Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Breast Cancer Detection Using Low-Frequency Bioimpedance Device

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Introduction: Early detection of breast cancer saves lives. Existing detecting techniques are invasive. Electrical bioimpedance is a noninvasive technique and has a high diagnostic potential.

Methods: An impedance value different from the normal can predict a physiological abnormality. The idea is to use a designed bioimpedance device to early detect breast cancer. A low-frequency current (1 kHz, 0.9 mA) is injected to each breast to measure the extracellular resistances. The resistances of the two breasts are then measured, and if there is a significant difference, warning is displayed. The performance was tested on a set of reference resistors, and the validation was done in vitro on (Na+Cl-) solutions and in vivo on a group of forty volunteer women.

Results: The results confirm that the electrical conductivity of an ionic solution is proportional to its concentration. The concentration and the resistance are strongly correlated (correlation coefficient of 0.97). The accuracy and the repeatability of the measures were satisfactory. Early detection means that we can detect small extracellular concentration variations into the breast (from 0.6 g/l). In vivo measurements made it possible to set the threshold at 50 ohm. If the difference between the two measured breast resistances is greater than this threshold, we advise the patient to consult a doctor promptly.

Conclusion: The difference between measured resistances of the right and left breast is a pertinent parameter to early detect the presence of a cancer. The lowest resistance value (RR or RL) can provide information on the breast affected by the cancer (right or left). Various improvements in the system are possible but already the results are encouraging. In the future, this system could be integrated into a bra.

Keywords: biomedical engineering, breast cancer detection, electrical bioimpedance, FPGA Virtex-5 LX30, LabVIEW FPGA, NI PXI-7841R

Introduction

Breast cancer is a serious condition that threatens the lives of most women. The reduction of the mortality rate and the improvement of the chances of cure are only possible if the tumor is managed at the first stages of its appearance. The mammary gland is an organ in permanent evolution. The cells are still growing and differentiating, making it more susceptible to cancerous transformations. In case of breast cancer, the cells can remain in the breast or disperse in the body through the blood or lymphatic vessels. The progression and/or dispersion of breast cancer take, most of the time, several months or even a few years.[1] Breast cancer usually develops in the milk ducts and lobules. The carcinogenesis process has four phases: initiation, promotion, progression and invasion.[2] The most common sign is the presence of

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a mass in the breast. It is irregular in shape and very different from the rest of the breast tissue. Parallel to the site where they develop, we also distinguish cancers according to their stage of evolution. The stage is defined by the size of the tumor (T0 to T4). T0, the cancer is confined within the ducts or lobules of the breast tissue and has not spread into the surrounding tissue of the breast. T1, the tumor in the breast is 2 centimeters (cm) or smaller in size at its widest area. T2, the tumor is larger than 2 cm but not larger than 5 cm. T3, the tumor is larger than 5 cm. T4, the tumor has grown into the chest wall or into the skin or the chest wall and the skin or inflammatory breast cancer. In this case, breast cancer is said to be infiltrating.[3] In Tunisia, the average tumor size diagnosed is 3 cm (Stage 2). Different screening methods such as mammography, ultrasound imaging and magnetic resonance imaging are used.[4–8] They differ in terms of efficiency, invasiveness, cost, availability and ease of use. The different screening techniques have advantages and disadvantages.

Bioimpedance can offer a new and effective alternative for early detection of breast cancer. Bioimpedance is suggested as another method of detecting cancer because cancerous tissues have different electrical characteristics than normal tissues.[9] By applying a current to an object through a finite number of electrodes, an electrical impedance system produces a precise impedance value of the object according to the electrical characteristics of the different tissues throughout the volume of the object. Numerous studies have shown that these systems can distinguish between cancerous and normal tissues.[10–15]

Materials and Methods

Bioimpedance corresponds to the opposition of tissues to the passage of a current. Various researchers have performed impedance measurements on healthy normal tissues as well as cancerous tissues of the human breast. However, some representative results are found.[6,16–18] From these impedance measurements it can be deduced that compared to normal tissues, malignant tumors showed a higher current conductivity.[17,18]

The conductance G, (in Siemens) reflects the ability of the electrolytic solution to pass the electric current. It is the inverse of the resistance R (in Ω). It can be concluded that malignant breast tumors have lower electrical impedance than normal tissues. Morimoto et al[13,14] suggested that impedance measurement can be used for the differential diagnosis of malignant and benign tumors. From the previous results, the mammary impedance measurement shows that malignant breast tumors have lower electrical impedance than normal tissues. Therefore, electrical impedance can be used as an indicator for the detection of breast cancer. There are significant differences between benign and malignant breast tumors[9,11,16] and.[19] Electrical impedance can therefore also be used to separate benign tumors from malignant tumors and thus reduce benign biopsies.[17,20]

To use this method in the early detection of breast cancer, we designed a new bioimpedance device. We aimed to have a noninvasive and efficient device which can be easily integrated into a bra in the future. The new bioimpedance device has been tested in vitro and in vivo. The use of alternating current in bioimpedance-based measurement systems aims to track the change in electrical impedance produced by structural or functional changes in the system under test. The different researchers had used a low amplitude AC current and a variable frequency for their impedance measurements on breast tissue.[12,21] When applying a low-frequency current, the cell membrane prevents the current from entering the cell, limiting it to pass only in the extracellular fluid. Since the extracellular resistance of a tumor is less than that of the healthy tissue, then a weak low-frequency current is sufficient to determine the extracellular resistance of the mammary tissues.[11] The use of low-frequency current has allowed us to simplify Fricke's model and reduce it to a simple extracellular resistance, since the low-frequency current cannot penetrate the intracellular medium, Figure 1. In the extracellular medium, we do not have the capacitive effect of the

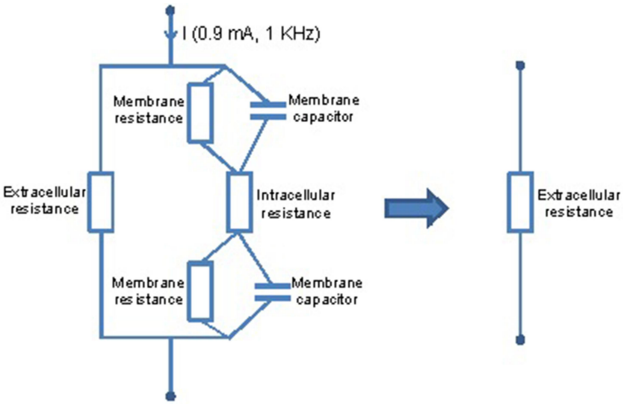

Figure 1 Simplification of the Frick's model following the use of a low-frequency current.
Abbreviations: Re, extracellular resistance; Ri, intracellular resistance; C, cell membrane capacitance.

membrane. The impedance is purely resistive and therefore the impedance Z can be equated with the resistance R.

Currents are considered low frequency if they are less than 5 kHz.[22] The majority of the lines of the electric field pass through the extracellular medium without being able to penetrate inside the cells. On the other hand, currents of high frequencies arrive easily to cross the capacitive membrane and the lines of the field thus pass by the two mediums intra and extra cellular indifferently.

The Designed Device

The prototype is composed by an acquisition card, the NI PXI-7841R, a chassis the NI PXI-1033, a shielded connector blocks the NI SCB-68 and development software, LabVIEW (LabVIEW Professional Development System with MathScript 8.6) with its LabVIEW FPGA module. The core of the NI PXI-7841R is an FPGA target, Xilinx's Virtex-5 LX30. The configuration of the FPGA was not done by the VHDL language but rather by graphical programming thanks to LabVIEW FPGA. The design prototype satisfies the electrical safety requirements of biomedical equipment.[23]

Injection Module

We just change the frequency of the injection signal. The injection current is a 1 kHz square wave, with 5 V amplitude and 0.9 mA intensity. When injecting current into the mammary glands, two considerations must be taken into account: the protection of the patient and the obligation to have two symmetrical outlets directed towards the two mammary glands.

Acquisition Module

Measurement of the impedance of each breast is performed by two voltage dividers connected to the FPGA prototype. The impedance of each breast is measured using one voltage divider. The acquisition module is connected to each breast by two electrodes.

From these two voltage dividers, the designed system determines the right breast resistance (R_R) by using (1) and the left breast resistance (R_L) by using (2) and then calculates the difference between the two measurements. V_{RB} represents the voltage tension collected between the electrodes placed on the right breast and V_{LB} is the tension collected in the left breast (V_{in} = 5 V).

$$R_R = R_1 \frac{V_{RB}}{V_{in} - V_{RB}} \quad (1)$$

$$R_L = R_1 \frac{V_{LB}}{V_{in} - V_{LB}} \quad (2)$$

If the difference is greater than a threshold, we display a warning message, asking the patient to promptly consult a doctor. If the difference is less than the threshold, we memorize the two resistance values for a possible comparison with future measured values. The program flowchart is presented in Figure 2.

To validate the designed system, we tested first the precision of the resistance determination and then we made in vitro measurements on (Na^+Cl^-) solutions and in vivo on a group of forty women volunteers. All subjects were voluntary and signed a consent document which specified the nature of the measures to be taken. In addition, the measures are non-invasive, non-dangerous and the current used is very low and has no effect on women volunteers. The biological tissues are composed of about 60% of water: two-thirds is inside the cells (cytoplasm) and the remaining third in the extracellular medium (interstitial medium). For

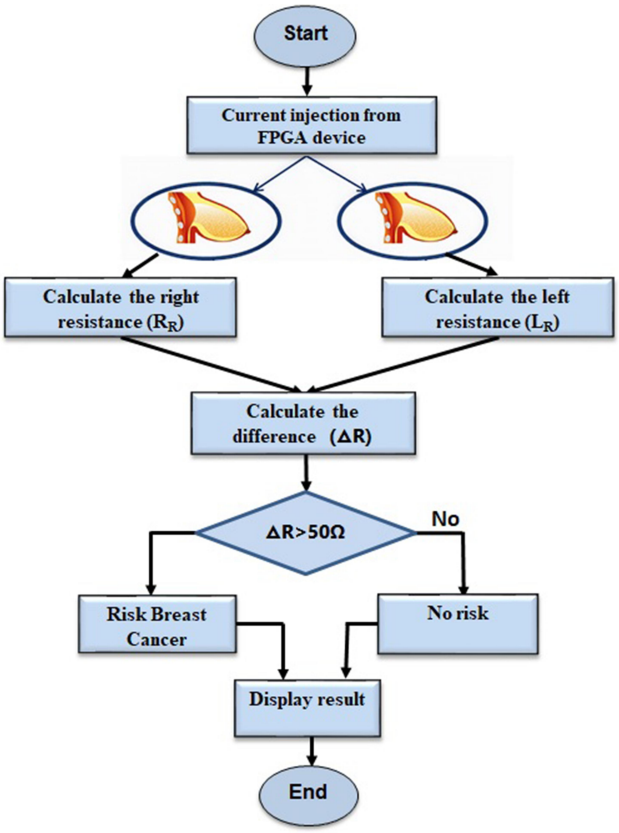

Figure 2 Program flowchart.

Table 1 Intracellular and Extracellular Concentrations of Ions

Ion	Intracellular Concentration (Calculation) mM[a]	Intracellular Concentration (Experimental) mM[a]
Na^+	7	15
K^+	162	150
Cl^-	3	5
$Ca2^+$	$1.7\ 10^{-4}$	10^{-4}
$Mg2^+$	0.97	1
$HCO3^-$	14	8

Note: mM[a], in millimolar concentration.

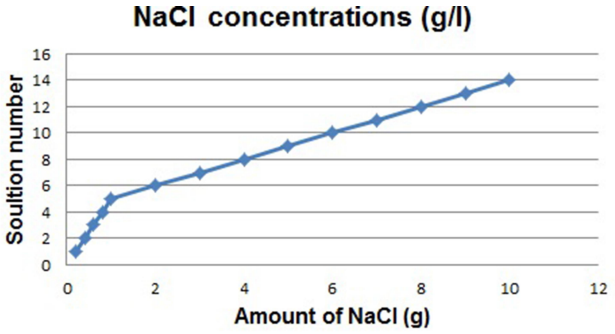

Figure 3 Different solutions of Na^+Cl^- with water volume = 340 mL.

low frequencies, the ionic conductivity of a tissue is highly dependent on the extracellular fluid present. The conductivity of biological tissues also depends on the temperature of about 2%/°C which is similar to the temperature coefficient of a saline solution. We have chosen (Na^+Cl^-) solutions because, extracellular liquids can be considered as aqueous solutions and the most numerous ions are by far the Na^+ and Cl^- ions, Table 1.[24]

Breast Phantoms

To perform in vitro measurements, we designed two identical hemispheric phantoms, made of plastic. The shape of a mammary gland is hemispheric in European and Asian women, rather conical in African women. The 2 nipples are spaced about 20 cm apart. The breast phantom size is 12 cm in height and 12 cm in diameter. Each phantom is connected to the designed system by four conductor wires (two for current injection and two for voltage measurement). To ensure that the conductor wires are immersed in the aqueous solutions of Na^+Cl^-, the phantom must be filled with a volume of water equal to 340 mL. Aqueous solutions of sodium chloride are prepared under the same conditions, only the amount of dissolved (Na^+Cl^-) which varies from one solution to another. The different concentrations prepared are presented in Figure 3. In the Na^+Cl^- solutions, in the absence of an electric current, the charges are immobile. When we apply an electric current, we observe a displacement of the charges and thus ionic conduction. The ionic solution behaves like an ohmic conductor. The aqueous solution of sodium chloride is a strong electrolyte. The presence of ions makes the solution a good conductor of electric current. We validated first the performance of the system designed in vitro using the two breast phantoms and the Na^+Cl^- solutions. Then in vivo on a group of forty volunteer women.

Results

The performance of the system designed was tested on a set of reference resistors and then validated in vitro and in vivo. In this section, we presented the results obtained. For in vitro measurements, we used the two breast phantoms filled by Na^+Cl^- solutions with different concentrations. In vivo measurements were made on a group of forty volunteered women.

Resistors Measurements

The designed system has been tested on a set of resistors. We measured a set of resistors by a UT33C digital multimeter and the designed device. Figure 4 presents the Bland-Altman analysis for resistor measurement accuracy. The percent error equals 0.31%.

In vitro Measurements

In this section, we simultaneously measured into the two breast phantoms the resistances of the different Na^+Cl^-

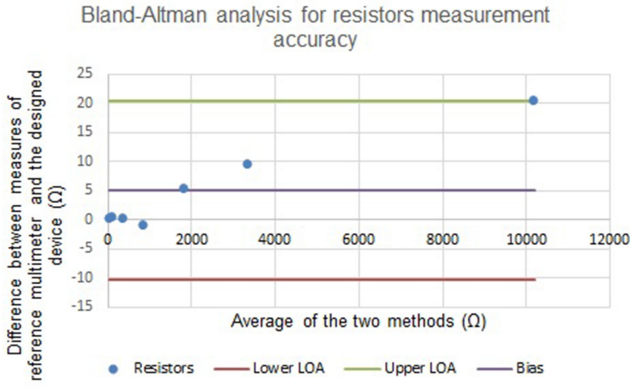

Figure 4 Bland-Altman analysis for resistors measurement accuracy, with Bias = 5.09, upper LOA= 20.36 and lower LOA= −10.18.

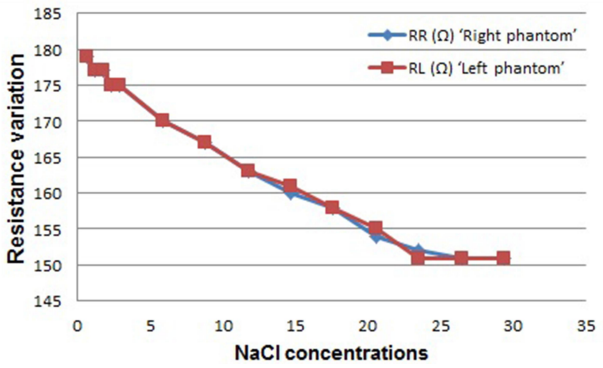

Figure 5 Resistance variation as a function of Na^+Cl^- concentration.

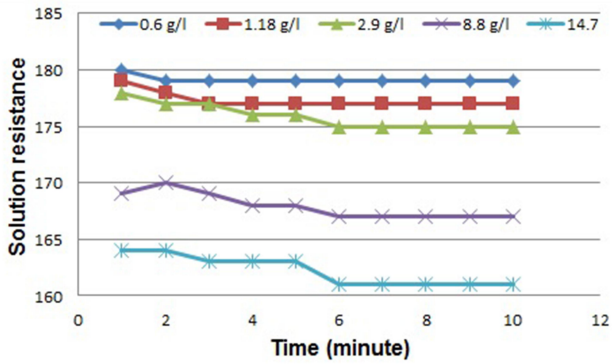

Figure 6 Evolution of the resistance as a function of time for different Na^+Cl^- concentrations.

solutions. Then we studied the correlation between the resistance and the concentration of the solution. Finally, we studied the repeatability of the measures. We used the designed system, the two breast phantoms and the fourteen different solutions. Figure 5 presents the resistances obtained in the two phantoms, RR for the phantom placed on the right (by analogy to the right breast) and RL for the phantom placed on the left (left breast).

The resistance R is inversely proportional to the Na^+Cl^- concentration C. In fact, the less concentrated solutions have greater resistance values compared to solutions of high concentrations. The two curves are decreasing, which shows that the resistance of an electrolyte is inversely proportional to its concentration. The measurements obtained confirm Kohlrausch's law: the electrical conductivity of an electrolyte is proportional to its concentration. From the concentration value (C = 26.5 g/l), the solutions become saturated, the sodium chloride is no longer soluble in water. The curves are stable and the resistances measured remain invariable and equal to 151 Ω. For our application, breast cancer screening, this limit is not a problem, because when the solution is saturated this will correspond to an advanced stage of the cancer and not to an early detection stage. A correlation analysis was done; the concentration and the resistance are strongly correlated. We obtained a correlation coefficient of '0.97′. The error between the adjusted values and the measured values is 0.969 Ω for the right phantom, and 0.972 for left phantom. The lowest concentration value we detected is 0.6g/l, certainly, we can go further but we must realize a more complex system. To study the repeatability, we used five different Na^+Cl^- solutions; we measured the resistance at each minute during 10 minutes (Figure 6). For each solution, from the fifth minute the resistance did not change any more. This observation allowed us to require a five-minute delay before each in vivo measurement.

In vivo Measurements

The designed system has been tested on forty volunteer women of different ages. The present study and protocol were conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee in Health and Science Disciplines (REC-HSD) of the Prince Sattam bin Abdulaziz University (approval no. REC-HSD-013-2020). The adopted experimental protocol begins by placing the woman in a supine position on her back. Then, on each breast, we placed four electrodes: Two for the injection of the low-frequency current and two for the acquisition of the signal. We waited five minutes (Figure 6, temporal stabilization of the measurement); then, we recorded the resistances measured and deduced the difference between the right and left breast resistances. The measurements obtained are illustrated in Table 2.

Discussion

The high resistance measured values indicate a denser breast,[5,25,26] The appearance of micro-calcifications in a woman's breasts alters the hydration of breast tissue and the permeability of the cell membrane, resulting in significant variations in electrical impedance,[7,10,25–27] Jossinet and Schmitt,[20] Morimoto et al[14] confirmed that malignant breast tumors have lower electrical impedance than surrounding normal tissues. Then for an early detection of breast cancer, a significant difference between the extracellular resistances obtained from the right and left

Table 2 In Vivo Measurements

Patient N°	Age-Ranges (year)	Weight (Kg)	Resistance of the Right Breast (Ω)	Resistance of the Left Breast (Ω)	Difference[a] (Ω)	Warning if Difference > 50Ω
1	17–29	47	231	240	9	No risk
2	17–29	59	301	277	24	No risk
3	17–29	55	401	403	2	No risk
4	17–29	70	555	601	46	No risk
5	17–29	72	386	379	7	No risk
6	30–39	62	513	537	24	No risk
7	30–39	57	700	655	45	No risk
8	30–39	73	610	630	20	No risk
9	30–39	80	713	678	35	No risk
10	30–39	66	523	550	27	No risk
11	30–39	82	730	741	11	No risk
12	30–39	65	630	670	40	No risk
13	50–59	92	820	835	15	No risk
14	40–49	69	639	593	46	No risk
15	40–49	62	454	479	25	No risk
16	40–49	73	670	707	37	No risk
17	40–49	86	497	531	34	No risk
18	40–49	79	527	488	39	No risk
19	40–49	89	588	541	47	No risk
20	40–49	91	590	603	13	No risk
21	40–49	75	658	699	41	No risk
22	40–49	66	700	655	45	No risk
23	50–59	78	911	953	42	No risk
24	50–59	66	730	695	35	No risk
25	50–59	87	850	875	25	No risk
26	50–59	71	730	850	120	Warning
27	50–59	68	540	559	19	No risk
28	50–59	69	420	426	6	No risk
29	50–59	65	900	921	21	No risk
30	50–59	56	389	410	21	No risk
31	50–59	82	680	723	43	No risk
32	60–69	73	600	648	48	No risk
33	60–69	78	590	566	24	No risk
34	60–69	71	440	478	38	No risk
35	60–69	80	490	513	23	No risk
36	60–69	78	600	553	47	No risk
37	60–69	59	570	521	49	No risk
38	60–69	92	870	909	39	No risk
39	60–69	71	540	577	37	No risk
40	60–69	80	630	591	39	No risk

Note: [a]Difference between measured resistances of the right and left breast.

breast can be a relevant parameter. We computed the difference between the resistance measures of the right and left breast. We retained the difference value equal to 50 Ω as a threshold. If the difference is greater than 50 Ω, this means that there is a serious risk and a warning message is displayed.

The results show that the difference is small than 50 Ω in thirty-nine cases. Only patient number 26 presents a high difference, 120 Ω. We asked here to go to the hospital and make a breast cancer screening. The examinations carried out at the hospital confirmed that she had a stage 2 breast cancer in her right breast. Actually, the extracellular resistance of the right breast is lower than that of the left breast, R_R = 730 Ω and R_L = 850 Ω.

The results presented above, show the relevance of the choices selected. Indeed, in vitro and in vivo

measurements have confirmed that the bioimpedance method can offer a serious alternative for the early detection of breast cancer. Early detection means that we can detect small extracellular concentration variations into the breast (from 0.6 g/l). Various improvements in the system are possible but already the results are encouraging. This method is non-invasive (no X-ray or any other ionizing radiation), low cost and can be used safely at home.

Conclusion

The designed system based on the use of a low-frequency current allowed us to realize a noninvasive device which can be integrated into a bra. The designed system is connected. Each woman can have it and perform a self-check whenever she wants (noninvasive and safe). Malignant breast tumors have lower electrical impedance than surrounding normal tissues. The use of low-frequency current has permit to focus only on the breast the extracellular resistance. The difference of the measured resistances of the right and left breast is a pertinent parameter to early detect the presence of a cancer. A difference greater than 50 Ω is sufficient to decide whether to visit a cancer center for further investigations. In this case, the lowest resistance value (R_R or R_L) can provide information on the breast affected by the cancer (Right or left). The in vitro study has permit to confirm the strong correlation between the concentration of the Na^+Cl^- and the resistance (r=0.97). After five minutes the measures became stable and the difference between the two phantoms is less than 1 Ω.

In order to improve our work, we will first carry out a measurement campaign on subjects suffering from breast cancer as well as on normal subjects. This measurement campaign will help us to improve our system and choose the best threshold. Then, we will increase the number of electrodes to accurately locate the tumor in the affected breast and to create an image that will be displayed on the smartphone. This will allow having a smart mammograph by the electrical bioimpedance method.

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Disclosure

The authors report no conflicts of interest in this work.

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