Abstract

Electrical bio-impedance can be used to assess skin cancers and other cutaneous lesions. Bio-impedance measurement technique is one of the non invasive techniques for analysis of skin diseases. This paper presents a portable bio-impedance measurement system using impedance converter AD5933. This system is useful in the analysis of skin cancer using bio-impedance technique.

Keywords: Bio-impedance, BCC, benign nevi, SCC.

1. INTRODUCTION

Improvements of measurement technology and data processing facilitate clinically interesting discrimination power between malignant and harmless skin lesions. There are different kinds of skin cancers amongst which malignant melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) are the most significant [1]. Actinic keratosis is considered as a potentially harmful lesion as it can degenerate to SCC. BCC and SCC are called non-melanoma skin cancers that can be treated with relatively simple surgery. If the development of cancer is relatively small, some remedies are cryosurgery (freezing), laser surgery or medicated creams prescribed by a doctor. Benign nevus is a common, harmless lesion type normally mistaken for melanoma. For diagnostic purposes benign nevus is often excised. It is economical to excise the nevi but carries the risk of infections and also not comfortable to the patients.

The skin cancer is usually detected by visually inspecting the lesions of patients using some rules like the ABCD rule [2]. The appearance of the lesion tells about the existence of skin cancer. Biopsy followed by histopathological examination of excised lesion helps in further analysis of the skin cancer. The skill of the observer plays an important role in determining the diagnostic accuracy of screening. An alternative to visual screening is dermoscopy [3]. A malignant proliferation of melanocytes is called melanoma and at an early stage of growth, it has a tendency to metastasize. The melanoma lesions need to detected and excised in their early stage of growth as no effective treatment of the metastatized tumor is available yet. Many devices are developed for the diagnosis and distinction of benign and malignant lesions. These devices are based on image analysis and epiluminescence microscopy and help physicians in the analysis of lesions. Malignant and benign skin lesions are distinguished based on the electrical differences between them. The non-invasive approach of electrical impedance scanning provides information about cell shape, structure and orientation, integrity of cell membranes, relative properties of intra- and extra-cellular fluids and ionic composition [4]. There is a wide degree of variation in the bio-electric properties between tissue types and states as indicated by various studies. The change in impedance is a measure of cancer and other diseases.

There are significant differences between the bio-impedance of normal and cancerous breast tissue and also between skin cancer and normal skin as indicated by ex vivo studies [5]. The parameters like irritation, allergic reaction (wheals), age, sex, location, and hydration amount for differences in the electrical impedance of the skin as indicated by in vivo studies [6].

2. MATERIAL AND METHODS

This paper explains a system to measure bio-impedance from human skin. The system for bio-impedance measurement is as shown in figure 1:

Fig. 1 Bio-impedance measurement system using AD5933 [12, 13]
The system mainly consists of system on chip impedance converter, AD5933; an ultra low power MCU, MSP430F6638; and electrodes. These components make the system portable and low cost. The System-on-Chip technology introduced in recent years is a result of advances in various technological fields like electronics, physics and materials. It enables to embed complex functional systems into a single integrated circuit. AD5933 from Analog Devices is a result of such technological advances that enables whole impedance spectrometer availability on a single integrated circuit. AD5933 is a System on Chip (SoC) solution that consists of all the functional components necessary for characterizing impedance over a range of frequencies using a bipolar configuration. Using AD5933, the range of typical measurement frequencies is 1 KHz to 100 KHz, the impedance dynamic range of 1 KΩ to 10 MΩ with a system accuracy of 0.5%. To control the internal functions and the measurement retrieval, the chip is also provided with a serial I2C interface. Other typical specifications of AD5933 include 2.7 V and 5.5 V single power supply operation and power consumption of 33 mW at 3.3 V. The chip dimensions are 8×6×2 mm. Figure 2 shows the functional block diagram of AD5933.

![Fig. 2 Functional diagram of AD5933][12]

### 2.1 Stimulation Stage
This stage consists of a Direct Digital Synthesizer (DDS), a 12-bit Digital to Analog Converter (DAC) and a Programmable Gain Amplifier (PGA). The DDS generates digital sine waves that could be configured for the specific impedance excitation frequency \( f_0 \). The PGA adapts to the generated voltage that will be applied to the impedance, \( Z_{US}(f) \).

### 2.2 Receiver Stage
This stage is made up of a Current to Voltage Converter (CVC), a Voltage Amplifier, an anti-aliasing Low Pass Filter (LPF) and a 12-bit Analog to Digital Converter (ADC). The current flowing through \( Z_{US}(f) \) is converted into voltage and fed to the next stage by the receiver stage.

### 2.3 Impedance Estimation Stage
The DDS module generates \( \cos (2\pi f_n t_n) \) and \( \sin (2\pi f_n t_n) \) signals. The impedance estimation stage samples the signals generated by DDS module and the digitized input signal \( x_{US}(f) \) using 1024 sample points. This stage uses the single Discrete Fourier Transform (DFT) to estimate the real and imaginary values of impedance.

### 2.4 Chip Control Stage
This stage controls all chip functions and is also responsible for storing measurement results along with other parameters using I2C core module. AD5933 uses a frequency sweep to characterize impedance over a range of frequencies. Thus, while analyzing a single frequency point, the sequence is repeated at a different frequency until the entire spectrum is obtained. AD5933 performs 1024-point single frequency DFT analysis known as sine correlation method in digital form. Each frequency is sampled to obtain 1024 sample points of output and input signals for estimation of real and imaginary components.

\[
X_{US}(f) = \sum_{n=0}^{N-1} \left( x_{US}(n) \times \cos(2\pi f_n t_n) - j \times \sin(2\pi f_n t_n) \right)
\]

\[X_{US}(f) = R_{US}(f) - j \times I_{US}(f) \]

\[R_{US}(f) = \sum_{n=0}^{N-1} x_{US}(n) \times \cos(2\pi f_n t_n) \]

\[I_{US}(f) = \sum_{n=0}^{N-1} x_{US}(n) \times \sin(2\pi f_n t_n) \]

The equation (1) calculates the value of 1024-point DFT. The equations (2) and (3) are useful in calculation of real part of DFT and imaginary part of DFT respectively, using sine correlation method [7]. A calibration factor is applied to the computed values of real and imaginary components to obtain the impedance magnitude and phase values. Several factors make AD5933 unsuitable for bio-impedance measurements. These factors...
include bipolar measurement configuration, voltage driven measurement, impedance range, applied voltage contains a DC voltage level. An Analog Front End (AFE) can be used in such situations to ensure that these factors are minimized or removed and meet electrical bio-impedance measurement requirements.

Figure 3 shows AFE for AD5933. This AFE will modify the AD5933 voltage-controlled bipolar device into a current-controlled tetra-polar configuration. It ensures patient safety and impedance measurement below 1KΩ as expected for human body.

![Fig. 3 Analogue front end for AD5933 [11]](image)

The electrical bio-impedance measurement is based on passive electrical properties of tissue and hence energy must be applied to the tissue sample to perform a deflection measurement. The measurement is carried out by applying electrical energy, voltage or current, to the tissue under study, and the resulting current or voltage, respectively, is measured. Thus, the electrical bio-impedance is obtained from the applied electrical energy and the response from the tissue. Electrodes are used for application of the electrical energy to the tissue and the measurement of the response from the tissue under study. The endogenous bio-potential of a tissue is sensed with the help of the skin electrode by establishing a contact with the skin. This creates an electrical interface between body and the measurement system that allows electrical charges to flow through the tissue. Non-polarizable electrodes like Silver-Silver Chloride (Ag/AgCl) allow transfer of charges, thus producing very little voltage, ideally none. When used in combination with measurement instrumentation that has high input impedance, ideally infinite, these electrodes are much suitable for measuring electrical bio-potential. Thus, for non-invasive physiological measurements, Ag/AgCl electrodes are most commonly used. The reaction between Ag, the metal, and Ag/AgCl, the salt, produces fast electrode kinetics that facilitates the current flow through the electrode, thus improving the interfacing. This is a non-toxic, stable electrode available at low cost. The electrode is less sensitive to frequency changes. These electrodes are interfaced with AD5933 along with analogue front end as shown in Figure 3.

The MSP430 microcontroller is a processing device that offers a platform of ultra-low-power processors. MSP430 provides high integration of the complete signal chain that is required for applications like spirometers, blood pressure monitors for personal applications, pulsoximeters and heart rate monitors. There are five low-power modes for this architecture. For portable measurement applications, it is optimized to achieve extended battery life. The device has 16-bit RISC CPU. In addition to this to maximize the code efficiency, the device has 16-bit registers, and constant generators. MSP430 has digitally controlled oscillator (DCO) that allows the device to wake up from low-power modes to active mode in typically 3μSec. The device has typical applications like thermostats, digital motor control, digital timers, analog and digital sensor systems, hand-held meters and remote controls.

The result bio-impedance measurement of a tissue is multivariate impedance spectra. Parameterization technique is used to simplify these spectra to fewer variables. Cole-Cole type equivalent circuits are used traditionally for fitting in bio-impedance dispersion [8]. These are virtual electronic circuits that fit the measured impedance spectra. The equivalent circuits provide empirically absolute values such as membrane conductivity and resistance of the extra- and intra-cellular environments with the assumption that the model is a reasonable description of the tissue. According to Cole, bio-impedance, Z, is a function of frequency, f, which can be approximated by the Cole-Cole equation (See Equation (4))

\[
Z(f) = R_x + \frac{R_0 - R_x}{(1 + \frac{f}{f_c})^{\alpha}}
\]  

(4)

In equation (4), fc (Hz) is the characteristic frequency of the actual dispersion. R0 and Rx (ohm) are resistances at low and high frequency, respectively. A constant α, to some degree, reflects the heterogeneity of the tissue. It attains a value between zero and 0.5, where zero represents a very homogeneous tissue. Aberg et al. [1] indicate that skin cancers are linearly more independent from reference skin than benign nevi. The squared correlation coefficient, r^2, of the relation between reference skin and lesion is higher for benign nevi than skin cancer. Thus, it is suggested that the degree of linear relationship between reference skin and lesion impedance could be used to distinguish skin cancer and benign nevi.
Principal component analysis (PCA) is a powerful tool for extraction of information from large multivariate data sets. PCA simplifies the data to a number of dimensions, principal components (PCs) that describe the main features, the structural variance, of the data. Two Principal Components typically describe more than 90 percentage of the variance within the normalized lesion impedance data [9]. Most of the in-vivo studies of the skin use measurements from an instrument called the impedance spectrometer. These studies are based on a comparison of four indices namely, magnitude index (MIX), phase index (PIX), real-part index (RIX), and imaginary-part index (IMIX). These indices are defined in equation (5), (6), (7), and (8).

\[
\text{MIX} = \frac{\text{Re}(200\text{kHz})}{\text{Re}(500\text{kHz})} \quad (5)
\]
\[
\text{RIX} = \arg(20\text{kHz}) - \arg(500\text{kHz}) \quad (6)
\]
\[
\text{RIX} = \frac{\text{Re}(500\text{kHz})}{\text{Re}(200\text{kHz})} \quad (7)
\]
\[
\text{IMIX} = \frac{\text{Im}(20\text{kHz})}{\text{Im}(500\text{kHz})} \quad (8)
\]

where Z20 kHz is the measured impedance at 20 kHz, Z500 kHz is the impedance at 500 kHz. Emtestam et al. [11], compared measurements of MIX, PIX, RIX, and IMIX over normal skin and over lesions of nodular BCC. Fishers’ Linear Discriminant (FLD) is a simple classifier which finds a discriminant direction within the data. The discriminant directions are the linear combinations of the data that both minimize the within-groups variations and maximize the between-groups variations.

3. DISCUSSION

In this paper a portable system is discussed for electrical bio-impedance measurement to be used for analysis of skin cancer. A significant decrease in the value of MIX or IMIX over BCC is observed compared with normal skin. Differences may result because BCC tumors may be better irrigated by the local blood supply than normal skin or benign lesions. Other reason for differences being the stratum corneum is thinner or better hydrated over BCC. The nuclei of BCC cells also tend to be larger and the intercellular spaces smaller than that for cells from normal skin. These structural differences cause measurable differences in the impedance of the tissue as a function of frequency. One of the reasons for observed differences is that malignant cell membranes tend to have different electrochemical properties than normal cells.

REFERENCES


AUTHORS

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