation* (A. Ivorra *et al.* 2005). In these spectroscopy studies the spectrum of the Electrical Bioimpedance (EBI) is obtained from measurements of electrical impedance at several frequencies. Therefore the measurement systems must be able to well measure the impedance at several frequencies simultaneously *e.g. using multisine excitation signals* (R. Bragos *et al.* 2001) and also to perform frequency sweeps along the measurement frequency range.

Impedance measurement systems implementing multisine excitation are rare and most of the available systems are frequency sweep systems. For biomedical application specific systems the lowest measurement frequency is 20 Hz with a frequency range over 4 decades in (A. McEwan *et al.* 2006), and the highest measurement frequency is around one MHz in both ImpediMed Imp™ SFB7 and SCIBASE impedance spectrometers. In general application systems the lowest and highest frequency are 10uHz and 10 MHz respectively obtaining a frequency range up to 10^{12} *e.g. Solartron 1294A*.

Measurements at very low frequencies increases the time to obtain *a complete impedance spectrum*, and the time resolution might be of critical importance, especially for dynamic studies with measurement systems with a large number of measurement channels (Y. Gang *et al.* 2006).

The Sine Correlation (SC) is the most used method to estimated impedance from deflection measurements of voltage and current *e.g. 4-electrode technique*. It is simple but it suffers from several constrains regarding the sampling process, and since the impedance estimation is done tone by tone it is not suitable for true multifrequency measurements.

In this paper, we introduce a new approach for impedance estimation. This approach is based in the application of the *Total Least Square* (TLS) Technique to solve linear systems, and it operates without any requirement regarding the period of the signal; in an ideal and noise-free measurement setup the methods only requires two measurement samples to estimate the complex impedance at a certain frequency. On top of that it allows impedance estimation with multisine measurements.

Methods

Measurement Setup

A common implementation of the 4-electrode method measurement setup for electrical bioimpedance is depicted figure 1. In this case the measurement system is a current driven system, injecting know current into the tissue sample and measuring the voltage drop at the tissue sample with a differential amplifier *e.g. instrumentation amplifier*. The function generator not only generates the injecting current but also generates two

reference signals with the same amplitude as the stimulating current: one in phase and the other in quadrature; this way enabling the possibility to estimate the impedance using the SC technique. Note that all the acquired signals are converted from analog to digital.

Figure 1. Descriptive diagram for a four-electrode technique measurement setup suitable for impedance estimation by both DSC and TLS methods.

Digital Sine Correlation

The SC technique allows both analog and digital implementations. In this work we test the digital implementation: Digital Sine Correlation (DSC).

This estimation technique is based in the fact that the voltage drop caused in a load by the flow of sinusoidal current *e.g. a pure tone*, can be decomposed in the sum of two orthogonal voltage components: one of the components will be in phase with the current, typically the voltage drop on a resistor, while the other component will be orthogonal to the injecting current *i.e. shifted 90 degrees*, typically the voltage drop on a reactance. It can be seen at once that this analysis implies the assumption that the load is an impedance with a resistive and reactive component connected in series. Therefore, the same current flows through both, resistance and reactance, and the total voltage is built up by the voltage drop in each components. See figure 1.

The impedance estimation approach is basically a modulation/demodulation operation that makes use of the trigonometry identities of the double angle. To estimate the resistive part of the load, the total voltage drop in the load, V_m , is multiplied by a signal in phase with the injecting current. The resulting signal is smoothed by a simple low pass filter, as in figure 2, and the resistance is obtained applying the following equation:

Figure 2. Functional diagram representing the implementation of the sine correlation technique in a 4-Electrode impedance measurement operation. **N.B.** I_o and *ref* are the amplitude values for the injected sinusoidal current and both reference signals, in phase and in quadrature, respectively.

$$R = \frac{2}{I_0 \times ref} \frac{1}{K} \sum_{k=0}^{K-1} ip_k = \frac{2}{I_0 \times ref} ip_0 \quad (1)$$

The reactance is estimated in a similar manner after multiplying the measured voltage with an orthogonal signal instead, see figure 2. The reactance is given by equation (2).

$$X = \frac{2}{I_0 \times ref} \frac{1}{K} \sum_{k=0}^{K-1} iq_k = \frac{2}{I_0 \times ref} iq_0 \quad (2)$$

where I_0 , ref , ip_0 , iq_0 are according Fig. 2 and K is the number of observations *i.e. measurement samples*.

Total Least Square

Since the deflection system depicted on figure 1 is nothing else but Ohm's law, as a linear system it can be expressed by the following expression

$$V_m[k] = i[k] \times Z[k] \xrightarrow{\omega = \omega_m} V_m[k] = I_0 \sin[\omega_m k] \times Z[\omega_m] \quad (3)$$

considering Z complex at a certain frequency ω_m as

$$Z[\omega_m] = R[\omega_m] + jX[\omega_m] \quad (4)$$

it is possible to decompose the voltage drop in the impedance as the voltage drop on the resistive element plus the voltage drop on the reactive element as follows:

$$I_0 \sin[\omega_m k] \times R[\omega_m] + I_0 \cos[\omega_m k] \times X[\omega_m] = V_m[k] \quad (5)$$

Equation (5) can be expressed as the linear system of equations in (6) and in its corresponding matrix form in (7):

$$\begin{bmatrix} \overbrace{I_0 \sin[\omega_m k]}^{\text{in phase}} & \overbrace{I_0 \cos[\omega_m k]}^{\text{in quadrature}} \end{bmatrix} \times \begin{bmatrix} R[\omega_m] \\ X[\omega_m] \end{bmatrix} = [V_m[k]] \quad (6)$$

$$[I]_{K \times 2} [Z]_{2 \times 1} = [V_m]_{K \times 1} \quad (7)$$

The TLS method specifically targets linear systems like in (7), considering the existence of observation errors in all signals. In this case the observation errors are present in both current reference signals as well as in the observation of the voltage drop in the tissue. The corresponding system can be expressed as follows:

$$I_{K \times 2} Z_{2 \times 1} = V_m_{K \times 1} \xrightarrow{\hat{I}Z \approx \hat{V}_m} (I + \Delta I)_{K \times 2} \hat{Z}_{2 \times 1} = (V_m + \Delta V_m)_{K \times 1} \quad (8)$$

where $\hat{X}$ indicates errors in the variable X .

Golub & van Loan TLS algorithm (G. H. Golub & C. F. Van Loan 1980) implements a digital deconvolution to solve equation systems like in (8) using the Singular Value Decomposition of input and output matrices. The TLS solution for $\hat{Z}$ from (8) is obtained as follows:

$$\begin{aligned}
 &\text{To solve } \hat{I}_{K \times 2} \hat{Z}_{2 \times 1} \approx \hat{V}_m \Rightarrow \begin{bmatrix} I & V_m \end{bmatrix}_{K \times 3} \begin{bmatrix} \hat{Z} \\ -1 \end{bmatrix}_{3 \times 1} \approx 0 \\
 &SVD\left(\begin{bmatrix} I & V_m \end{bmatrix}\right) = U \cdot \text{diag}(\sigma_1, \sigma_2, \sigma_3) \cdot V^T \\
 &\text{best approximation for } \begin{bmatrix} \hat{I} & \hat{V}_m \end{bmatrix} = \begin{bmatrix} I & V_m \end{bmatrix} - \begin{bmatrix} \Delta I & \Delta V_m \end{bmatrix} \\
 &\begin{bmatrix} \hat{I} & \hat{V}_m \end{bmatrix} = U \cdot \text{diag}(\sigma_1, \sigma_2, 0) \cdot V^T \\
 &\begin{bmatrix} \Delta I & \Delta V_m \end{bmatrix} = \begin{bmatrix} I - \hat{I} & V_m - \hat{V}_m \end{bmatrix} = u_3 \cdot \sigma_3 \cdot v_3^T \\
 &\quad \downarrow \\
 &\begin{bmatrix} \hat{I} & \hat{V}_m \end{bmatrix} v_3 = 0 \xrightarrow{\text{TLS solution}} \begin{bmatrix} \hat{I} & \hat{V}_m \end{bmatrix} \times \begin{bmatrix} \hat{Z} \\ -1 \end{bmatrix} = 0 \Rightarrow \begin{bmatrix} \hat{Z} \\ -1 \end{bmatrix} = - \frac{v_3}{v_{3,3}} \\
 &\text{Since } \hat{Z} = \begin{bmatrix} \hat{R} \\ \hat{X} \end{bmatrix} \text{ therefore } \hat{R} = - \frac{v_{1,3}}{v_{3,3}} \quad \text{and} \quad \hat{X} = - \frac{v_{2,3}}{v_{3,3}}
 \end{aligned}$$

Therefore with measurements forming the current matrix I and measurements forming the voltage matrix V_m it is possible to solve $\hat{Z}$ at a single frequency ω_m from (8).

Performance test

All the performed tests have been implemented in Matlab. The simulations have been run for both methods to estimate the impedance in presence of Added White Gaussian Noise (AWGN). The impedance load had a constant module of $20 \, \Omega$ and an angle covering the full range from pure resistance to pure capacitance.

Noise Robustness: In the simulations noise has been added to all the observations. The AWGN added to the current reference signals and the voltage measurement is uncorrelated with Standard Deviation values to achieve levels of Signal to Noise Ratio (SNR) from 1 to 20.

Sampling Rate: The number of samples per period used to perform the estimations has been increased from 2 to 20.

Numbers of periods: The number of periods used to perform the estimations has been change from 0.5 to 10.

Results

In this section the estimation error for the module of the impedance obtained from each performed test case is plotted and the performance of the estimation methods is compared.

Effect of the SNR

Figure 3 shows the performance of both methods estimating the module of the impedance in presence of AWGN. The traces show the obtained absolute value of the relative estimation error versus the SNR. It can be seen that the performance of both methods increases with the value

Figure 3. Relative error in the estimation of the impedance value in the presence of Added White Gaussian noise in the measurement observations.

of SNR and that for high levels of SNR the best performance is obtained with the TLS method while the performance of the DSC is superior for lower values of SNR.

Sampling Rate Effect

The influence of the number of samples per period in the estimation of the impedance can be observed in figure 4. In the case of the DSC method, increasing the number of samples decreases the error in the estimation. While in the case of the TLS method, the estimation error decreases for increasing the number of samples until it reaches an inflexion point, global minimum, after that the error increases asymptotically. Both the value of the asymptote and the position of the minimum depend on the SNR level of the observations.

Figure 4. Influence of the number of samples per period in the estimation of the impedance magnitude in the presence of AWGN in the observations.

Figure 5. Influence of the number periods on the estimation of the magnitude of the impedance value in the presence of Added White Gaussian noise in the measurement observations.

Effect of the Number of Periods

Figure 5 shows the influence of the number of periods contained in the data set to estimate the impedance in the performance of the estimation. The performance of the TLS method exhibit the same behaviour as with increasing number of samples per period, inflexion point and asymptotic increasing trend, compare figures 4 and 5. In the case of the DSC, the general trend of the performance behaves similarly as in the previous case, but there is a remarkable difference in the behaviour of the estimation error. The estimation error exhibits a stair-case effect producing several local maxima between integer numbers of half periods.

Discussion

It is clear that the DSC method exhibit a superior robustness against noise, especially when increasing the size of the data set, number of samples and periods. This is due to the fact that the DSC method contains an intrinsic averaging mechanism, see equations (1) and (2) which increases the rejection ratio especially against AWGN for increasing the size of the data set.

Apparently the TLS method is especially weak against large levels of noise. This TLS implementation is basic and it is specifically weak to uncorrelated noise of Gaussian distribution, but there are other TLS approaches like the structured or generalized TLS that probably would perform better in presence of Gaussian noise.

The several local maxima in the estimation error observed between integer values of half-periods in figure 5 is a natural consequence from the modulation of a sinusoidal tone by it-self, it is a bias problem similar to

leakage in spectrum estimation with varying window length, but in this case viewed at only one frequency.

Conclusion

Considering the noise levels expected in bioimpedance measurements applications, the reported result suggest that the digital deconvolution method may be used for impedance estimation with satisfactory performance.

In the case of low frequency measurements the use of the Total Least Square technique might, most probably, contribute to decrease the measurement resolution time. But in general lines, to be able to assess in the possible time reduction introduced by using the Total Least Square technique for the impedance estimation, a full analysis of the processing power required by the implementation of the SVD must be done, as well as to investigate the performance of other alternative Total Least Square approaches *e.g. Structured, Generalized, Truncated*.

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ELECTRICAL BIOIMPEDANCE
CEREBRAL MONITORING.
A STUDY OF THE CURRENT DENSITY
DISTRIBUTION AND IMPEDANCE
SENSITIVITY MAPS ON A 3D
REALISTIC HEAD MODEL

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Electrical Bioimpedance Cerebral Monitoring. A Study of the Current Density Distribution and Impedance Sensitivity Maps on a 3D Realistic Head Model

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Abstract—There have been several studies of the application of electrical bioimpedance technology for brain monitoring in the past years. They have targeted a variety of events and injuries e.g. epilepsy or stroke. The current density distribution and the voltage lead field associated with an impedance measurement setup is of critical importance for the proper analysis of any dynamics in the impedance measurement or for an accurate reconstruction of an EIT image, specially a dynamic type. In this work for the first time, the current density distribution is calculated in a human head with anatomical accuracy and resolution down to 1 mm, containing up to 24 tissues and considering the frequency dependency of the conductivity of each tissue. The obtained current densities and the subsequent sensitivity maps are analyzed with a special focus on the dependency of the electrode arrangement and also the measurement frequency. The obtained results provide us with interesting and relevant information to consider in the design of any tool for Electrical Bioimpedance Cerebral Monitoring.

Index Terms— Electrical Bioimpedance, Electrical Impedance Tomography, Brain Damage, Cerebral Monitoring.

I. INTRODUCTION

MEASUREMENTS of Electrical Bioimpedance (EBI) is a well established method for the study of various properties of body tissues and it is a mature technology in the medical field [1]. It is used for patient monitoring, diagnosis support and for different types of clinical studies [2] e.g. *Impedance pneumography*, *Skin Cancer Screening* [3] and *assessment on body composition* [4].

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Electrical impedance tomography (EIT) aims at producing static or dynamic images related to the conductivity distribution of the measured region [5]. The range of the possible applications of EIT in medicine is wide [2] and it includes cerebral monitoring [6-8].

Recent research in neurological applications of EBI has been intensive and provided promising results. e.g. methods for monitoring of *Cerebral Blood Flow* [9] and detection of *hypoxic brain damage* [10]. Within electrical impedance spectroscopy (EIS), especially in association with EIT, the research activity has also been very intense in the past years [11-18]. However, a clinical breakthrough of EIT or EIS in routine use is still waiting.

In measurements of impedance, the contribution of a specific part of the volume under study depends on the current injection and the associated voltage measurement configuration [19]. Thus the configuration of the injecting and sensing electrodes is very important for the performance of an electrical bioimpedance study, especially for dynamic EIT studies.

For EBI studies in the human head, the issues of current distribution have been studied by others in the past [20-22], but only through the use of crude models of the head, and without considering the frequency dependency of the electrical properties of biological tissue.

In this work we study the current density distribution in the head and its dependency on the frequency dependence of the electrical properties as well the electrode placement. The study focuses specially on the effect of the measurement frequency and the electrodes arrangement on the impedance sensitivity maps and its implication for electrical bioimpedance cerebral monitoring.

II. METHOD

A. The Head Model

For the simulation in this study, we have used a fully 3-D human head model obtained from a tissue classified version of the *Visible Human Project*¹ developed at Brooks Air Force Laboratory, (TX) shown in Fig. 1. The head model consists of 24 tissues which are listed in Table I. The brain

¹ [Online] Available on March 23rd, 2007:

www.nlm.nih.gov/research/visible/visible_human.html

Fig. 1. Head model used.

TABLE I
TISSUE'S DIELECTRIC PROPERTIES USED FOR THE SIMULATIONS

Tissue	Conductivity σ [S/m]		
	50 Hz	50 kHz	500 kHz
Blood	0.70	0.70	0.75
Blood Vessel	0.26	0.32	0.32
Body Fluid	1.5	1.5	1.5
Bone Cancellous	0.08	0.08	0.087
Bone Cortical	0.02	0.021	0.022
Bone Marrow	0.0016	0.0031	0.0038
Cartilage	0.17	0.18	0.21
Cerebellum	0.095	0.15	0.17
Cerebro-Spinal Fluid	2	2	2
Eye Aqueous Humour	1.5	1.5	1.5
Eye Cornea	0.42	0.48	0.58
Eye Lens	0.32	0.34	0.35
Eye Sclera-Wall	0.50	0.51	0.56
Fat	0.02	0.024	0.025
Glands	0.52	0.53	0.56
Gray Matter	0.075	0.13	0.15
Ligaments	0.27	0.39	0.39
Lymph	0.52	0.53	0.56
Mucous Membrane	0.00043	0.029	0.18
Muscle	0.23	0.35	0.45
Nerve Spine	0.027	0.069	0.11
Skin Dermis (Dry)	0.0002	0.00027	0.044
Tooth	0.02	0.027	0.0047
White Matter	0.053	0.078	0.095

N.B. Only the conductivity of tissue has been considered for the calculations. For this range of frequencies the effect of the permittivity can be neglected.

in this model consists of eight tissues: CSF, gray matter, blood, cerebellum, ligament, white matter, nerve/spine, and glands.

The electrical properties, obtained from the Brooks Air Force Laboratory database² [23-25], are modelled using the 4-Cole-Cole model [26]. The tissue conductivities used in this paper, are as given in Table I.

B. Impedance Method

For the calculations of simulated electric current field in the human head model, we used a 3-D impedance method [27-29]. The head model is described using a uniform 3-D Cartesian grid and composed of small cubical cells, called

voxels, 1x1x1 mm. Under the assumption that in each voxel, the electric properties are homogeneous and isotropic, the head model can be considered as a 3-D resistance network of impedances. Kirchhoff voltage law around each loop in the obtained network generates a system of equations for the loop currents. The currents are injected at the electrodes and then distributed according to Kirchhoff laws. This system of equations is solved numerically using the standard iterative method of successive-over-relaxation. The current densities within the head are then calculated from these known current loops and consequently the current density distribution is obtained.

It can be noted that the skin-air interface is naturally resolved using the impedance method which inherently imposed the boundary condition that the current flow across this boundary is zero, since the conductivity of air is zero.

C. Sensitivity Distribution

As defined by Kauppinen [22], "the sensitivity distribution of an impedance measurement gives a relation between the measured impedance, Z , (and changes in it) caused by a given conductivity distribution (and its changes)". *i.e.* It gives an idea about the contribution of the conductivity of each voxel the measured impedance signal. And it is given by the following expression [30].

$$S_{Vm} = \frac{\vec{J}_{LEm} \bullet \vec{J}_{LIm}}{I^2} \quad (1)$$

Where:

S_{Vm} is the sensitivity for an impedance measurement of the volume conductor V , the symbol $\bullet$ is the dot product and J_{LE} and J_{LI} , are the current density fields (*i.e.* impedance lead fields) associated with the current and voltage leads for the impedance measurement setup m .

N.B. J_{LE} and J_{LI} must be obtained with reciprocal current I . *i.e.* same current injected for each stimulation.

Equation (1) expresses the sensitivity to conductivity changes in the volume conductor V , and how a change in the conductivity contributes to a change in the total measured impedance Z . Note that the sensitivity, S_V , may be positive, negative or null, depending of the orientation of the two lead fields. This way a change in the conductivity of a specific voxel may cause an increment or a decrement in the measured impedance or it may even be even completely unaffected by the conductivity change if the lead fields in the voxel are perpendicular to each other.

D. Simulation Scenarios

In this study three different arrangements of electrodes have been studied, see Fig. 2. In all three of them, we consider that the pair of injecting electrodes overlaps with the pair of voltage sensing electrodes.

N.B. Such electrode placement creates two identical lead fields, $J_{LIm} = J_{LEm}$, therefore according to (1) S_{Vm} will be always positive and equal to $\frac{J_{LIm}^2}{I^2} = \frac{J_{LEm}^2}{I^2}$.

For each of the measurement setups, the current density

² [Online] Available on March 23rd, 2007: <http://niremf.ifac.cnr.it/tissprop/>

Fig. 2. The three different measurement setups used in the simulations. (A) The electrodes are in opposite configuration. (B) The electrodes are in far-adjacent configuration and in (C) the electrodes close adjacent configuration. The coordinates of the electrodes are given in the legend

distribution and the corresponding impedance sensitivity map have been calculated for the frequency range from 50 Hz to 500 kHz.

III. RESULTS

The current density distributions and its corresponding impedance sensitivity maps for each of the measurement setups at the frequencies 50 Hz, 50 kHz, 500 kHz are shown in the following figures.

In Fig. 3 and 4 it is possible to observe how the frequency of the current affects the current density distribution in a different manner depending of the arrangement of the pair electrodes. In Fig. 3, electrodes diametrically opposed, such an influence can be noticed fairly well; especially in the CSF and in the deep structures of the brain where the current spreads easier at high frequencies. In the case where the electrodes are closer to each other, Fig. 4, the frequency dependency can specially noticed in the muscle tissue as well as in the CSF and deep intracranial regions.

Fig. 4. Current density distribution and its corresponding impedance sensitivity map for measurement setup case C at three frequencies: 50 Hz, 50 kHz and 500 kHz.

Fig. 3. Current density distribution and its corresponding impedance sensitivity map for the measurement setup case A at three frequencies: 50 Hz, 50 kHz and 500 kHz.

The effect of the electrode placement can be observed in Fig. 5 where the current density distribution at 50 Hz is depicted for each of the three different electrode positions. It is easy to appreciate how the spreading of the current depends on the separation of the electrodes, especially when focusing in the regions of maximum current density; near the electrodes and through the Cerebro-Spinal Fluid. Note that the white matter is the intracranial tissue where the

Fig. 5. Current density distribution and its corresponding impedance sensitivity map at 50 Hz for all three measurement setups. Case A in the left

Fig. 6. Current density distribution and its corresponding impedance sensitivity map at 50 Hz for diametrically opposed electrodes, axial view.

current density is least sensitive to the electrode positioning.

In Fig. 6, the effect of the muscle tissue can be noticed, it has a high enough conductivity to drain current, especially in the back, but not high enough to also drain a lot in the front, the face region. The effect of the high conductivity of the muscle can be appreciated well in Fig. 5. The current density through the muscle tissue increases remarkably from case A to case C.

In Fig. 4 and 5 it is possible to observe how the impedance measurement sensitivity decreases radially to the head from the electrodes when those are diametrically opposed, case A. While in Fig. 3, 4 and 5 is shown that the sensitivity decreases from the electrodes tangentially to the head, more tangentially the closer the electrodes are to each other, case B and C.

IV. DISCUSSION

In general terms the obtained current density distributions agree with those reported by Rush and Malmivuo [20, 31], with the difference thou, that the large insulating effect of the skull bone reported in [31] is not seen here. This might be due to two important differences: Their concentric spheres model only includes a few tissues and the conductivity ratio between the skull bone and the rest of the tissues used by both of them was 80, a much larger value than the values used here. See Table I.

A. Tissue Particularities

The current spread differently in each type of tissue, which is not a novel finding, but the ability to quantify this fact is very important for the design of any impedance monitoring tool aimed to detect any undergoing processes in the brain.

Knowledge about the fact that the current density is higher in CSF than in grey matter and higher in grey matter than in

white matter is important for the detection of the type of activity or aetiology that the impedance system aims to monitor *e.g. meningitis in CSF, electrical activity in the cerebral cortex, etc.*

B. Effect of placement

The observed dependence of the current density distribution and the placement of electrodes was expected, but it is surprising to observe the low current densities in certain areas with white matter tissue independently of the position of the electrodes. This fact has not been reported before.

C. Effect of frequency

It is interesting to observe how the frequency of the stimulating current influences the current density distribution in a slightly different manner, when the electrodes are close to each other than when the electrodes are diametrically opposed. Such a difference can be due to the fact that the muscle tissue exhibits a strong frequency dependency and in the case of the electrodes close to each other, the muscle tissue contributes in a large proportion to the effective volume conductor, therefore an increase in conductivity accompanied with a large volume facilitates the current draining.

This dependency between frequency and electrode placement is particularly relevant for EIS studies, since the measured impedance data often contains a broad frequency range.

D. Impedance Sensitivity Maps

The obtained impedance sensitivity data is in general concordance with those reported in [31], with the value decreasing in the same manner. The difference in the impedance measurement sensitivity between different parts of the brain is considerable and this is important to understand, because this means that a small change in the conductivity in one region of the brain can be propagated to the impedance measurement 100.000 times better than the same change in another region.

Since in the brain, many of the events, pathological or natural, are associated with different anatomical structures, the design a measurement system with high impedance sensitivity for a specific region of study is a critical design requirement. Thus to know its dependency on the electrode position and the stimulation frequency is crucial.

Similarly, most of the aetiologies of the brain events exhibit impedance changes better at certain frequencies; therefore the influence of the stimulating current in the impedance sensitivity distribution is another factor to consider.

V. CONCLUSION

This is the first time that the current density distribution in brain and its influence in the impedance measurement sensitivity maps are studied with such a detail, anatomical

and frequency ways. One important conclusion from the study is that, contrary to what has been generally believed, the skull bone does not constitute an insulating layer that will hamper the recording of impedance changes within the deep parts of the brain.

To know the distribution of the impedance sensitivity is very important for the analysis of any change in the value of an impedance measurement and it is critical for certain applications based in time analysis of spectroscopy impedance data or dynamic EIT.

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ELECTRICAL BIOIMPEDANCE CEREBRAL MONITORING

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Introduction

Electrical Bioimpedance, EBI, is now a mature technology in medicine, with applications in clinical investigations, physiological research and medical diagnosis (H. P. Schwan 1999). The first monitoring applications of bioimpedance techniques, *impedance cardiography*, date back to 1940. Since then, bioimpedance measurements have been used in several medical applications, from lung function monitoring and body composition to skin cancer detection. A complete historical review is available in Malmivuo (J. Malmivuo & R. Plonsey 1995). A medical imaging modality based on bioimpedance, *Electrical Impedance Tomography*, EIT, has also been developed (R. H. Bayford 2006).

EBI has been used to study the effect in the brain of spreading depression, seizure activity, asphyxia and cardiac arrest since 1950s' and 1960s'(S. Ochs & A. Van Harreveld 1956), but the most important activities in electrical cerebral bioimpedance research has been during the last 20 years (D. S. Holder 1987, D. S. Holder & A. R. Gardner-Medwin 1988). Examples of areas of study are *brain ischemia*, *spreading depression*, *epilepsy*, *brain function monitoring*, *perinatal asphyxia*, *monitoring of blood flow and stroke*.

Background

The basic functional units of an EBI measurement system for cerebral monitoring are the following: an electric current generator, a voltage meter, the surface electrodes for current injection and voltage pick up as well as the connecting electrical leads. The injected current causes a voltage drop in the tissue that is sensed and the measured bioimpedance is calculated from the resulting quotient from voltage over current, know as Ohm's Law. See Figure 1 and (1).

$$Z(\omega) = \frac{V(\omega)}{i(\omega)} \quad (1)$$

Figure 1. Functional diagram of a measurement system for Electrical Bioimpedance Cerebral Monitoring.

An important feature of the application of EBI for cerebral monitoring is that it is applicable in some of the situations where brain is particularly at risk as well as for long-term monitoring situations where available imaging techniques: MRI, CT-scan are not suitable *e.g. during an ongoing cardiopulmonary by-pass operation, in intensive care, for acute stroke assessment in ambulances.*

Other features of bioimpedance technology are that it is harmless for the patient, portable and very affordable in comparison with other monitoring techniques already in used. These specific features place EBI as the technology of choice to fill the need for brain monitoring in the medical scenarios mentioned above and several others.

Electrical Properties of Biomaterials and Bioimpedance

Biological material, tissue and cells, have electrical properties (conductivity σ and permittivity ϵ) that allow electrical current to flow in the presence of an electric field (K. S. Cole 1968). These electrical properties depend of the constitutive elements and structure of tissue therefore; changes in structure or biochemical composition modify the electrical properties, σ and ϵ , of the tissue, and consequently the electrical impedance changes.

Every type of tissue and body fluids in the human body exhibits specific values of conductivity and permittivity that are frequency dependent. Therefore, each tissue can be characterized by its particular electrical impedance spectrum, and measurements of electrical impedance can be used to differentiate between tissues or to assess the state of the tissue. The most complete compilation of the dielectric properties of biological tissues is found in (C. Gabriel 1996).

Electrical Impedance Tomography

EIT exploits the fact that the electrical properties differ between tissue types to create an image representing the conductivity distribution of a volume conductor. Despite its name, EIT does not reconstruct an object slice by slice because electrical current cannot be confined to a plane, instead the current will flow through the whole volume conductor following the gradient of the electrical field.

As several conductivity distributions may provide the same voltage boundary detected by the sensing electrodes, reconstruction of the impedance image requires that some assumptions are made and also that a model is used for fitting the voltage boundary data.

There are two methods for EIT imaging: absolute and difference imaging. The first one, also known as static method, obtains a conductivity image from a set of impedance measurements. The difference imaging method uses a set of two measurements taken at two different times to

create a conductivity image of the differences. This method is used for dynamics studies, for monitoring changes in the tissue.

EIT imaging exhibits a poor spatial resolution as compared to other imaging techniques but the time resolution, in the order of microseconds, is unique for EIT. Affordable, portable and non-invasive are other exclusive features to EIT within brain imaging monitoring. For a deep understanding of EIT, see a recent review (R. H. Bayford 2006).

Figure 2. The effect of the cell membrane capacitance in the current path lines.

Electrical Impedance Spectroscopy Analysis

One straight-forward effect of the frequency dependency of electrical properties of tissue is the effect of the cellular membrane. Figure 2 shows the influence of the frequency on the current path lines. The capacitive effect of the membrane contributes to the electrical properties of tissue and depends of many factors: the number of cells, the size of the cells, the thickness of the cell membranes, type of cells, etc.

Because the plasma membranes of the tissue cells act as a capacitive element, most of a direct current (DC) in biological tissue, flows through the extracellular space, *e.g. interstitial fluid, plasma etc.* Hence the impedance

$$g_{DC} = \sigma_e \frac{2(1-f)}{(2+f)} \quad (2)$$

$$g = \sigma_e \frac{2(1-f) \sigma_e + (1+2f) \left(\frac{\sigma_i (\sigma_m + i\omega C_m) a}{\sigma_i + (\sigma_m + i\omega C_m) a} \right)}{(2+f) \sigma_e + (1-f) \left(\frac{\sigma_i (\sigma_m + i\omega C_m) a}{\sigma_i + (\sigma_m + i\omega C_m) a} \right)} \quad (3)$$

Equations Legend:

g is the complex conductivity of tissue, σ_e is the conductivity of the extracellular fluid, $S \times m^{-1}$, σ_i is the conductivity of the intracellular fluid $S \times m^{-1}$, σ_m is the membrane conductivity, $S \times m^{-1}$, c_m is the surface membrane capacity, Farads $\times m^{-2}$, ω is the angular frequency, radians $\times s^{-1}$, i is the imaginary number $\sqrt{-1}$, a is the cell radius and f is the volume fraction of concentration of cells.

N.B. the expression for g_{DC} corresponds to the general expression for g when $\omega = \infty$ and σ_m is approximate to 0.

at DC is mainly determined by the conductivity of the extracellular fluid, the available surface to the electrical field for the charges to flow through, and the length of the propagation path. See figure 2 and equation (2). At higher frequencies the capacitive effect shunts the electrical current, allowing the electrical current to propagate also via the intracellular space and the tissue conductivity can be model as in equation (3).

Notice in equation (3) that the conductance of tissue depends not only on the dielectric properties of the constituents but its morphology and frequency. For this reason each tissue has specific electrical properties and consequently presents a specific impedance spectrum. This fact allows the differentiation between tissues and assessment of health state by spectrum analysis of the tissue impedance. This is the principle behind several impedance-based medical applications *e.g.* *Skin cancer screening* (P. Aberg *et al.* 2004), *breast cancer assessment* (M. Assenheimer *et al.* 2001).

Potential Applications

There are several areas of neurology that may benefit from the application of EBI technology as a means to obtain useful indicators about the undergoing activity of brain threatening mechanism.

Brain Monitoring during Cardiac Surgery

The high vulnerability of brain tissue to hypoxia (T. Acker & H. Acker 2004) together with the ability of impedance measurements to detect hypoxic cell swelling (F. Seoane *et al.* 2005) place EBI technology as a candidate method for early detection of hypoxic brain damage during cardiac surgery.

Perinatal Asphyxia

It has been proven (F. Seoane *et al.* 2005) that the cell swelling associated with hypoxic-ischemic injury can be sensed and measured via EBI.

Brain Function and Epilepsy

The electrical properties of the cell membranes are non-linear (A. L. Hodgkin 1947) and during neural depolarization the opening of the voltage-sensitive ion channels modify the membrane impedance (D. S. Holder 1992).

The principle behind detection of epilepsy using EBI measurements relies on the fact that the impedance of an epileptic region will be appreciably different of the rest of the brain because of the large electrical activity associate to the epileptic seizure, accompanied by local cell swelling and ischemia (T. Olsson *et al.* 2006).

Stroke

There are two kinds of stroke, ischemic stroke and haemorrhagic stroke. Both result in alterations in the composition and the structure of the affected area. In the case of ischemic stroke the blood flow to an area of the brain is interrupted and consequently there is a lack blood and oxygen that results in ischemic cell swelling. In the case of haemorrhagic stroke, the rupture of blood vessels allows the leaking of blood from the cerebrovascular system to accumulate in the intercellular space causing a haematoma. These two different sequences of pathophysiological events alter the electrical properties of the affected area and the alteration can be detected by means of non-invasive electrical impedance measurements (L. X. Liu *et al.* 2006).

Cerebral Blood Flow Monitoring

Autoregulation of cerebral blood flow is a protective mechanism that stabilises cerebral perfusion during changes in blood pressure, often induced as a consequence of intracranial hypertension or cerebral ischemia. The use of intracranial measurements of EBI can detect cerebral blood flow autoregulation, (M. Bodo *et al.* 2005) suggesting that rheoencephalography could be developed into a non-invasive method for early detection of brain injury.

Current Research Issues in Electrical Bioimpedance Cerebral Monitoring

Electrical bioimpedance technology provides useful features for cerebral continuous monitoring and encouraging results have been seen in various clinical applications. However, there are still many issues to be addressed before the technology is developed into a clinical tool for cerebral monitoring.

Biophysical Understanding

Generally there is a lack of understanding about the relationship between the underlying pathophysiological mechanisms associated to a particular insult *e.g. cell swelling, intracranial haemorrhage etc.* and the influence on the electrical properties of tissue. The knowledge about impedance dynamics and the injury or adaptation mechanisms is still coarse. The ultimate effect of the damaging insult on the electrical properties of the tissue is relatively well known and the fundamental hypotheses are supported by experimental results. However the effect on the electrical properties of the tissue constituents, of the biochemical and histological processes active during the corresponding adaptation or injury mechanism is, in most cases, completely unknown.

Impedance Data for Tissue Spectra Characterization

The specific electrical properties of each biological tissue confer an impedance spectrum virtually unique to each particular tissue. Available

biological dielectric data is compiled and available in (C. Gabriel 1996). As the origin of the data is mostly excised animal samples and human corps the values of these data are not necessarily representative for in vivo tissue.

A proper spectral characterization of healthy tissue will empower the identification and classification applications based in EBI spectroscopy. It is essential to have spectral information of healthy tissue as well as enough spectral data to fully characterize the impedance spectra of the injured tissue.

Current Density Distribution in the Head

There are several factors that determine the current density distribution within the head. These factors influence the current density distribution directly or indirectly. The ultimate direct factor is the electrical impedivity distribution in the head. The frequency and the placement of electrodes are factors that indirectly affect the current density distribution.

Effect of the skull

When current is injected into the head, the current density is much smaller in deep intracranial region than in the superficial layers, skin and scalp (J. Malmivuo *et al.* 1997, F. Seoane *et al.* 2007b). Recent simulations with a realistic model have shown that the effect of the skull is less shielding than earlier believed (F. Seoane *et al.* 2007b), and it has been shown that the current density distribution depends largely on the electrical properties of each specific tissue. A smaller current density in the intracranial structures is explained not only by the shielding layer of low conductive bone. The conductive extracranial layer of muscle tissue together with the large area available for the current to flow within the brain are also responsible for the small intracranial current density.

Volume under Study, Placement of Electrode and Sensitivity Maps

Electrode placement significantly influences in the current density distribution, as seen in figure 3, thus a particular arrangement of electrodes will be better for the study of a certain region. Not only the position of the pair of injecting electrodes but also the position of the pair of sensing electrodes is important. The arrangement of the injecting and sensing electrodes determines the sensitivity map therefore different placement of the pairs of electrodes gives different sensitivity maps. These maps may contain positive and negative as well as null regions, *e.g. if the pair of electrodes were overlapping each other the sensitivity map will be only positive*. For this reason, some electrode arrangements are more suitable for study of certain phenomena than others. An adjacent placement of electrodes will give information mainly from the cortex, desirable for the study of certain pathologies *e.g. epilepsy*, while the same electrode arrangement will provide very little information from the centre of the brain, less favourable for detection of haemorrhage in the brain ventricles for instance.

Figure 3. Current Distributions in the human head for two different placement of electrodes. A complete axial view.

In EIT, the placement of electrodes is determined by the selected measurement strategy: opposite method, cross method, neighbouring method and adaptive method. The corresponding sensitivity maps associated with each of them have been studied in (P. Kauppinen *et al.* 2006).

Spatial Resolution in EIT

The main limitation of EIT is the poor spatial resolution. The accuracy of the image has improved as new processing methods have been introduced, but it is still poor compared to traditional imaging methods used in clinical practice like MRI, CT, Ultrasound, etc.

Number of Channels

A progressive increase in the number of measurement channels of the EIT systems, from 16 electrodes used back in 1987 up to with 128 electrodes (Y. Gang *et al.* 2006), has contributed to improve the quality and the resolution of the impedance images (T. Mengxing *et al.* 2002), as expected.

Reconstruction Algorithms

The reconstruction algorithm contains several simplifications and assumptions that worsen the accuracy of the reconstructed image, thus the selection of a specific algorithm and its components are critical for the spatial resolution of an EIT image.

The complexity of the models used for the forward problem has been increased from simple heterogeneous 2D-spherical models to 3D-layered concentric sphere and even realistic anatomic models based in MRI-images

(A. D. Liston *et al.* 2002). The increase in the complexity of the models has been accompanied with the corresponding improvement in resolution and quality of the image (A. D. Liston *et al.* 2002, A. P. Bagshaw *et al.* 2003).

The work done in reconstruction algorithms for EIT during the last decade and the generated scientific literature is immense and part of it is contained in the review work done by Lionheart (W. R. B. Lionheart 2004).

Future Trends

Researchers and physicians have realized of the potential of EBI technology for monitoring of the brain, consequently the proliferation of bioimpedance techniques targeting the dynamics of basic pathophysiological mechanism is natural and expected.

A better biophysical understanding of the dynamics of EBI during the aetiologies of interest along with a good knowledge regarding the current density distribution and the impedance sensitivity maps in the brain will most probably lead to the development of aetiology-specific operation modes in EBI measurement systems.

The Promising Magnetic Induction EIT

Magnetic Induction Electrical Impedance Tomography, MI-EIT, is a modality of EIT. In MI-EIT the current is not directly applied into the tissue through electrodes, it is magnetically induced by coils (S. Al-Zeibak & N. H. Saunders 1993). This way it is possible to reduce the effect of the low conductivity of the skull bone and eliminate certain limitations related to the electrodes (H. Scharfetter *et al.* 2003).

MI-EIT has been under study and continuous development for the past years (S. Al-Zeibak & N. H. Saunders 1993, J. Rosell *et al.* 2001, H. Scharfetter *et al.* 2003) and recently its application in cerebral monitoring has been intensified.

Conclusion

Changes in the electrical properties of brain tissue do reflect certain physiological activities in the brain. These activities may originate from normal processes *e.g. the membrane depolarization during an evoked potential* or it might be the result of brain damage *e.g. ischemic oedema after stroke* or it might be the injury mechanism itself *e.g. hypoxic cell swelling*. Therefore the use of electrical bioimpedance measurements of the brain can play an important role supporting early diagnosis of several brain-related conditions.

The development of electrical bioimpedance technology has been intense and continuous especially during the last decade, but it has not been enough to reach the necessary status to be applied in clinical practice as brain monitoring tool yet. However, through experimental research results, hardware developments and simulation studies, there may be a breakthrough soon.

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Terms and Definitions

Brain Stroke: A cerebrovascular accident that occurs as a consequence of brain ischemia or cerebral haemorrhage; ischemic stroke and haemorrhagic stroke respectively.

Electrical Conductivity: a dielectric property that indicates the ability of a material to allow the flow of electrical charges.

Electrical Bioimpedance: The physical magnitude that indicates the total impediment that a biomaterial offers to the flow of free electrical charges and the orientation of bounded electrical charges towards an existing electrical field.

Bioimpedance Tomography: Also known as Electrical Impedance Tomography, it is a medical imaging technique in which an image of the dielectric properties of biological tissue is inferred from surface electrical measurements.

Epilepsy: a neurological disorder in which abnormal electrical activity in the brain causes seizures.

Hypoxia: Reduction of oxygen supply to tissue below physiological level.

Ischemia: A low blood flow state leading to hypoxia in the tissue.

Seizure: Abnormal electrical activity in the brain tissue, which is usually accompanied by motor activity and or sensory phenomena. Its origin can be epileptic or non-epileptic