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Design of a complex bioimpedance spectrometer using DFT and undersampling for neural networks diagnostics

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ABSTRACT

Electrical impedance spectroscopy offers many applications in the medical field due the fast response, non-invasiveness and low cost. One promising area is the use of this method for diagnostics. This paper describes the design and experimental evaluation of a multifrequencial complex bioimpedance analyzer. Impedance amplitude and phase were calculated using Discrete Fourier Transform (DFT) and high frequency signals were measured with undersampling. The prototype was able to measure values from 1 Ω to 50 kΩ (frequency range from 50 Hz to 500 kHz). The accuracy of the technique was compared with a commercial equipment. The analysis of passive components resulted in a mean error of 2.9% for the magnitude and 0.69 degrees for the phase. Besides, an initial study for head and neck cancer detection through neural networks is shown. One used bioimpedance values as well as gender, age and body mass index as inputs. The network used 120 training and 40 validation data and was able to simulate 77.5% of the two types of diagnostic correctly.

1. Introduction

Despite the wide use of bioimpedance methods, there are still many applications that can be studied. One knows that the patient's electrical impedance suffers considerably changes in certain diseases [1]. In some cases it is possible to detect variations in this parameter even before symptoms. Some works have already been made applying this technique to help the analysis of skin [2,3], tongue [4], prostate [5] and breast cancer [6], as well as in the early diagnosis of lymphedema [7,8].

The aim of this paper is to develop a complex bioimpedance spectrometer in order to be used in clinical diagnostics, including tumor detection. The prototype uses Discrete Fourier Transform (DFT) to measure resistance and reactance values. High frequency signals are analyzed through the undersampling principle.

The second part of the manuscript studies the relation between the whole-body electrical impedance and cancer diagnostics. Although there is a connection between both parameters, one still have not been able to determine the exactly model for this system due the great number of variables involved. However, neural networks technique is able to overcome these barriers. Therefore one expects that this method can separate healthy and sick individuals in different classes.

A future application of this technique is the diagnostic of patients through the bio-electrical impedance analysis (BIA) [9]. In the case of cancer detection, this technology would be cheaper and more accessible than the current diagnostics processes such as X-rays, CT scanning and magnetic resonance imaging.

1.1. Bioimpedance spectroscopy

BIA is widely used for the determination of total body water (TBW), fat free mass (FFM), tissue characterisation, apnea monitoring, venous thrombus detection, tomography, cardiography, pneumography and blood compounds analyze [10–12]. The method of bioimpedance applies low intensity currents in physiological fluids or tissues through electrodes. In this case the transport of electrical charges is done through free ions and factors like temperature and concentration can influence the ionic dissociation, changing its electrical properties [13,14]. In order to avoid the polarisation effect, only alternating current (AC) should be used [15]. Although researches with electric impulses have been done [16], sine waves are still mostly studied due the easy treatment process.

Besides the signal characteristics, other factors can also influence this technique. The organism has tissues with different substances, compositions and shapes, resulting in different resistivities for each organ. While muscles and blood are good conductors, skin, fat and bones act mostly as isolators. Even in the same organ,

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the electric characteristics can change with electrode position because of the different cells' shapes [15].

In low frequency currents (until 5 kHz) biological tissues show high capacitance values due the isolation of the cellular membrane. When higher frequencies are used, this parameter decreases, and in 1 MHz the current crosses the whole cytoplasm. Tissues also have similar behaviour to the cells. Therefore in lower frequencies, tissues with greater cellular density will show higher impedance than tissues with more extracellular fluid [15].

The permissibility comportment of a biological tissue is called dispersion. There are three fundamental types: α, β and γ. The dispersion α happens in low frequencies and is due to the diffusion phenomenon of free ions outside the cells. The dispersion β comes from the charge and discharge of the cellular membrane capacitance through intra and extra-cellular liquids (100 kHz until 30 MHz). The dispersion γ is caused by the bipolar relationship of the free water molecules in the medium (10 GHz until 100 GHz) [17].

The Cole graph represents the resistive and capacitive characteristics of tissue impedance with the frequency. One important data in this analysis is the modulus of the phase angle, which in theory can change between 0° and 90° and in most people is found between 3° and 10°. For medium frequencies, small angles mean a decrease in the capacitive reactance, corresponding to cellular death. Higher values of phase represent an increase in the capacitance, which reflects a great number of cells [18]. The total body impedance in Cole's diagram is caused mainly by muscles' values [19].

Due the fast development of electronics technology, high frequency dielectric spectroscopy is a promising tool for tissue characterisation and compounds quantification. Besides, the low cost, fast response, simple implementation and safety make this technique very interesting for clinical diagnostics.

1.2. Neural networks

Artificial neural networks (ANNs) are a non-linear statistical data modellings of biological neural systems that simulate mathematical functions such as complex relationships between inputs and outputs or data patterns. This adaptive system is divided in layers and interconnected through a great number of neurons or nodes [20].

Each node is a computational device that receives a number of input signals, associated with weights to represent stimulating or inhibiting influences. The projection of this sum is applied to a transfer function to produce activation of the neurons that is forwarded towards the nodes until it reaches the network output. The behaviour of an ANN depends on both the weights and this input–output function. The transfer function typically falls into one of three categories: linear (ramp), threshold or sigmoid [21].

The most important feature of the neural network approach is that any continuous function defined on a compact domain can be fitted with a pre-defined arbitrary degree of accuracy. In addition, the flexibility and the ability to maintain a good performance even in the presence of significant amounts of noise in the input increases the use of this tool in prediction, classification and control problems [22].

ANNs require sets of training and validation data. Backpropagation is the most commonly used training algorithm. Adjustable parameters are the weights and biases that act as offset terms by shifting the transfer functions horizontally [23]. The training starts by processing forward a set of samples of known response. At the end, the magnitude of the error between experimental and predicted responses is calculated and used to adjust all variables of the system, in a reverse step that finalizes an iteration or epoch. The repetition of this sequence with a large number of spectra of random order and wide concentration ranges will improve the relationship between x and y, enabling the ANN to produce reasonable output for unknown input. On the other hand, unnecessary interactions can lead to overfitting, therefore a stop criterion should be used. The decision rule can be either a maximal number of epochs or a standard error of prediction [24].

A single neuron is not sufficient to perform a specific task. Therefore, the nodes have to be interconnected. The multilayer perceptron (MLP) architecture is the most used neuron layout. There are numerous rules that give an indication of how large a neural network should be, most of them are based on the size of the training data or the number of input and output nodes. If the total number of neurons is too small, the resulting neural network will not be able to accurately represent the training information and errors will be significant. On the other hand, a large number of nodes could lead to redundant paths, heavy processing algorithms and overfitting [25].

A neural network with only one hidden layer can approximate any function with any desired accuracy. One advantage in this case is that the model obtained is quasi-independent from the set of initial weights. However, for some functions the number of neurons needed between input and output can be very large. In this situation, a neural network with two hidden layers might have better performance. The disadvantage of more hidden nodes is that different sets of initial random weights can lead to different combinations of transfer functions to build empirical models. Therefore it is recommended to systematically reduce the number of hidden neurons as much as possible, in order to achieve simpler and more robust models [23].

2. Materials and methods

Fig. 1 shows the block diagram of the impedance meter prototype. By using a tetrapolar configuration, the influence of electrodes' impedance is almost eliminated. The circuit consists of an oscillator, a current source, an amplifier module, a sample-and-hold, an analog to digital converter (A/DC), a microcontroller, a keyboard, a graphic display, and a serial interface. Since all signals are digitally processed, the analogical circuitry is not complex.

A Direct-Digital Synthesizer (DDS) AD9831 generates sinus waves from a few mHz up to 1 MHz. This circuit requires only a single 32-bit word for programming. A current source of 800 μA is used for patient's safety [14]. The voltage generated in the subject is measured through an association of differential and programmable gain amplifiers (PGA), with a maximum gain of 160. The first PGA stage (THS702) has an error of 0.04%, which may be multiplied by 16 in the second stage.

The prototype uses the Discrete Fourier Transform to extract both real x and imaginary y components from a sampled signal. To compute these vectors one needs to know the period of the original waveform and the sampling rate, as shown in Eqs. (1) and (2):

$$x = \frac{2}{N}\sum_{k=0}^{N-1} s(k) \cdot \cos\left(2\pi\frac{k}{N}\right) \quad (1)$$

$$y = \frac{2}{N}\sum_{k=0}^{N-1} s(k) \cdot \text{sen}\left(2\pi\frac{k}{N}\right) \quad (2)$$

where N is the total number of samples, k is the sample index, t is the sampling rate, $s(t)$ is the measured value and T is the period of the wave. After finding x and y it is possible to obtain the magnitude (A) and phase (θ) of impedance, as shown in Eqs. (3) and (4):

$$A = \sqrt{x^2 + y^2} \quad (3)$$

Fig. 1. Block diagram of the impedance spectrometer prototype.

$$\theta = \arctan\left(\frac{-y}{x}\right) \quad (4)$$

The standard measurement frequency for commercial bioimpedance devices is 50 kHz [15]. Digital processing of signals in this range is not difficult. However, at higher frequencies one can have serious limitations in the electronics technology. The microcontroller's ADC had an upper sampling limit of 12.56 kHz. According to the Nyquist criterion only signals lower than 6.28 kHz could be measured. However, one used the undersampling technique to allow high frequency signals to be processed as well [26,27]. This technique is based on the principle that even with sampling signals in a frequency smaller than the Nyquist criteria, the resulting data still contains the same phase and amplitude information from the original wave.

The only requirement in order to use the DFT with undersampling is a small signal tracking time, which can be satisfied using a fast sample-and-hold circuit (HA5351). Also, although undersampling allows the use of low rates, the higher the sampling frequency, the smaller the measurement error. To sweep the whole frequency spectrum one could use a fixed sampling frequency. However this option may be more sensible to harmonics errors. To improve accuracy of the measurement, a variable sampling period (Ts) was used according to the following equation:

$$Ts = Ts\_\min + \frac{T}{sc} \quad (5)$$

where T is the measured wave period, Ts_min is the hardware smallest sampling period and sc is the desired number of samples per signal cycle.

3. Simulations and results

3.1. Meter prototype

The analogical circuit and the digital signal processing can add errors to the system due the imprecision of the PGA gain, the sample and hold delay, the A/D converter resolution and the DTF calculation itself. Fig. 2 shows a simulation of a DFT treatment in MatLab. One can compare the measurements of an adjustable sampling frequency from Eq. (5) limited in 12.56 kHz with a fixed rate in the same value. The ordinate axis represents the frequencies of the sampled signals, ranging from 10 kHz to 1 MHz. This is the window where undersampling is applied. Analyzing the amplitude and phase behaviours of the constant sampling rate, one can observe that both errors increase around the harmonics in 12,589 Hz, 25,118 Hz and 25,1188 Hz. In this case the DFT simulation showed a mean error of 4.55% for magnitude and 4.33 degrees for phase. On the other hand, the variable sample frequency from Eq. (5) decreases the mean error in 0.34% for magnitude and 0.08 degrees for phase.

Due to the small current that flows through the patient's body, physiological artefacts and circuit's parasite currents can become noise sources. To improve the accuracy, the averaged of many measurements was used. One found that 20 repetitions are enough for a good performance with an acceptable acquisition time.

In order to validate the prototype's response, one compared the measurements with a calibrated KC-605 LCR meter from Kokuyo Testing Instruments & Systems. This device is able to measure from 42 Hz up to 5 MHz with accuracy of 0.1%. The tests were made at room temperature (23 °C) in the laboratory of the Institute of Technology and Development (LACTEC). The first validation essay was made with resistors. Since they have a very small phase angle for the frequency range analyzed, it was possible to observe the prototype's phase response. Typical bioimpedance values are smaller than 10 kΩ, consequently the prototype was specified for small loads. The mean errors for magnitude and phase of test resistors in frequencies from 50 Hz to 1 MHz are shown in Fig. 3.

Magnitude errors do not follow a clear pattern but, as expected, phase response stays almost constant in all ranges. For small resistance values (such as 1 Ω), the measurement errors increase due the resolution of the A/D converters and the limited amplifier's gain. For high resistance values, the amplifiers' input impedance is the main source of errors. The developed prototype was able to measure complex impedance values from 1 Ω to 50 kΩ in a frequency range from 50 Hz until 1 MHz with 2.9% magnitude and 0.69 phase mean errors.

Essays with capacitance and inductance showed that the prototype was able to measure phase angles from −180 to +180 degrees. The impedance errors of a RC circuit were also analyzed (Fig. 4). In order to simulate physiological values of the human body, a 895 Ω resistor was connected in series with a 3.3 nF capacitor, both in parallel with a 617 Ω resistor.

The phase of the circuit showed greater deviation to high frequencies, reaching 0.82 degrees at 800 kHz. The module of the impedance error for the RC circuit was approximately 1.5% in low and 3% in the high frequencies. The lack of precision to measure the real gain of the PGA can have caused the higher magnitude error starting in 60 kHz.

In vivo bioimpedance measurements were made with frequencies ranging from 1 kHz to 1 MHz. Current gel electrodes were placed in the back of the right hand and on top of the right foot. Voltage gel electrodes were placed approximately 4 cm from the current electrodes, towards wrist and ankle. The system was able to measure six different frequencies per minute with twenty repetitions for each. Physiological changes and movement artefacts during this period are probably the cause of oscillations in the impedance in Fig. 5. The characteristic frequency is found in 48 kHz where Xc is 49 Ω and the resistance is 423 Ω.

Fig. 2. Magnitude and phase errors in a MatLab simulation of the DFT processing using Eq. (5) for a sampling frequency limited in 12,560 kHz.

Fig. 3. Magnitude and phase mean errors of test resistors in the impedance spectrometer prototype.

Fig. 4. Magnitude and phase mean errors of a RC circuit in the impedance spectrometer prototype.

3.2. Neural networks

Among the various types and topologies of neural networks, the network chosen was a Multilayer Perceptron (MLP) with Backpropagation training. This training applies the technique of gradient descent to minimize the total mean square error (MSE) of the output. The training involves three stages: the response at the output of the network to input signals, calculation of the associated error and adjusting of the weights. After training, the network application involves only the processing of the inputs, with a fast response time.

The study was approved by the Institutional Ethics Board Committee of the Faculty of Medical Sciences of Santa Casa de São Paulo. Two classes of diagnostics were used: one for healthy people and another for individuals with head or neck cancer. One used 60 training and 20 validation vectors for each class as well as the diagnosis associated with them. Each input vector was composed of six parameters: gender, age, BMI (body mass index), R (resistance), $|Xc|$ (capacitive reactance) and PA (phase angle).

Body mass index (BMI) was calculated by dividing weight by squared height. The impedance values shown in Fig. 6 were measured with the tetrapolar technique using a current of 800 μA (50 KHz). Although patients had neck and head cancers, total body impedance may reflect the general effects of the disease. Therefore, the gel electrodes were placed in the right foot and hand. Sick individuals tend to have lower values, however, it is not possible to separate both classes completely only with the resistance and reactance. In this case, one believes that neural network can detect the complex relationships between these electrical parameters, BMI, age gender and tumors.

Table 1
Artificial neural network (ANN) input and output formats.

Parameter	Patient 1		Patient 2	
	Original	ANN	Original	ANN
Gender	Female	0	Male	1
Age (years)	35	0.39	65	0.72
Resistance (Ω)	551	0.60	357	0.39
Reactance (Ω)	61	0.70	19	0.22
Phase angle (°)	6.32	0.67	3.05	0.32
BMI (kg/m^2)	21.26	0.59	16.33	0.45
Expected result	Healthy	−1	Sick	1

The software MatLab was chosen to perform the neural network, as well as the training and validation of the results. One advantage of this platform is that it offers a toolbox with graphic interface specific for the processing of ANNs. The network layout, weights values after the training phase and an example of its activation with a test input vector are shown in Fig. 7. The input layer had 6 neurons, one for each parameter. In order to level all the inputs, each vector was normalized in the range between "0" and "1", as shown in Table 1. The number of neurons in the intermediate layer was 13. One used only one neuron in the output layer to classify the response according to the value of activation. During the training, the two result classes were represented by the values "−1" and "1", respectively. In the test phase, the first class for healthy individuals was identified values less than "0" The second class, which corresponds to sick people, was represented by numbers equal or greater than "0".

Table 2 shows the main characteristics of the network and its performance. Since the type of network is backpropagation, when

Fig. 5. Total body impedance (Cole graph) measured by tetrapolar configuration measured between the right hand and right foot.

Fig. 6. Bioimpedance measurements of healthy subjects and cancer patients.

Fig. 7. Neural network activation with a test input vector (SNNS platform).

a learning pattern is clamped, the activation values are propagated to the output units, resulting in an error. Than one distributes the difference of an output unit to all the hidden units that are connected to this cell. The 120 training vectors were divided equally in healthy and sick individuals data, mixed randomly in order to avoid the overtraining. The 40 test vectors also contained the same number of positive and negative diagnostics. Before starting the training, one initialized the weights randomly between "−1" and "1". The decision to finish the training phase was either a maximal number of epochs (10,000) or a mean square error (MSE) criterion of equal or less than 0.3%. The learning coefficient reflects the velocity in which the weights are updated. In this case the transfer function used was purely linear; therefore, the output activity is proportional to the total weighted output. The learning algorithm used to adapt networks (learning function) was gradient descent, which is an optimisation method for minimizing an objective function that is written as a sum of differentiable functions. From the 40 test vectors used, the network was able to diagnostic 31 cases correctly with values lower than "0" for healthy individuals and equal or higher than "0" for sick people.

4. Discussion

There are many complex impedance spectrometers available today in the marked such as the Solartron 1260 which is able to measure from 10 μHz to 32 MHz with accuracy of 0.1% for the magnitude and 0.1 degrees for the phase. However, in order to be used in humans' essays, the equipment needs comply with IEC60601-1 safety and electromagnetic compatibility requirements. We expect that our prototype will be approved for human use since its earth and patient leakage values are under the norm limits.

The prototype developed was useful in demonstrating the feasibility of the method, but despite good results many improvements can still be done. The input impedance will be increased by adding buffers, in order to allow higher loads. An improvement of the processing time is also necessary, and can be addressed by using a faster A/D converter and microprocessor (or Digital Signal Processors). A shorter sampling period would also allow the measurement of impedances in a wider frequency range. This would require replacing the current DDS, which is limited to 12.5 MHz. It would also be interesting to use A/D converters with bipolar inputs, reducing the number of summing amplifiers in the system and, therefore, decreasing circuit delays. The use of dual A/D converters could eliminate the need for sample-and-hold circuits. Self-correction algorithms are an alternative to compensate measurement errors. Such methods find a non-linear equation to compensate errors in the response of phase and modulus data. Results obtained show that undersampling with the DFT algorithm is an efficient and promising method for multifrequency bioimpedance measurements.

Table 2
Main characteristics of the 6-13-1 network and its performance.

Software	MATLAB
Type of network	Backpropagation
Number of input neurons	6
Number of intermediate layers	1
Number of neurons in the intermediate layer	13
Number of output neurons	1
Number of classes	2
Class identification	Activation value from the output neuron
Training vectors	120
Test vectors	40
Weight initialisation	Random values from −1 to 1
Training epochs	10,000
MSE of training	0.3
Learning coefficients	0.05
Percentage of accuracy in the diagnosis of test vectors	77.5%

The neural network studied was able to simulate 77.5% of the two types of diagnostic correctly. Considering the small amount of data available for training, the application of the MLP Backpropagation neural network can be considered as promising. The error values are satisfactory, since there were a high level of biologic variations and impedance standard deviation. A more detailed classification, where the network output would lead to the prognostic of the patient's clinic state seems also possible. It would probably only require a higher amount of training/test cases for each class. This work shows that the use of neural networks as classifiers using data from bioimpedance may enable early diagnosis and prognosis of tumors. As result, such technique could increase the chances for healing or help providing a better treatment for patients.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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