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Jesús Alejandro Martínez Juárez

Dielectric Spectroscopy Sensor Design. Blood Dielectric Initial Study.

Universidad Popular Autónoma del Estado de Puebla

Advisor: Ma. del Rocío Baños Lara, PhD., Faculty of Medicine, UPAEP, Centro de Investigación Oncológica Una Nueva Esperanza-UPAEP
Examining Committee: Aurelio Horacio Heredia Jiménez, PhD. Faculty of Engineering, UPAEP
Examining Committee: Arllene Mariana Pérez González, PhD. Faculty of Engineering, UPAEP

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Dielectric Spectroscopy Sensor Design.

Blood Dielectric Initial Study.

Candidate:

Mechatronics Engr, Jesús Alejandro Martínez Juárez, student of Master of Science in Biomedical Engineering program, UPAEP

Thesis Committee:

Advisor: Ma. del Rocío Baños Lara, PhD.

Faculty of Medicine, UPAEP

Centro de Investigación Oncológica Una Nueva Esperanza-UPAEP

Examining Committee: Aurelio Horacio Heredia Jiménez, PhD.

Faculty of Engineering, UPAEP

Examining Committee: Arllene Mariana Pérez González, PhD.

Faculty of Engineering, UPAEP

Collaborating Institutions:

Centro de Investigación Oncológica Una Nueva Esperanza-Universidad Popular Autónoma del Estado de Puebla (CIO-UNE-UPAEP)

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Author: Jesús Alejandro Martínez Juárez

Abstract

Leukaemia is characterized by the production of not mature leukocytes, causing the concentration of healthy cells to drop. Acute lymphoblastic leukaemia (ALL) is one of the most common types of this cancer.

Dielectric properties are parameters that determine the effects of electric fields on the matter. Studies have shown that pathological differences between normal and cancer cells affect their composition and morphology, shaping their dielectric spectrum.

In Mexico, cancer is the leading cause of death due to disease from 5 to 24 years; leukaemia covers approximately 50% of these cases. Late diagnosis is one of the main problems for patients to survive, in part due to the lack of specialized equipment and no recommended routine screening test.

The objective of this research was to design, test, and validate a low-cost, portable dielectric sensor, capable of acquiring signals to perform a dielectric spectroscopy study of the blood and thus detect irregularities related to ALL.

A dielectric sensor, based on a parallel-plate cell design was developed. Dielectric spectroscopy analyses were carried out, at 1 MHz, with blood samples from a pilot group of ALL patients and healthy donors. Results showed a mean relative permittivity of 8,312 for the healthy-female group, with ages ranging from 22-27 years, and a mean relative permittivity of 8,043 for the ALL-female group, with ages ranging from 12-13 years.

A low-cost, portable dielectric spectroscopy sensor was successfully designed and implemented, which is suitable to perform analyses either on blood or other sample types. Results were obtained, however, in order to relate dielectric properties of blood to ALL, further investigation needs to be performed with a much more narrowed and specific grouping.

Keywords: dielectric spectroscopy sensor, parallel-plate sensor design, dielectric properties, acute lymphoblastic leukaemia, blood relative permittivity.

Acknowledgements

This thesis is dedicated to my parents; my mother, Norma, and my father, Jesús. Thank you for teaching me to always believe in myself to achieve any goal I pursue, no matter how hard it may be. Thank you for teaching me to never give up and to always work hard to surpass any obstacle I may encounter in life. Thank you for your love, time and support. Without them and everything you have done for me, this would not have been possible.

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Tables and Figures Index

Abbreviations, acronyms and symbols

Abbreviation	Meaning	Page
WBC	White blood cells	8
ALL	Acute lymphoblastic leukemia	9
CLL	Chronic lymphoblastic leukemia	9
AML	Acute myeloid leukemia	9
CML	Chronic myeloid leukemia	9
CNS	Central nervous system	11
DNA	Deoxyribonucleic acid	11
$\varepsilon\hat{}$	Complex relative permittivity	13
ε'	Relative permittivity	13
σ	Conductivity	13
ω	Angular frequency	13
Hz	Hertz	13
β	Beta	13
EDTA	Ethylenediamine tetraacetic acid	15
AC	Alternating current	18
PTFE	Polytetrafluoroethylene	19
EP	Electrode polarization	20
STL	Standard tessellation language	31
PCB	Printed circuit board	32
Ω	Ohms	33
MS/s	Mega samples per second	33
C_0	Empty cell capacitance	33
DC	Direct current	34
Ωm	Ohm-meter	35
V	Volts	40
A	Amperes	40

General Background

Blood Composition

Blood makes up about one-twelfth of an adult's body weight, which averages 5 liters of blood [1], [2]. About 50 to 55% of the blood is composed of plasma, which is the liquid medium through which different cellular components are transported and distributed. 90% of the plasma is water that contains dissolved substances such as glucose, hormones, enzymes, and waste such as urea and lactic acid. It also contains proteins such as albumin, fibrinogen and globular proteins or globulins; globulins types are the alpha, beta and gamma. The first two, help to transport lipids and gamma globulins, are mostly antibodies [1], [3]. The remaining percentage of the blood is composed of 3 types of specialized cells. Red cells or erythrocytes (45-50% of blood) that transport oxygen; white cells (leukocytes) that are part of the body's defense system; and platelets (thrombocytes) that are involved in the coagulation process. Leukocytes and thrombocytes make up 1-2% of the blood [1], [2]. The body's immune system focuses on the specialized cells mentioned above, leukocytes. These cells respond to the invasion of different types of microorganisms. There are different types of leukocytes, such as monocytes, lymphocytes, neutrophils, basophils and eosinophils [4]. All these are derived from the bone marrow, which is the soft, spongy tissue found in the central cavity of most bones [5], [6].

There are different disorders and affectations that can occur in the blood, either with respect to erythrocytes, lymphocytes or thrombocytes. One of these disorders is leukemia.

Leukemia

Leukemia is the cancer of the blood or bone marrow. As mentioned earlier, the bone marrow produces blood cells. Leukemia occurs when there is a problem in the production of these cells. It usually affects white blood cells (WBC), however, some leukemias begin in other types of blood cells, such as erythrocytes [7].

In this type of disorder, cancer cells (usually white blood cells) remain in an unmature sate, and they multiply in the bone marrow. This causes the concentration of healthy cells to drop dramatically. When this happens and the

blood has an excess of malignant white cells, different problems arise [8]–[12]. The deficiency of erythrocytes causes anemia, the reduction in healthy leukocytes leaves the body without the ability to fight infections and thrombocyte deficiency stops the blood from clotting in wounds [8].

Often the cancer cells are distributed through the bloodstream, causing enlarged lymph nodes, spleen and liver.

Treatments and types of leukemia

The treatments that are currently used depend on the type of leukemia, how much it has spread, and in general the current health of the patient. Mainly, they are the following [10], [11], [13]:

- Chemotherapy: Medications are used to destroy cancer cells in the blood and bone marrow.
- Radiation: uses x-rays to destroy cancer cells or prevent their growth.
- Biological therapy: also called immunotherapy, helps the immune system to find and destroy malignant cells.
- Targeted therapy: drugs are used to block specific genes or proteins that cancer cells need to grow.
- Stem cell transplant: the affected cells in the bone marrow are replaced by healthy cells; patients receive previous chemotherapy.
- Surgery: The spleen is removed if it is filled with cancer cells and is pressing other organs.

There are different types of leukemia, but the main ones are:

- Acute Myeloid Leukemia (AML)
- Acute Lymphoblastic Leukemia (ALL)
- Chronic Myeloid Leukemia (CML)
- Chronic Lymphocytic Leukemia (CLL)

In AML and ALL, the acute term indicates that this type of leukemia progresses rapidly and if it is not treated, it can be fatal in just a few months [10], [11], [14].

Acute myeloid leukemia occurs when the bone marrow begins to produce blasts, which are cells that have not fully matured. These blasts would normally

develop into white cells, with the exception of lymphocytes. It is important to note that this type of leukemia has several subtypes, depending on the cell type from which this leukemia developed [15], [16]:

- Myeloblastic (M0)
- Myeloblastic (M1)
- Myeloblastic (M2)
- Promyelocytic (M3)
- Myelomonocytic (M4)
- Monocitic (M5)
- Erythroleukemia (M6)
- Megakaryocytic (M7)

Acute lymphocytic leukemia also occurs when abnormal cells are produced in the bone marrow. This type of leukemia evolves rapidly, replacing healthy cells, which would produce lymphocytes, with malignant cells that do not mature. It is typically associated with having a greater population of B lymphatic cells than T cells. The incidences of ALL are mostly in people under 15 years and older than 45 years [17], [18].

Chronic myeloid leukemia, like AML, affects blood-forming cells in the bone marrow. A genetic change occurs in these cells when they are immature (erythrocytes, thrombocytes and leukocytes, with the exception of lymphocytes). However, this leukemia has a relatively slow growth. One difference of this type of leukemia is that it has been shown to be associated with an abnormal chromosome, the Philadelphia chromosome [19], [20].

Chronic lymphocytic leukemia, such as ALL, originates from cells that would become lymphocytes. In CLL, malignant cells accumulate slowly and many times there are no obvious symptoms for some years [21], [22].

Diagnosis

The symptoms of leukemia can easily be confused with those of other diseases. Therefore, different tests should be done to determine the true cause of the symptoms and, if the results are positive for leukemia, more tests should be done to determine the type of symptoms.

In general, the first thing that occurs is the patient manifesting signs and symptoms, after this an exhaustive review of the patient's medical history is done, to know all their symptoms, for how long they have been presented, and possible risk factors. Along with the review of the clinical history, a physical examination is done. With these two procedures, it is intended to identify mainly 5 syndromes: anemic, infectious, purpuric, infiltrative, and metabolic disturbances syndrome. Symptoms like fever, fatigue, enlarged lymph nodes, areas of bleeding or bruising etc. are sought.

A thorough examination must be made seeking for central nervous system (CNS) infiltration manifestations. Generally, a complete neurological exploration is recommended during the initial patient evaluation. In patients with neurologic symptoms a magnetic resonance imaging (MRI) and / or computed tomography scan (CT) should be performed.

In case of suspicion of leukemia, it is proceeded with more in-depth examinations. Hematic biometry, blood chemistry, electrolyte panel, liver function test with lactate dehydrogenase and acute phase reactants are some of the tests that should be performed under leukemia suspicion.

Blood tests are performed to determine the complete count of each type of cell in the patient's blood. Similarly, a blood smear is performed to be inspected under a microscope. Abnormal amounts of cells and changes in the form of these can reaffirm the suspicions of leukemia. However, to be able to give a confirmatory diagnosis, it is necessary to do an aspiration and biopsy of the bone marrow and it is confirmed with a concentration of more than 20% - 30% of blasts (depending the leukemia type). In a recently diagnosed patient, a lumbar puncture (LP) must be performed in order to search for asymptomatic (CNS) infiltration [23].

Once the diagnosis of leukemia is confirmed, it must be classified for subsequent correct treatment by means of various tests and examinations.

One of these tests is based on chromosomes. Normally, human cells have 23 pairs of chromosomes, each with a certain size and shape. In some types of leukemia, there are changes in these chromosomes. Sometimes, 2 chromosomes exchange part of their deoxyribonucleic acid (DNA). This is called

translocation and can usually be observed using a microscope. In other types of leukemia, the cells may have an irregular number of chromosomes, either missing or having more of them. All this helps not only to diagnose the type of leukemia, but also to have an idea of how the patient will respond to the different treatments that can be administered.

Other very important procedures for identifying the type of leukemia are flow cytometry and immunohistochemistry. Both procedures are used for immunophenotyping. This means that they classify cancer cells according to certain proteins that are present in them. For this, samples of the malignant cells are incubated with antibodies that adhere only to certain proteins. The difference between these two tests is that in the immunohistochemistry, the sample is analyzed using a microscope, and in flow cytometry it is carried out by means of a specialized machine [10], [11], [24].

Particular Background

Dielectric Properties

Dielectric properties are intrinsic parameters that determine the effects of electric fields on matter. They play a dominant role in the overall consideration of interaction between electromagnetic fields and matter. They are measured mainly in relative permittivity and effective conductivity [25] [26].

The dielectric permittivity ε and conductivity σ of a material are, respectively, the charge and current densities induced in response to an applied electric field of unit amplitude [27].

The dielectric properties of materials are obtained from their measured complex relative permittivity, ε̂ expressed as:

$$\hat{\varepsilon} = \varepsilon' - j\varepsilon''$$

where ε' is the relative permittivity (or dielectric constant) of the material and ε'' the out-of-phase loss factor associated with it such that:

$$\varepsilon'' = \sigma / \varepsilon_0 \omega$$

σ is the total conductivity of the material which, dependent on the nature of the sample, it can include a contribution from a frequency-independent ionic conductivity, σ_i. In this expression, ε_0 is the permittivity of free space and ω the angular frequency of the field. The SI unit of conductivity is siemens per metre ($\mathrm{S\,m^{-1}}$) which indicates that in the above expression ε_0 is expressed in farads per metre ($\mathrm{F\,m^{-1}}$) and ω in radians per second. The dielectric properties are determined as ε' and ε'' values, or ε' and σ values, as a function of frequency.

The dielectric properties of a biological tissue result from the interaction of electromagnetic radiation with its constituents at the cellular and molecular level. In synthesized form, the main features of the dielectric spectrum of a biological tissue are the following:

- The relative permittivity of a tissue can reach values of up to 106 or 107 at frequencies below 100 Hz.
- It decreases at high frequencies in three main steps known as the α, β and γ dispersions. Other dispersions may also be present.

- The γ dispersion, in the gigahertz region, is due to the polarization of water molecules.
- The β dispersion, in the hundreds of kilohertz region, is due mainly to the polarization of cellular membranes which act as barriers to the flow of ions between the intra and extra cellular media. Other contributions to the β dispersion come from the polarization of protein and other organic macromolecules.
- The low frequency α dispersion is associated with ionic diffusion processes at the site of the cellular membrane.
- Tissues have finite ionic conductivities commensurate with the nature and extent of their ionic content and ionic mobility [28].

β Dispersion

This dispersion is also known as interfacial polarization. occurs at intermediate frequencies and originates mostly from the capacitive charging of the cellular membranes and those of membrane-bound intracellular bodies. According to previous experiments, damage to the cell membrane changes the features of the β dispersion. Numerous biomedical applications are based on the variation of the parameters of the β dispersion with pathological conditions involving changes in cell physiology and morphology [29].

Blood Dielectric Properties

All of the human body tissues, fluids, cells, have their very own and unique dielectric properties. Many of these are already reported in literature [30] [31], but the fact that is of special importance for this research, is the existence of different dielectric properties for each of the blood cells.

As an example, it has been demonstrated previously that cell dielectric parameters for human leukocyte subpopulation, in this case specific membrane capacitance (C_{mem}), internal conductivity (σ_{int}), and the internal permittivity (ε_{int}), can be derived from electrorotation spectra by an optimization procedure using a single-shell dielectric model. A clear difference in the dielectric properties can be appreciated among these leukocyte subpopulations. This information, a summary of the means and standard deviations of the mentioned parameters is presented in [32] Tab 1.

Cell Type	Number	Radius	C_{mem} (mF/m^2)	σ_{int}	ε_{int}
T-lymphocytes	91	3.29 ± 0.35	10.5 ± 3.1	0.65 ± 0.15	103.9 ± 24.5
B-lymphocytes	49	3.29 ± 0.26	12.6 ± 3.5	0.73 ± 0.18	154.4 ± 39.9
Monocytes	43	4.63 ± 0.36	15.3 ± 4.3	0.56 ± 0.10	126.8 ± 35.2
Granulocytes	33	4.71 ± 0.23	11.0 ± 3.2	0.60 ± 0.13	150.9 ± 39.3

Table 1. Blood cell dielectric parameters.

Several studies have been carried out to determine the dielectric properties of the blood [33]–[37]. However, these have been somewhat generalized, as they usually just consider the variables of frequency, temperature, and the use of any anticoagulant in their experiments. They are not specific enough to consider several variables that may impact the dielectric spectrum in a relevant way. Age, gender [38], blood group [39], health status (if it was a healthy participant or had any type of special condition/chronic disease) and the time between the sample extraction and analysis are normally not mentioned. Moreover, just a few of them make emphasis on the β dispersion range zone. Based mainly on [31], [34], [36], the dielectric permittivity ε' for a normal/healthy blood sample can be approximated to $4.9x10^3$, and the conductivity to $7.61x10^{-1}$ (S/m), under the conditions of temperature being 37ºC, frequency of 1MHz and the sample container having anticoagulant (EDTA).

Oncological Dielectric Properties

Also, it is highly important to stand out what it is known about the dielectric properties from the oncological standpoint. The pathological differences between normal and cancerous cells affect their composition and morphology, shaping their dielectric spectrum.

These morphological changes affect the dielectric properties in the frequency range of the β dispersion and can be quite significant.

There have been studies that analyze differences in impedivity between normal and precancerous cervical cells in the frequency range of 100 Hz up to 10 MHz (where the β dispersion already takes place), and their results showed significant differences at frequencies lower than 10 KHz.

This has led to an increasing interest in different applications to detect cancerous regions. One example is the approach of using three – dimensional microwave tomography procedures and signal analysis. When the suspected region is available for dielectric measurements, the procedure consists of the characterization and comparative analysis of the dielectric spectrum. All of this with the mayor goal of detecting precancerous stages even before they are visible with other types of methods. [40].

Regarding leukemia, remarkable research was the one done by David Colton and Peter Monk in 1995. It was being investigated the use of microwave imaging as a new approach to detect leukemia, since, according to them, the increase in capacitance where there are diseased cells should cause the permittivity of the bone marrow to increase and the conductivity to decrease significantly. The actual amount of change in the permittivity and conductivity depends on the frequency of the interrogating wave, since these parameters are frequency-dependent, this caused by a phenomenon known as dispersion [41].

Later, this difference in the dielectric parameters between normal and cancerous cells was also supported by research where the dielectric properties of human lymphocyte suspensions were studied by Time Domain Dielectric Spectroscopy. In this case, nine populations of malignant and normal lymphocytes were evaluated. The analysis of the dielectric parameters of cell structural parts were performed in the framework of Maxwell-Wagner mixture formula and the double shell model of cell. The specific capacitance of the cell membranes was estimated by Hanai-Asami-Koisumi formula. The results showed that the dielectric permittivity, capacitance and conductivity of cell membranes were higher for normal lymphocytes than for the malignant ones.

A more detailed information of the results of the previously mentioned research is shown in [42] Tab 2, where ε_m stands for permittivity of cell membrane, σ_m for conductivity of cell membrane, ε_{ne} for permittivity of nuclear envelope, σ_{ne} for conductivity of nuclear envelope, σ_{cp} for conductivity of cytoplasm and σ_{np} for conductivity of nucleoplasm.

Cell Type	ε_m	$\sigma_m\ x\ 10^{-6}\ S/m$	ε_{ne}	$\sigma_{ne}\ x\ 10^{-3}\ S/m$	$\sigma_{cp}\ (\frac{S}{m})$	$\sigma_{np}\ (\frac{S}{m})$
B – cells						

B-normal	12.8±1.6	56±29	106±35	11.1±7.2	1.31±0.08	2.04±0.29
Magala	11.4±2.4	8.8±0.7	72.5±11.6	3.7±0.9	0.55±0.2	1.08±0.03
Farage	9.8±1.1	9.1±1.4	60.3±22.6	4.4±2.5	0.48±0.14	1.07±0.43
Raji	8.8±1.1	8.2±0.6	79.9±34.4	4±1.6	0.58±0.02	1.02±0.25
Bjab	8±0.7	11±5.3	108±35	2.1±0.7	0.88±0.11	1.39±0.54
Daudi	7.2±0.7	9.5±1.4	66.1±7.5	2.7±0.3	0.85±0.09	1.44±0.35
T – cells						
T-normal	11.1±1.4	27.4±6.2	85.6±16.7	8.8±0.6	0.65±0.13	1.26±0.27
Peer	9.5±0.7	12.9±3.6	61.6±17	2.1±0.6	0.81±0.09	1.42±0.2
HDMAR	7.4±1.2	14.5±4	101.2±55.3	3±0.2	0.88±0.25	1.58±0.28

Table 2. Dielectric parameters of cell structural parts for cell populations studied in [42].

Dielectric Spectroscopy

Definition

Dielectric spectroscopy is the science that relates the dielectric properties to the underlying microscopic mechanisms of polarization and conduction. These dielectric phenomena are determined by and are informative about the structure and composition of the material [43].

It is frequently used to study the response of a sample exposed to an applied electric field of fixed or changing frequency. It provides information on molecular dynamics as well as on important material parameters. One of the main purposes of this technique is to evaluate the dielectric properties such as dielectric constant (ε′), dielectric loss (tan δ), etc., of polymers, polymer nanocomposites, and nanomaterials. This technique can operate in a wide range of frequencies, from very low frequencies as μHz, up to very high frequencies like THz [44]–[46]. In order to achieve the best accuracy possible, each frequency range requires a different measurement principle and sample holder.

This technique has many different applications, for example, it is used in several biosensor systems, which involves a label-free method to probe bacterial concentration and to spot the presence of dangerous pathogens such as Escherichia coli O157:H7, Salmonella, yeast cells, etc. It is also known as bioelectrical impedance analysis in the field of human health monitoring and is used to determine body composition, total body water mass, free fat mass, etc.[44].

Despite its many benefits, capabilities, and extensive development history, the use of this method is not highly widespread, because the wide frequency

range 10^{-6} - 10^{12} Hz, overlapped by discrete frequency domain methods, has required complex and expensive equipment [46].

Dielectric Spectrometer

In order to perform an analysis in the audio and radio frequency regions, in general, a dielectric spectrometer consists mainly of the following components [47], [48]:

- A system for accurate measurement of the complex admittance or impedance of the sample cell in a wide frequency range.
- Temperature-stabilized sample holder.
- Additional modules that can control other external parameters such as dc bias and pressure, or logs the time at which the measurements were taken.
- A computerized system for instrument control and data acquisition and processing.

The most basic representation of a dielectric spectrometer circuit is the one of an alternating current (AC) signal generator, Vt, connected to a capacitor (Cs, which is the sample cell), as shown in (*Fig. 1)*. However, there are different factors that affect the circuit behavior and need to be modelled in the circuit design.

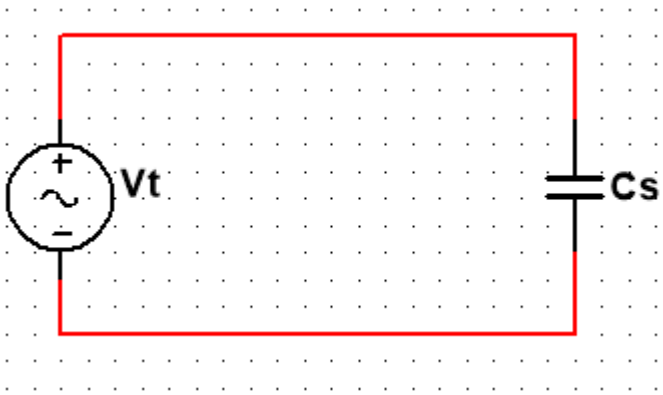

Figure 1. Equivalent most basic circuit for dielectric spectrometer analysis.

Based on [46], [49]–[52], the most accurate representation of the circuit for a (parallel-plate) dielectric spectrometer is as shown in (*Fig. 2).* Vt being the AC voltage signal that will be applied to the sample, the cables, connections, and solder resistivity being Rc, the polarization ion layer near the electrodes can be

considered in terms of a resistor and a capacitor (Cp and Rp) connected in series and finally, the sample cell can be modelled as a capacitor, Cs, connected in parallel with a resistor, Rs.

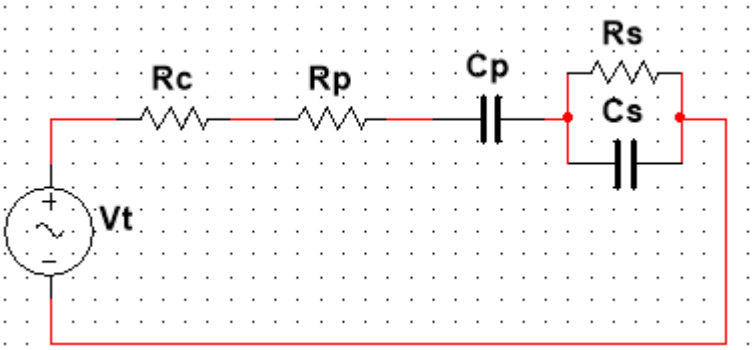

Figure 2. Most accurate equivalent circuit for (parallel-plate) dielectric spectrometer analysis.

For this frequency range, measuring cell geometries mainly fall into four basic categories: parallel-plate capacitor, cylindrical capacitors, strip lines and coaxial probes [53].

In the case of parallel-plate capacitors, the sample is placed between the two electrodes in a "sandwich" arrangement, (*Fig. 3)*. For measurements on liquid samples (fluids or solutions), a good practice is the use of spacers in order to adjust and ensure the proper electrode spacing. The materials to be used for the spacers should exhibit low and frequency-independent dielectric constants and low losses, e.g., silica fibers or small stripes of polytetrafluoroethylene (PTFE) or polyethylene [51].

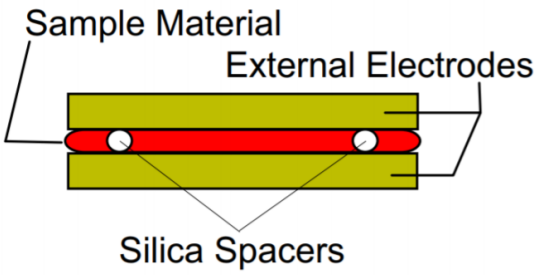

Figure 3. Parallel plate capacitor diagram, with liquid sample (cross sectional view) [51].

Inaccuracies in Dielectric Measurements

The measurement accuracy usually is not uniform, but depends on the frequency of the measurements and the actual sample capacity. There are

several factors that may affect this accuracy, but the most relevant are the following [51]:

- Cables used.
- Inaccuracies in sample geometry.
- Insufficient electrical contact between sample and electrodes.
- Edge capacities.
- Electrode polarization.

Electrode Polarization

When applied to biological or other highly conductive system containing ions, the dielectric spectroscopy technique usually experiences troublesome phenomena: the ions tend to move toward the electrode/sample interface under the influence of an electric field, leading to the development of ionic double layers in these regions, see (*Fig. 4)*. The applied voltage drops rapidly in these layers, which implies a huge electrical polarization of the material and a near-absence of the electric field in the bulk sample at low frequencies.

The resultant capacitance of these layers can dominate the signal at the lower frequencies This phenomenon, known as electrode polarization (EP), depends on the electrical conductivity and temperature of the sample, the structure, composition and even roughness of the electrode surface [46], [49]–[51], [54].

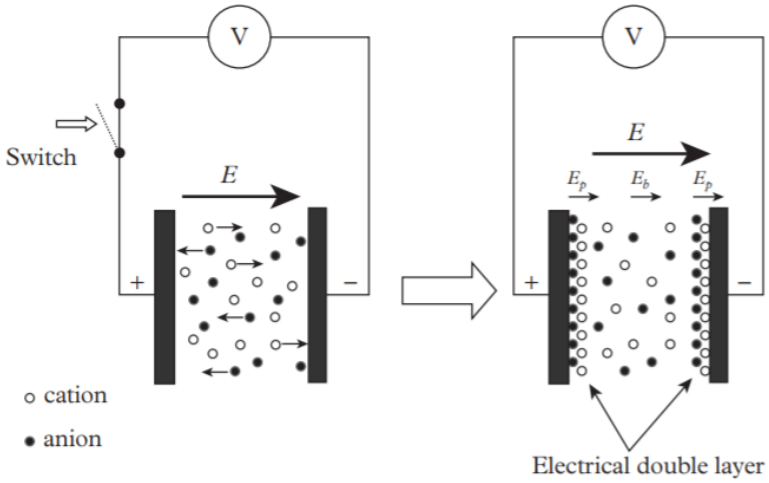

Figure 4. Formation of ionic double layers at the electrode-sample interfaces [54] .

Research Justification

In México, cancer is the main cause of death by disease in the range between 5 and 24 years old [55]–[57] Tab.3, Tab. 4. It is estimated that between 5,000 and 6,000 new cases appear each year and a very alarming fact is that 65% of these cases are diagnosed in late stages of the disease [55].

Order of Importance	Causes	Mexican List Key	Deaths
1	Accidents	E49-E53, E57-E58	1,340
	Traffic of motor vehicles	E49B	619
2	Malignant tumors	08-15	1,024
	Leukemia	14D	558
3	Congenital malformations, deformities, and chromosomal abnormalities	47	451
	Congenital malformations of the circulatory system	47E	228

Table 3. Main causes of mortality from 5 to 15 years.

Order of Importance	Causes	Mexican List Key	Deaths
1	Accidents	E49-E53, E57-E58	5,838
	Traffic of motor vehicles	E49B	3,532
2	Aggressions	E55	5,240
3	Congenital malformations, Intentional self-inflicted	E54	1,809
4	Malignant tumors	08-15	1,644
	Leukemia	14D	637

Table 4. Main causes of mortality from 15 to 24 years.

According to a study made in México from 2008 to 2014, for all of these new cancer cases, leukemia covers about the 50%, as shown in [55] (*Fig. 5)*.

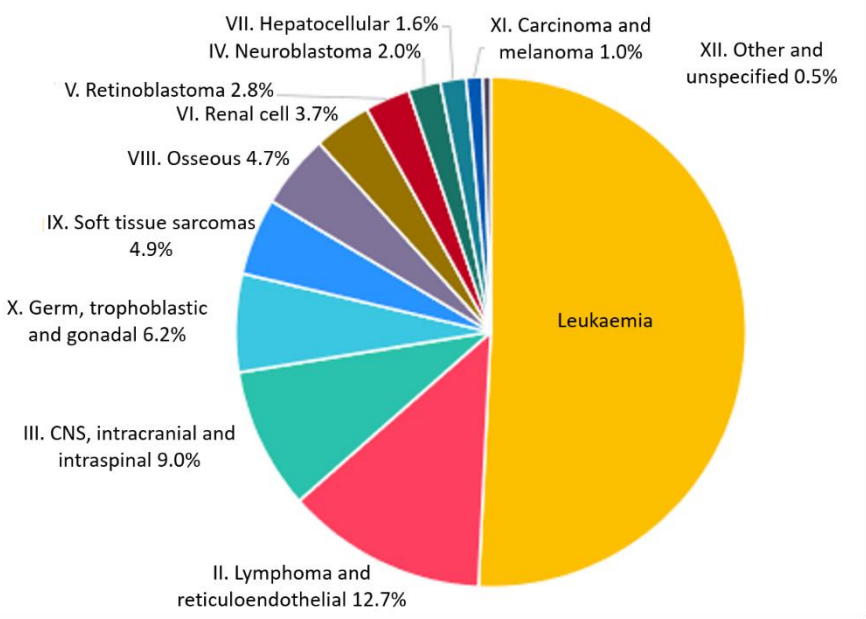

Figure 5. Distribution of new cancer cases by neoplasia types.

Another important statistic is the survival rate for this disease. To discuss cancer survival statistics, the 5-year survival rate is used, which refers to the percentage of patients who lived at least 5 years after their cancer is diagnosed [58]. The 5-year survival rate was 46.9% for leukemia in México for 2008 – 2014 [55] (*Fig. 6*).

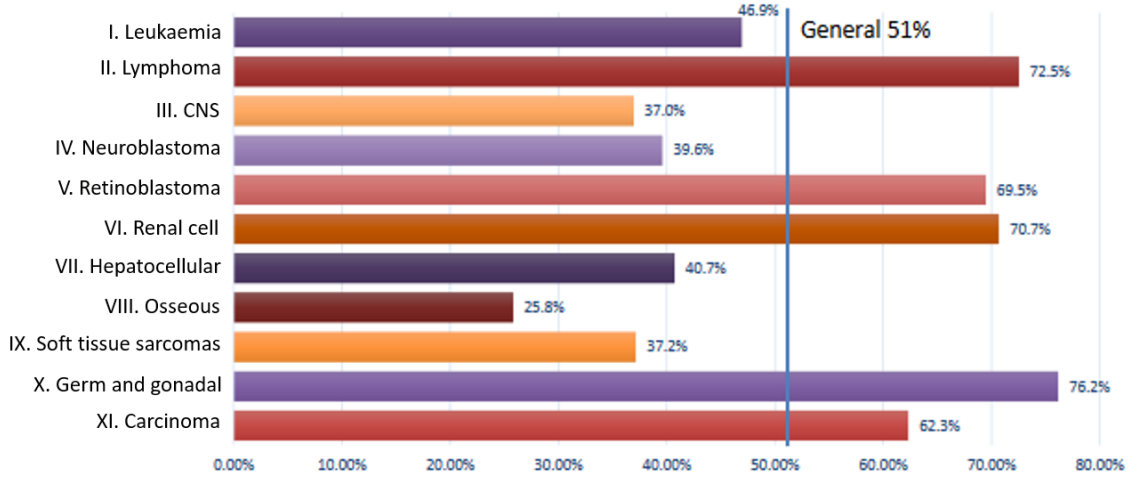

Figure 6. 5-year survival rate in México, from 2008 - 2014.

Previous data show a mortality rate of 53% in average for these years. Nevertheless, this percentage has not reduced significantly in the last years, as shown in a survey made by the INEGI from 2011 – 2016 [59] (*Fig. 7)*.

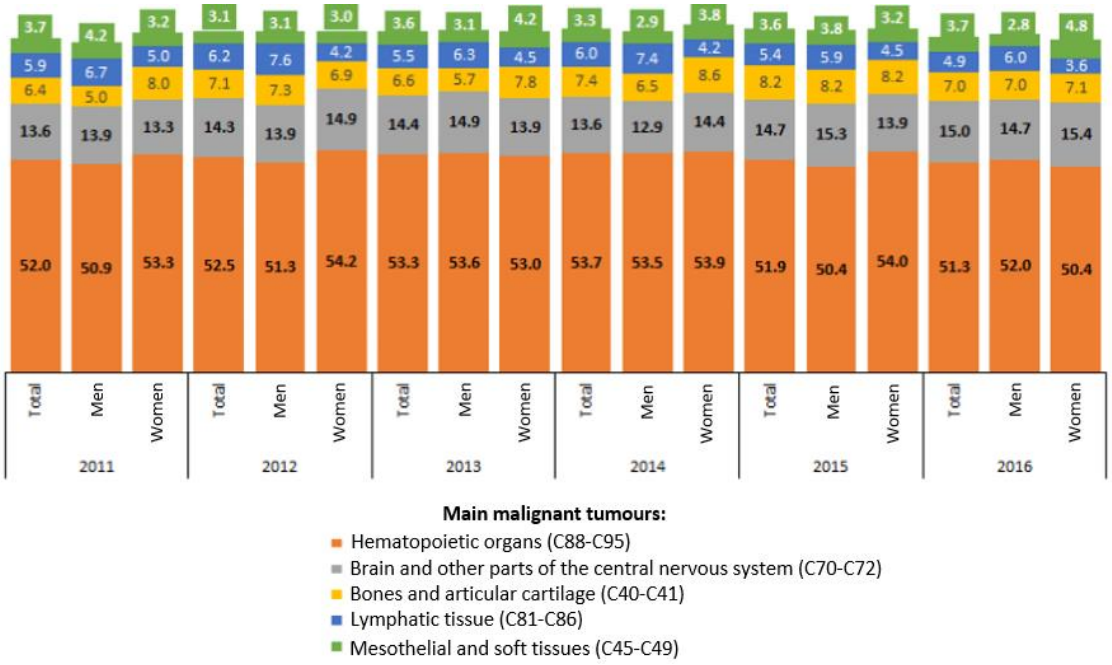

Figure 7. Mortality rate for the 5 principal malignant tumors from 0 – 17 years.

One approach to help decrease the mortality rate caused by the main types of leukemias in México is by detecting them in their early stages, however, there are several drawbacks to achieve this objective. Regarding the late diagnosis, the American Cancer Society recommends to perform routinary detection exams for certain types of cancer (included leukemia) even in persons that do not show any symptoms, due to the fact that these cancers would be easier to treat if they are detected in early stages. Unfortunately until now there are no detection exams that are recommended to be performed in a routinary basis [60].

Another important factor in the late detection of leukemia in México, is the lack of specialized equipment needed to correctly diagnose this disease. Predominantly all of this equipment is concentrated only in the most important cities of the country, which leaves a lot of minor cities and rural communities without the opportunity to have the proper medical analysis when any of the leukemia symptoms arise [61].

Thus, one way to address the issues raised above is to investigate and design a technique or device that could be suitable for routinary testing, mainly taking into account that is safety compliant, suitable to transport and distribute to minor cities, and that the usage cost is reasonable for the target population.

Problem Statement

Based on all the oncological dielectric properties background, it is known that, indeed, there is a difference between the dielectric spectrum of cancerous and healthy cells, more specifically, in leukemia. However, these analyses have been implemented with highly sophisticated equipment (which can be difficult and expensive to acquire) and it has not been done on patients' blood. Furthermore, the blood dielectric properties research that has been done, generally, has not made special emphasis to the β dispersion range zone (where the oncological differences are mainly exposed) and lacks to consider the impact of important variables such as age, gender, blood group, health status and the time between the sample extraction and analysis

It can be theorized that a high concentration of malignant cells in the blood with different dielectric properties should generate different measurable properties in a blood sample, especially in the β dispersion zone.

With all the background described previously, in this thesis the following research question is posed.

What are the differences in the relative permittivity property of the blood of a healthy individual compared to an ALL patient?

Hypothesis

Differences in the relative permittivity of blood under normal conditions and the blood of a patient with acute lymphoblastic leukemia should generate measurable and processable signals through the appropriate instrumentation to detect and / or monitor this disease.

Objectives

General Objective

To design, to test and to validate a portable and low-cost sensor that, using electrodes, is capable of acquiring the respective signals to perform a dielectric spectroscopy study of the blood and thus describe characteristics of acute lymphoblastic leukemia cells.

Specific Objectives

1. To design a sensor to perform dielectric spectroscopy.

2. To validate the sensor.

3. To perform a dielectric spectroscopy analysis.

4 To measurement the relative permittivity of peripheral blood from a control population of healthy individuals and patients with ALL.

5. To contrast the results of relative permittivity in the two study groups.

Novelty

Portable, low-cost sensor able to acquire the necessary signals to perform a dielectric spectroscopy analysis. Recognize the differences in the dielectric properties between healthy individuals and ALL patients.

Materials and Methods

Research Design [62]

Based on the type of study: cases and controls. In this type of study, it starts with a group of subjects with an outcome of interest that corresponds to the cases and a control group that did not suffer the outcome (controls) is selected.

Due to the imposition or not of the maneuver: observational. It is outside the investigator's control.

Due to temporality, the study is cross-sectional, since it will be developed at a specific moment.

Due to the directionality in obtaining the information, the study is retrolective, since the information is obtained once the maneuver and the result have occurred.

Spatial-Temporal Location

This research was carried out with samples from UNE beneficiaries, and from patients from the Hospital del Niño Poblano and Hospital General del Sur Puebla; in the period of time from August 2020 to September 2020. The dielectric properties analyses were performed at the UNE-UPAEP Cancer Research Center.

Study Population (Source, Eligible, Target)

Source population: Beneficiaries of the Una Nueva Esperanza shelter, patients from the aforementioned hospitals and healthy people outside these institutions and close to the researchers of this project, who want to participate as healthy controls.

Eligible population: Patients with a diagnosis of ALL under treatment from 0 to 25 years of age.

Sample population: For convenience, 7 samples were analyzed (regardless of the number of individuals), 4 samples from healthy individuals and 3 from patients with ALL at any stage of treatment or surveillance.

Inclusion, Exclusion and No inclusion Criteria

LLA Population

Inclusion criteria

- Individuals of 0 - 25 years, both genders, with a previous or current diagnosis of ALL by immunophenotype, who agree to participate in this research or whose guardians authorize the participation of underaged in the study. The authorization to participate will be through the signing of consent and in the case of those over eight years of age, and under 18, patients must sign the informed assent.

Exclusion criteria

- Patients with other types of cancer, different from ALL.
- Patients aged 0 - 25 years who present any chronic pathology.
- Children under 25 years of age with no previous or current diagnosis of ALL.
- Individuals over 25 years of age with a previous or current diagnosis of ALL.
- Individuals who do not agree to participate in the research.
- Underaged who sign the informed consent but whose parents do not sign the consent.
- Underaged who do not sign the informed consent but whose parents sign the consent.
- Underaged who do not sign the informed consent and whose parents do not sign the consent.

Elimination criteria

- Patients whose file is incomplete or without the necessary information for the study.
- Patients whose diagnosis of cancer other than ALL is reported at the end of the investigation.

- Patients whose biological samples are available, but not the immunophenotype issued by the institution's laboratories.
- Patients who do not want to participate any longer in the study

Control Group Population
Inclusion criteria

- Individuals aged 0-25 years, of both genders, apparently healthy and with blood cytometry results within normal limits.

In the case of minors under 18 years of age, they must sign the informed assent and the guardians must sign the informed consent; In the case of those over 18 years of age, individuals who agree to participate in this research by signing the informed consent will be included.

Exclusion criteria

- Individuals over 25 years of age.
- Individuals aged 0-25 years with any type of cancer or other chronic pathology.
- Individuals of legal age who do not wish to participate in the research.
- Underaged who sign the informed assent but whose parents do not sign the consent.
- Underaged who do not sign the informed assent but whose parents sign the consent.
- Underaged who do not sign the informed assent and whose parents do not sign the consent.
- Individuals who have hematic cytometry results that reveal a pathological condition.
- Participants who for any reason decide that their data or the results of the analysis of their samples, will not appear in the study. For this they will have to sign a letter of consent revocation, the letter is in the annexes section.

Elimination criteria

- Patients who are diagnosed during the study with a chronic disease.

- Patients who do not want to participate any longer in the study

Variables and Measurement Units

Variable	Variable Type	Operational Definition	Measurement Scale	Variable Type	Indicators / Units
LLA diagnosis	Qualitative Nominal	Reported on file	Nominal	Independent	With or without ALL diagnosis
Diagnosis	Qualitative Ordinal	Reported on file	Ordinal	Independent	LLA subclassification
Treatment stage	Qualitative Ordinal	Reported on file	Ordinal	Dependent	Listed in any of the stages: No treatment Induction to remission Consolidation Maintenance Surveillance
Age	Qualitative continuous	Reported on file	Ratio/rate	Independent	Years
Gender	Qualitive nominal	Reported on file	Nominal	Independent	Male/Female
Ethnicity	Qualitative Ordinal	Reported on file	Nominal	Independent	Latino, Caucasian, Asian, African American
Place of origin	Qualitative Ordinal	Reported on file	Nominal	Independent	City and state
Family cancer background	Qualitative Nominal	Reported on file	Nominal	Independiente	Yes / No

Control Group Definition

The control group was made up of apparently healthy individuals who do not suffer from ALL or another type of cancer, with blood cytometry values within normality, 0-25 years, of both genders, close to the researchers involved in this research, who voluntarily decided to participate in this project and signed the informed consent or, where appropriate, the assent.

In this group can also be placed the individuals from whom a blood sample had been obtained for another reason unrelated to the study, but who, when healthy, met the inclusion criteria, and signed the informed consent and / or assent.

Sensor Design

Physical Design

The physical design of the sensor was carried out in the SolidWorks software, (*Fig. 8)*. Once done, it was exported in Standard Tessellation Language (.STL) format to be 3D printed. A PLA (polylactic acid) filament was used.

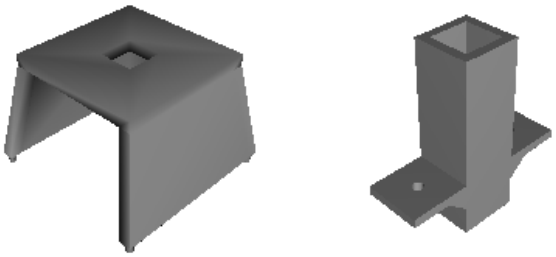

Figure 8. Sensor 3D render in SolidWorks.

For the sample cell holder, a parallel-plate capacitor design was implemented. A square copper sheet with sides of length 12 mm and thickness of 2 mm was used to build the electrodes, *Fig. 9*. As the samples to be analyzed were fluids, the use of spacers of 2.2 mm of diameter was necessary in order to keep the correct and even spacing between the electrodes [51] (all measurements were done with a standard Vernier). As mentioned before, for these spacers it is recommended to use PTFE, silica fibers or polyethylene mainly due to the low dielectric constant. In this case, the selected material was PTFE that contained methacrylate as well. The dielectric constant ε' for these materials

is approximately between 2-2.8 [63] and the resistivity, on average, reported as 1x10^15 [64], [65].

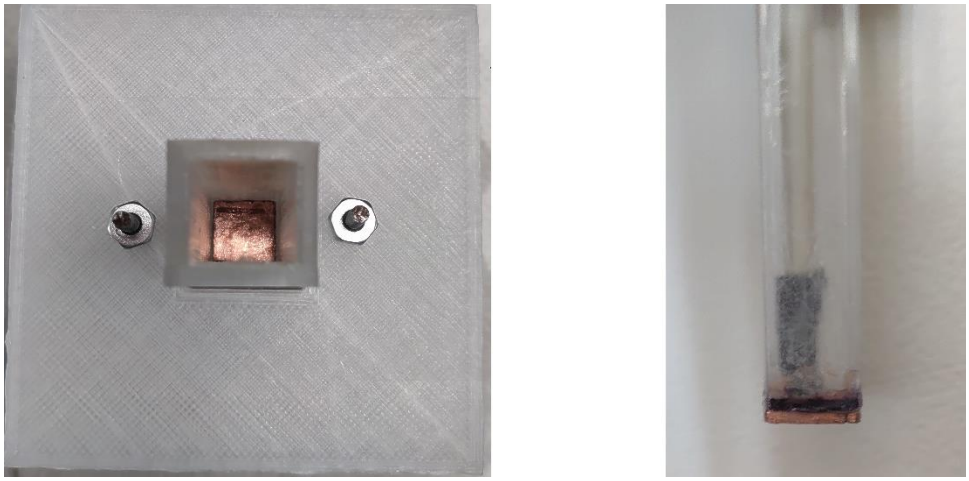

Figure 9. Copper electrodes utilized to build the sample cell.

Given the sample cell measurements, the approximate volume capacity is 0.34848 ml. This is the blood volume that is analyzed. A Pasteur pipette is used to collect the sample. Even with the correct sample volume collection, it is important to ensure that every measurement has the same amount of fluid. For this purpose, the cell design includes 2 drain holes at opposite sides of the cell that will let out the drops of any sample leftover, see (*Fig. 10)*.

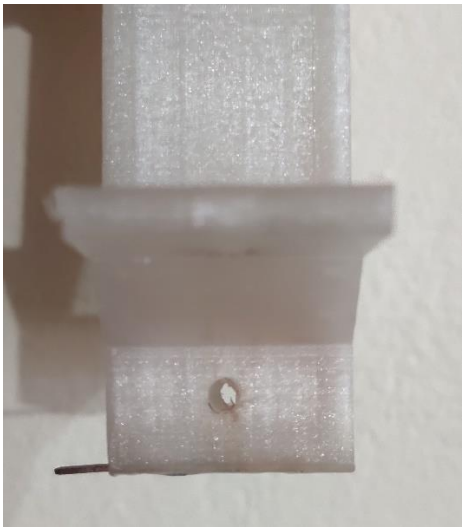

Figure 10. Drain holes on the sample cell.

Electronic Design

For the electronic connections, the components used were mainly UTP and Dupont cable, a standard copper printed circuit board (PCB) and tin solder.

The resistance of the respective components was measured with a Fluke 179 True RMS Multimeter and was approximately 48 Ω.

To generate the signal applied to the sample, the module XR2206 was used, (*Fig. 11)*. This is a monolithic function generator by Exar Corporation. This module was selected due to the fact of being able to generate high quality sine, square, triangle, ramp and pulse waveforms. These outputs can be both, amplitude and frequency modulated by an external voltage. The output signal frequency ranges from 0.01 Hz to more than 1 Mhz. Another convenient feature is the low-sine wave distortion, 0,05%, typical. The small size of this module is also suitable for a portable device design [66].

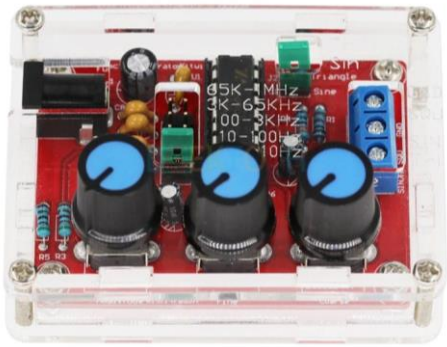

Figure 11. XR2206 module.

To acquire the respective signals, a OWON VDS 1022i PC oscilloscope was utilized, (*Fig. 12)*. It has a bandwidth up to 25MHz and a sample rate up to 100MSa/s [67].

Figure 12. OWON VDS 1022i.

The next important point regarding the electronic design is the empty cell capacitance, C_0, of the sample cell. Given the formula:

$$C_0 = \frac{\varepsilon A}{d}$$

Where:

- ε = permittivity of free space = $8.854\text{x}10^{-12}$
- A = surface area of plates = $1.44\text{x}10^{-4}$ m2
- d = distance between plates = $2.2\text{x}10^{-3}$ m

$$C_0 = \frac{(8.854\text{x}10^{-12})(1.44\text{x}10^{-4}\ \text{m2})}{2.2\text{x}10^{-3}\ m} = 0.579534\ pF$$

With all of the previous specifications and the information presented in the previous Dielectric Spectrometer section, the following circuit was proposed, simulated and then implemented for circuit analysis, (*Fig. 13)*.

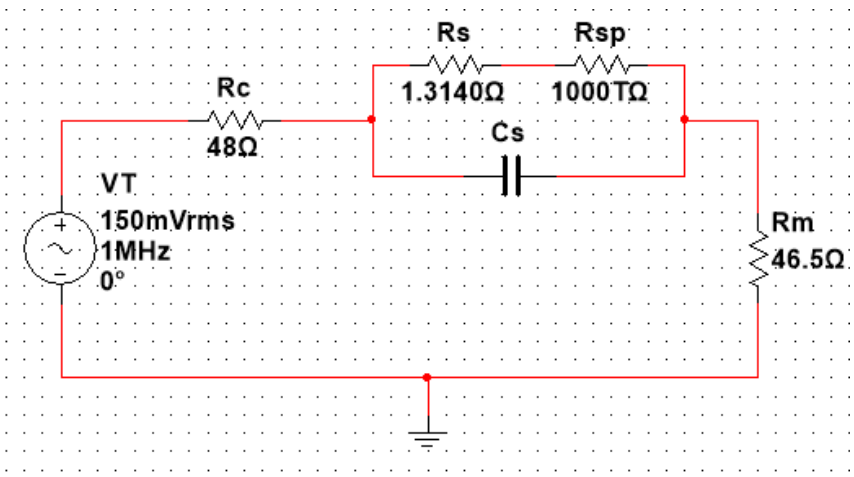

Figure 13. Final proposed circuit.

V_T represents the main voltage source, the signal that will be applied to the blood sample (by the XR2206 module, powered by 12 V direct current (dc)), of value 150∠0º mV rms at a frequency of 1Mhz. The V_T value is chosen by convenience. Rc involves the resistivity generated by cables, the PCB and tin solder, its value, as mentioned before, is approximately 48 Ω. The next section, Cs connected in parallel with Rs and Rsp represents all of the physical sample cell. Cs has an unknown value, as it is based on the sample contained, it is the value of interest. Rs and Rsp stand for the resistance of the sample inside the capacitor. In this case, the "sample" is composed by the blood and the separators used, so it was needed to take into account the resistance of both "materials".

Rsp, based on the PTFE and methacrylate resistivity, has an average reported value of $1\text{x}10^{15}\ \Omega\text{m}$. For Rs, the value will be based on the blood resistivity. In this case, even when the measurements involved different types of blood (because of age, gender, blood type, health condition) this value can be generalized due to the fact of almost being negligible against the Rsp. As mentioned in the Blood Dielectric Properties section, blood has a reported conductivity value of $7.61\text{x}10^{-1}$ (S/m). Conductivity, σ is the reciprocal of the resistivity, 1/ρ [68], so with this statement, the resistivity value can be calculated. $\rho = \frac{1}{\sigma} = \frac{1}{7.61\text{x}10^{-1}} = 1.3140\ \Omega\text{m}$. Finally, Rm is just a proposed resistor of 46.5 Ω, in order to be able to physically measure the voltage drop in the resistor to calculate the total current (I_T).

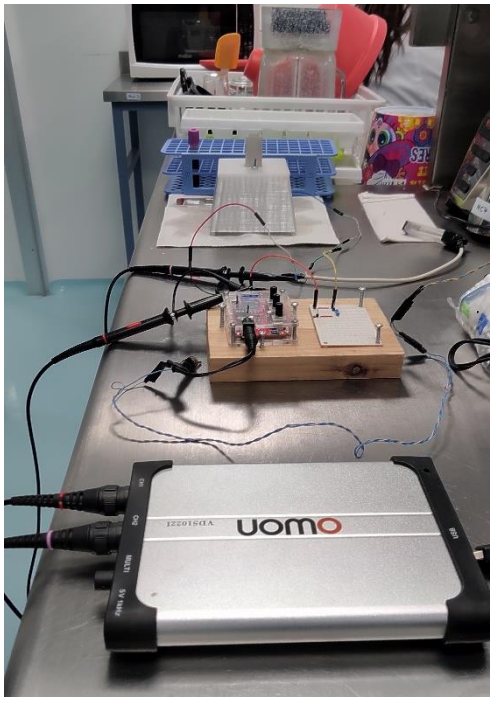

Figure 14. Complete set-up.

Cleaning and Disinfection [69]

- Gloves, face masks and safety glasses were used for proper cleaning.
- Cleaning and disinfection were carried out in a container for blood residues, on which chlorine was initially applied.

Components without electrodes

- Chlorine was initially applied on the component to be cleaned to remove excess of contaminants (taking care that the residues fell into the container for blood residues).
- Later, they were cleaned with detergent and a suitable brush.
- Finally, they were disinfected with 70% ethanol.

Components with electrodes

- 70% ethanol was initially applied on the component to be cleaned to remove excess of contaminants (taking care that the residues fell into the container for blood residues).
- Later, they were cleaned with detergent and a suitable brush.
- Finally, isopropyl alcohol was applied.

Reusable cleaning instruments

- Chlorine was initially applied to the instrument (taking care that the residues fell into the container for blood residues).
- Later, was cleaned with detergent.

Analytical Methods

Data Collection

Sociodemographic data was obtained from the clinical file: age, sex, ethnicity, family hereditary history, diagnosis, immunophenotype and stage of treatment, they were recorded individually by participant. See data collection certificate in annexes. To obtain the immunophenotype, interlaboratory bias was avoided by verifying the methods and techniques used.

Blood Samples

Samples from the population that comes from UNE were taken from peripheral blood at the time they were channeled to receive chemotherapy.

Peripheral blood samples from patients coming from hospitals were taken by trained personnel from the institutions themselves, also when receiving chemotherapy.

Peripheral blood samples from the members of the control group (voluntary donors) were taken by CIO-UNE-UPAEP personnel. To confirm that

these voluntary donors do not have hematological alterations, a blood cytometry was performed at no cost.

At the same time as the blood samples were collected, the blood pressure, pulse and body temperature data of the participants was taken.

In the case of the individuals that will make up the control group (healthy individuals), the blood samples and the filling in of the data collection card was carried out at the CIO, in Una Nueva Esperanza. The sampling of 5 mL of peripheral blood and the filling of the card was carried out by qualified personnel, and it was collected in a tube with anticoagulant.

Hematic Cytometry

It was carried out with 13 microliters of whole blood, in the Counter 19 automatic hematological analyzer (Wiener lab), to evaluate 19 hematological parameters (total white blood cells, number of lymphocytes, number of monocytes, number of granulocytes,% of lymphocytes,% of monocytes ,% granulocytes, total red cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, red cell distribution width coefficient of variation, standard deviation of red cell distribution width, platelets, mean platelet volume, plateletcrit and platelet cell distribution width).

Sensor Accuracy

In order to characterize the sensor, dielectric properties of 70% ethanol and a healthy individual blood sample were measured with the prototype to compare against literature.

In the case of 70% ethanol, based on literature, the reference relative permittivity value of 70% ethanol at 25ºC, measured at a frequency of 1 MHz is 42 [70]–[72].

For the blood sample the reference value was $4.9\text{x}10^3$, as mentioned in the Blood Dielectric Properties section.

The average error factor in percentage for the relative permittivity value was of 3.1892%.

Dielectric Analysis

The analyzes were done at 1MHz, due to the fact of this frequency being the most efficient one considering two points; it is already inside of the β dispersion zone and it is the highest frequency that can be reached with the proposed equipment (the highest frequency is selected in order to try to avoid as much as possible the electrode polarization effect). The analyzes were performed on average 40 minutes after the sample extraction. Meanwhile, the samples were kept at 37 ºC.

In order to obtain the desired relative permittivity value, the circuit shown in (*Fig. 13)* needed to be solved to find Cs complex capacitance [73]. A standard AC circuit analysis was performed [74]–[79]. To better explain the process, a real analysis of a healthy individual will be used as example.

Initial conditions / known values:

- Frequency = 1.011 MHz (Measured with OWON oscilloscope)
- $V_T = 149.5 \angle 0º \text{ mVrms}$ (Measured with OWON oscilloscope)
- $V_{Rm} = 62.64 \text{ mVrms} \angle 29.05º \text{ mVrms}$ (Measured with OWON oscilloscope)
- $Rm = 46.5\ \Omega$ (Measured with Fluke multimeter)
- $Rc = 48\ \Omega$
- $Rs = 1.3150\ \Omega$
- $Rsp = 1000\ T\Omega$

Procedure:

- First, all the possible components will be treated as complex impedance values. In this case, all the known components are resistors. Given the formula $Z_r = R$, the impedances for all these resistors will be just a real value (no imaginary part, i) of magnitude equal to their resistance value. E.g., for $Rm = 46.5\ \Omega$, $Z_{Rm} = 46.5\ \Omega$.
- The next step will be to get the total current I_T. For this purpose, is why a known resistor was placed at the end of the circuit. With the OWON oscilloscope the voltage at this resistor was measured and compared to the signal generator V_T in order to get the signal phase. By Ohm's law:

$$V = IZ$$

$$I = \frac{V}{Z}$$

$$I_T = \frac{V_{Rm}}{Z_{Rm}}$$

$$I_T = \frac{62.64\ \text{mVrms} \angle 29.05º\ \text{mVrms}}{46.5\ \Omega} = 1.347096 \angle 29.05º\ \text{mA}$$

- With the total current, the voltage drop at Rc can be calculated.

$$V = IZ$$

$$V_{Rc} = I_T Z_{Rc}$$

$$V_{Rc} = (1.347096 \angle 29.05º\ \text{mA})(48\ \Omega) = 64.660645 \angle 29.05º\ \text{mVrms}$$

- Having the voltage drops V_{Rc} and V_{Rm}, the voltage drop at the complete cell, $V_{completeCell}$, (C_s in parallel with R_s and R_{sp}) can be calculated.

$$V_T = V_{Rc} + V_{completeCell} + V_{Rm}$$

$$V_T - V_{Rc} - V_{Rm} = V_{completeCell}$$

$$V_{completeCell} = 149.5 \angle 0º\ \text{mVrms} - 64.660645 \angle 29.05º \text{mVrms}$$

$$- 62.64\ \text{mVrms} \angle 29.05º\ \text{mVrms}$$

$$V_{completeCell} = 72.672306 \angle -58.274967\ \text{mVrms}$$

- As mentioned before, this is the voltage for the complete cell, (C_s in parallel with R_s and R_{sp}), as they are connected in parallel, this voltage will be the same for the equivalent resistor of $R_s + R_{sp} = R_{ssp} = 1.3140\ \Omega + 1000\ T\Omega$ and for C_s. In other words, $V_{Cs} = V_{Rssp} = 72.672306 \angle -58.274967\ \text{mVrms}$.
- Now the value of V_{Cs} is known, it is missing the I_{Cs} in order to calculate the sample capacitance. To get I_{Cs}, Kirchhoff's current law was used. This law states that, for any node (junction) in an electrical circuit, the sum of currents flowing into that node is equal to the sum of currents flowing out of that node. In this case, as seen in (*Fig. 15)*, $I_T = I_{Rssp} + I_{Cs}$.

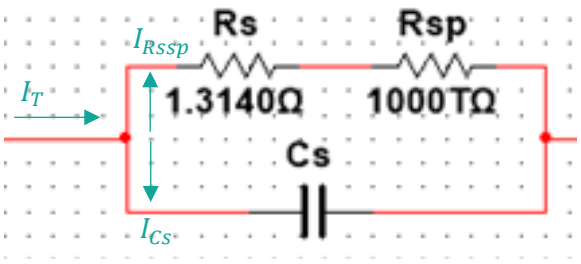

Figure 15. Currents distribution at node at the sample cell parallel connection.

- I_T is a known value and I_{Rssp} can be obtained by using:

$$I_{Rssp} = \frac{V_{Rssp}}{Z_{Rssp}} = \frac{72.672306 \angle -58.274967 \text{ mVrms}}{1.3140\ \Omega + 1000\ T\Omega} =$$

$$7.2672306x10^{-5} \angle -58.274967 \text{ pA}$$

Thus:

$$I_{Cs} = I_T - I_{Rssp}$$

$$I_{Cs} = 1.347096 \angle 29.05º \text{ mA} - 7.2672306x10^{-5} \angle -58.274967 \text{ pA} =$$

$$I_{Cs} = 1.347096 \angle 29.05º \text{ mA}$$

- With V_{Cs} and I_{Cs}, the next step is to get C_s complex capacitance value. This was based on the $V = IZ$ formula. For this capacitor, $V_{Cs} = I_{Cs}Z_{Cs}$. In order to get C_s a substitution must be made. In this case, the impedance Z_{Cs} corresponds to the capacitive reactance, X_{Cs}, of this element ($Z_{Cs} = X_{Cs}$). Given $Z_{Cs} = X_{Cs} = -\frac{1}{2\pi f C_s} i$, the following substitution can be made:

$$V_{Cs} = \frac{(I_{Cs})(-i)}{(2\pi f)(C_s)}$$

- Solving for C_s …

$$C_s = \frac{(I_{Cs})(-i)}{(2\pi f)(V_{Cs})}$$

$$C_s = \frac{(1.347096 \angle 29.05º \text{ mA})(-i)}{(2\pi)(1.011x10^6\ Hz)(72.672306 \angle -58.274967 \text{ mVrms})}$$

$$C_s = 2.918089 \angle -2.675033º \text{ nF}$$

- Finally, based on the formula presented in the Dielectric Properties section [73]…

$$\hat{\varepsilon} = \varepsilon' - j\varepsilon''$$

$$\hat{\varepsilon} = \varepsilon' - j\varepsilon'' = \frac{C_s}{C_0}$$

$$\hat{\varepsilon} = \varepsilon' - i\varepsilon'' = \frac{2.918089 \angle -2.675033º \text{ nF}}{0.579534\, pF}$$

$$\hat{\varepsilon} = \varepsilon' - i\varepsilon'' = 5029.747177 - 235.000282i$$

- The real part corresponds to ε', the relative permittivity. $\varepsilon' = 5029.747177$. The reference value for a generalized healthy blood sample is $4.9\text{x}10^3$.

Results

The relative permittivity (at 1MHz and 37ºC) of healthy female blood samples with EDTA anticoagulant agent and ages ranging from 22 - 27 years are shown in (*Fig. 16)*. The figure shows relative permittivity values inside the range of 8067 up to 8661, with a mean of 8312, and a standard deviation of ± 271.9. In the ALL group, shown in (*Fig. 16)*, the ages ranged from 12 – 13 years, with relative permittivity values inside the range of 6414 up to 10694, with a mean of 8043, and a standard deviation of ± 2316.

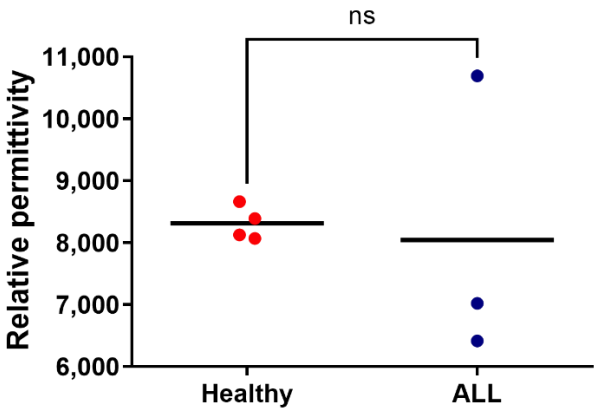

Figure 16. Mean relative permittivity.

These two groups were compared in different hematic parameters shown in (Fig. 17) using a student's t-test. For the relative permittivity parameter, shown in in (Fig. 17a), a 'no significantly different' result was obtained, with a P value of 0.8213. In the case of white blood cells (WBC), (Fig. 17b), and red blood cells (RBC), (Fig. 17c), both showed a 'significantly different' result, with P values of 0.0031 and 0.0227 respectively. Finally, for the platelets parameter shown in (Fig. 17d), a 'no significantly different' result was obtained, with a P value of 0.2682.

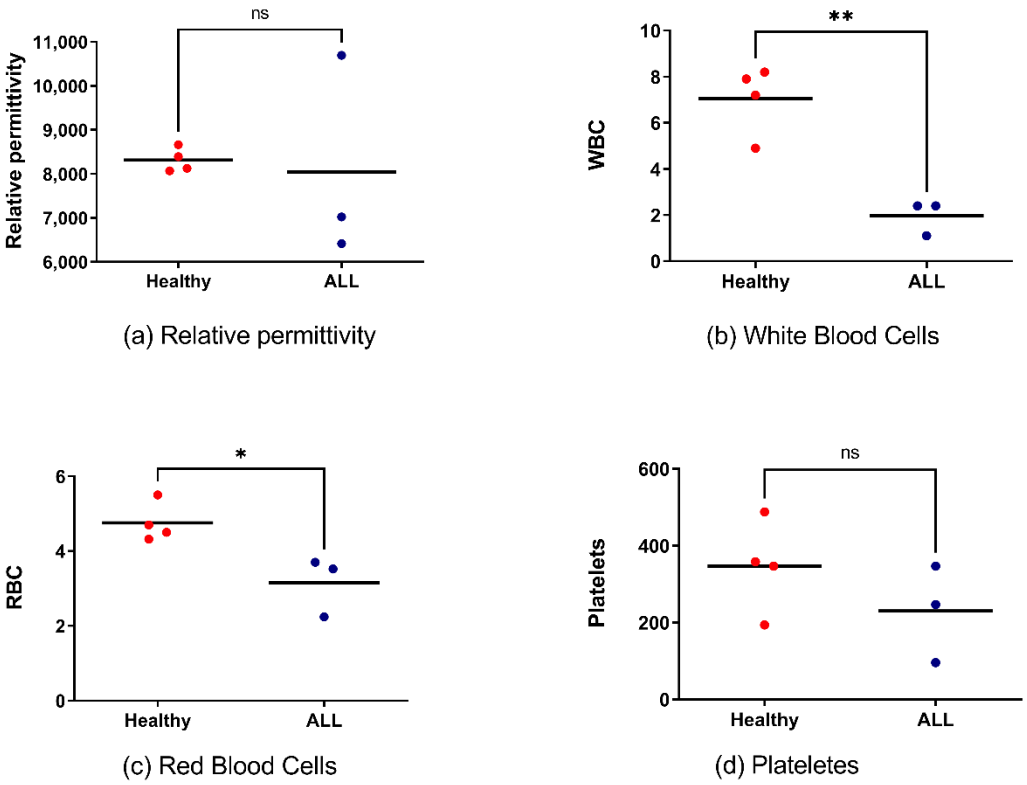

Figure 17. Hematic parameters comparison.

Conclusions

A low-cost, portable dielectric sensor was successfully designed, developed and implemented in order to start acquiring dielectric parameters' information from the blood. It is appropriate to remark that the sensor and design presented in this thesis may serve other purposes as well, meaning that can be applied to study different type of materials and / or fluids as well.

The relative permittivity value for healthy female blood samples at 1Mhz described in this thesis shall work as a more specific reference value to be added to the somewhat generalized information contained in literature.

However, the analyses done for this thesis were just an initial test and step in order to refine and make more efficient, both, the sensor designed and the procedures involved, as well as getting to know deeper all the possible variables that could have a significant impact in the results.

Despite the inconclusive result shown in this thesis for the relative permittivity parameter in ALL diagnosis, these records will serve as a potential reference in order to continue expanding the literature, due to the fact of the lack of information that exists regarding this type of analysis in ALL.

In order to correctly characterize and relate dielectric properties of blood to, in this case, ALL, further investigation needs to be done with a much more narrowed and specific grouping.

Taking as reference the analyzes done in this research, the grouping (apart from the small number of samples) may be the main factor that must be improved in order to obtain a more significant result. In this case, the broad age range may have had a negative impact in achieving a relevant result.

The best-case scenario suggested (in this thesis) would be to group and analyze by gender, then age, blood type, ALL type and finally stage of the disease and be compared with the value of a healthy subject of the same gender, age and blood type.

The purpose of grouping and filtering even by the stage of the disease is to have the possibility of using this type of analysis to be able to discern how the

anomalies are evolving over time, as well as before, during and after treatments, and potentially assist in monitoring this type of conditions.

Perspectives

From the device design standpoint, there are several improvements that can be applied to the prototype. First of all, it would be highly useful to perform the analysis in a specific frequency range. The most efficient range for the purposes of this research, would be from 10 kHz up to 1 MHz. This would include the frequencies where the most relevant changes related to oncological changes have been found.

Next, the most suitable electrodes to be utilized are the ones made from platinum with a black platinum chemical treatment. The reason to select this type of superficial electrodes, is due to the fact of being the most efficient ones in decreasing the impact of the electrode polarization effect. As lower frequencies are being proposed to be included in the analysis, this electrode polarization phenomena can alter in a significant manner the results at the lowest frequencies. Even if this perturbation will be considered and modelled in the circuit design, hence mathematically filtered, it is important to decrease it as much as possible starting from the physical implementation.

Finally, regarding the device, the last important addition would be the implementation of an automated temperature control scheme to the sample cell in order to ensure the same conditions for each sample without using external equipment.

Regarding the blood dielectric study, the inclusion and exclusion criteria need to be adjusted in order to narrow down and have a more specific patient and control group. The groups would be integrated by individuals with age ranging from 0-15 years, and, if possible, grouped by blood type, ALL type and stage of the disease. Also, a lipid profile would be useful as these parameters may have a significant impact in the dielectric properties of the sample.

Bioethical Guidelines

This investigation represents a greater than minimal risk because it requires the collection of blood.

All participants (healthy or with ALL) and their guardians received an explanation of the procedure to be performed on their patients and the purpose of the study, in addition to the risks that the procedure may entail.

Samples from patients with ALL were the remanent taken for studies prescribed for medical reasons, whereas samples from apparently healthy patients were voluntarily donated. In both cases blood was taken by the UNE diagnostic staff. The procedures were carried out in accordance with the rules and regulations established in the “Ley General de Salud en Materia de Investigación para la Salud” [80], “Consejo de Organizaciones Internacionales de las Ciencias Médicas” (CIOMS) and the NOM-012 [81].

Procedures and Responsible Persons for Communicating Study Results to Participants

When the results of the study are available, the researchers agree to make a report to each of the study participants who have requested to receive their notification; reporting the result obtained and its meaning.

Plans for the Use of Research Results

The results of this investigation will be used to obtain a relationship between the dielectric properties obtained and the LLA.

Informed Consent Letter for Participant Over 18 Years of Age [82]

Fecha: _____/_____/_____

Proyecto:

Análisis de propiedades dieléctricas de sangre. Condiciones normales y pacientes con LLA

Sede donde se realizará el estudio: Una Nueva Esperanza A.B.P.

Nombre del participante:

_____

A usted se le está invitando a participar en este estudio de investigación médica. Antes de decidir si participa o no, debe conocer y comprender cada uno de los siguientes apartados. Este proceso se conoce como consentimiento informado. Siéntase con absoluta libertad para preguntar sobre cualquier aspecto que le ayude a aclarar sus dudas al respecto.

Una vez que haya comprendido el estudio y si usted desea participar, entonces se le pedirá que firme esta forma de consentimiento, de la cual se le entregara una copia firmada y fechada

Su participación consistirá en donar una muestra de sangre, además de proporcionar datos generales relevantes para la investigación.

Nombre	
Fecha de Nacimiento	
Género	
Estatura	
Peso	
E-mail	
Teléfono celular	

Justificación del estudio

Se sabe que las células leucémicas presentan diferentes propiedades físicas (dieléctricas) que las células sanas a las cuales reemplazan. Se ha analizado la posibilidad de detectar estas propiedades mediante el uso de señales en el espectro de radiofrecuencias y placas de desarrollo comerciales de bajo costo pero sin resultados concluyentes. Por otra parte, se ha informado que la frecuencia de las señales generadas es segura para mediciones *in vivo* para futuros proyectos e investigaciones.

Objetivo del estudio

Determinar las propiedades dieléctricas de las muestras sanguíneas obtenidas de los participantes, por medio del uso de un dispositivo prototipo.

Beneficios del estudio

Los beneficios de este estudio no podrán observarse en el corto plazo. Se espera que después de que se realice más investigación en este tema, se pueda

generar un dispositivo no invasivo para detectar y monitorear ciertos tipos de leucemia.

Procedimientos del estudio

En caso de aceptar participar en el estudio se le harán algunas preguntas, y se tomará una muestra de aproximadamente 5 mililitros de sangre periférica, durante su canalización, previo a su quimioterapia o bien, durante la toma de muestra para otros estudios. La muestra será recolectada en tubos Vacutainer con anticoagulante. Se realizarán análisis de espectroscopía dieléctrica de dichas muestras.

Riesgos asociados con el estudio

La toma de muestra de sangre (5 mililitros) representa un riesgo mayor que el mínimo. Posterior a la toma de sangre se puede presentar dolor y/o moretones, sin embargo, este riesgo se reducirá con el adecuado procedimiento y cuidados posteriores a la toma de muestra. En caso de que usted desarrolle algún efecto secundario que requiera otro tipo de atención, ésta se le brindará, por favor comuníquese con nosotros en caso de necesitarla.

Aclaraciones

- Su decisión de participar en el estudio es completamente voluntaria.
- No habrá ninguna consecuencia desfavorable para usted, en caso de no aceptar la invitación.
- Si decide participar en el estudio puede retirarse en el momento que lo desee (aun cuando el investigador responsable no se lo solicite), pudiendo informar o no, las razones de su decisión, la cual será respetada en su integridad. En este caso, tendrá que firmar una carta de revocación del consentimiento informado, favor de informarnos para otorgársela.
- No tendrá que hacer gasto alguno durante el estudio.
- No recibirá pago por su participación.
- En el transcurso del estudio usted podrá solicitar información actualizada sobre el mismo, al investigador responsable.
- La información obtenida en este estudio, utilizada para la identificación de cada paciente, será mantenida con estricta confidencialidad por el grupo de investigadores.
- En caso de que usted desarrolle algún efecto adverso secundario no previsto, tiene derecho a una indemnización, siempre que estos efectos sean consecuencia de su participación en el estudio.
- Si considera que no hay dudas ni preguntas acerca de su participación, puede, si así lo desea, firmar la carta de consentimiento Informado que forma parte de este documento.

Yo, _____ he leído y comprendido la información anterior y mis preguntas han sido respondidas de manera satisfactoria. He sido informado y entiendo que los datos obtenidos en el estudio pueden ser publicados o difundidos con fines científicos. Convengo en participar en este estudio de investigación. Recibiré una copia firmada y fechada de esta forma de consentimiento.

_____ _____

Firma del participante. Fecha

_____ _____

Testigo 1 Fecha

_____ _____

Testigo 2 Fecha

Esta sección debe ser completada por el investigador (o su representante):

He explicado al Sr (a). _____ la naturaleza y los propósitos de la investigación; le he explicado acerca de los riesgos y beneficios que implica su participación. He contestado a las preguntas en la medida de lo posible y he preguntado si tiene alguna duda.

Acepto que he leído y conozco la normatividad correspondiente para realizar investigación con seres humanos y me apego a ella.

Una vez concluida la sesión de preguntas y respuestas, se procedió a firmar el presente documento.

_____ _____

Nombre y firma del investigador Fecha

En caso de dudas o aclaraciones relacionadas con el estudio podrá dirigirse a:

Investigador Responsable

Jesús Alejandro Martínez Juárez Tel. 833 145 3374

Ma del Rocío Baños Lara Tel. 222 577 2596

En caso de dudas o aclaraciones sobre sus derechos como participante podrá dirigirse a:

Comisión Nacional de Bioética: Calzada Arenal No. 134, Tlalpan, Arenal Tepepan, 14610 Ciudad de México, D.F. Teléfono: 01 55 5487 2760

Informed Consent Letter for Parent or Guardian [82]

Fecha: _____/_____/_____

Proyecto:

Análisis de propiedades dieléctricas de sangre. Condiciones normales y pacientes con LLA

Sede donde se realizará el estudio: Una Nueva Esperanza A.B.P.

Nombre del participante:

_____

A su hijo o paciente a su cargo, se le está invitando a participar en este estudio de investigación médica. Antes de decidir si participa o no, debe conocer y comprender cada uno de los siguientes apartados. Este proceso se conoce como consentimiento informado. Siéntase con absoluta libertad para preguntar sobre cualquier aspecto que le ayude a aclarar sus dudas al respecto.

Una vez que haya comprendido el estudio y si usted permite que su hijo o paciente a su cargo participe, entonces se le pedirá que firme esta forma de consentimiento, de la cual se le entregara una copia firmada y fechada.

Su participación consistirá en donar una muestra de sangre, además de proporcionar datos generales relevantes para la investigación.

Nombre	
Fecha de Nacimiento	
Género	
Estatura	
Peso	
E-mail	
Teléfono celular	

Justificación del estudio

Se sabe que las células leucémicas presentan diferentes propiedades físicas (dieléctricas) que las células sanas a las cuales reemplazan. Se ha analizado la posibilidad de detectar estas propiedades mediante el uso de señales en el espectro de radiofrecuencias y placas de desarrollo comerciales de bajo costo pero sin resultados concluyentes. Por otra parte, se ha informado que la frecuencia de las señales generadas es segura para mediciones *in vivo* para futuros proyectos e investigaciones.

Objetivo del estudio

Determinar las propiedades dieléctricas de las muestras respectivas obtenidas de los participantes, por medio del uso de un dispositivo prototipo.

Beneficios del estudio

Los beneficios de este estudio no podrán observarse en el corto plazo. Se espera que después de que se realice más investigación en este tema, se pueda

generar un dispositivo no invasivo para detectar y monitorear ciertos tipos de leucemia.

Procedimientos del estudio

En caso de aceptar participar en el estudio se le realizarán algunas preguntas sobre el paciente a su cargo, y se tomará una muestra de aproximadamente 5 mililitros de sangre periférica del participante, durante la canalización del mismo, previo a su quimioterapia o bien, durante la toma de muestra para otros estudios. La muestra será recolectada en tubos Vacutainer con anticoagulante. Se realizarán análisis de espectroscopía dieléctrica de dichas muestras

Riesgos asociados con el estudio

La toma de muestra de sangre (5 mililitros) representa un riesgo mayor que el mínimo. Posterior a la toma de sangre se puede presentar dolor y/o moretones, sin embargo este riesgo se reducirá con el adecuado procedimiento y cuidados posteriores a la toma de muestra. En caso de que el paciente desarrolle algún efecto secundario que requiera otro tipo de atención, ésta se le brindará, por favor comuníquese con nosotros en caso de necesitarla.

Aclaraciones

- Su decisión de participar en el estudio es completamente voluntaria.
- No habrá ninguna consecuencia desfavorable para usted o para el paciente a su cargo, en caso de no aceptar la invitación.
- Si decide participar en el estudio puede retirarse en el momento que lo desee (aun cuando el investigador responsable no se lo solicite), pudiendo informar o no, las razones de su decisión, la cual será respetada en su integridad. En este caso, tendrá que firmar una carta de revocación del consentimiento informado, favor de informarnos para otorgársela.
- No tendrá que hacer gasto alguno durante el estudio.
- No recibirá pago por su participación.
- En el transcurso del estudio usted podrá solicitar información actualizada sobre el mismo, al investigador responsable.
- La información obtenida en este estudio, utilizada para la identificación de cada paciente, será mantenida con estricta confidencialidad por el grupo de investigadores.
- En caso de que el paciente desarrolle algún efecto adverso secundario no previsto, tiene derecho a una indemnización, siempre que estos efectos sean consecuencia de su participación en el estudio.
- Si considera que no hay dudas ni preguntas acerca de su participación, puede, si así lo desea, firmar la Carta de Consentimiento Informado que forma parte de este documento.

Yo, _____ he leído y comprendido la información anterior y mis preguntas han sido respondidas de manera satisfactoria. He sido informado y entiendo que los datos obtenidos en el estudio pueden ser publicados o difundidos con fines científicos. Convengo en que mi

hijo, hija o paciente bajo mi cuidado, participe en este estudio de investigación. Recibiré una copia firmada y fechada de esta forma de consentimiento.

_____ _____

Firma del padre o tutor. Fecha

_____ _____

Testigo 1 Fecha

_____ _____

Testigo 2 Fecha

Esta sección debe ser completada por el investigador (o su representante):

He explicado al Sr(a). _____ la naturaleza y los propósitos de la investigación; le he explicado acerca de los riesgos y beneficios que implica su participación. He contestado a las preguntas en la medida de lo posible y he preguntado si tiene alguna duda.

Acepto que he leído y conozco la normatividad correspondiente para realizar investigación con seres humanos y me apego a ella.

Una vez concluida la sesión de preguntas y respuestas, se procedió a firmar el presente documento.

_____ _____

Nombre y firma del investigador Fecha

En caso de dudas o aclaraciones relacionadas con el estudio podrá dirigirse a:

Investigador Responsable

Jesús Alejandro Martínez Juárez Tel. (833) 145 33 74

Ma del Rocío Baños Lara Tel. 222 577 2596

En caso de dudas o aclaraciones sobre sus derechos como participante podrá dirigirse a:

Comisión Nacional de Bioética: Calzada Arenal No. 134, Tlalpan, Arenal Tepepan, 14610 Ciudad de México, D.F. Teléfono: 01 55 5487 2760.

Letter of Assent [82]

Fecha: _____/_____/_____

Proyecto:

Análisis de propiedades dieléctricas de sangre. Condiciones normales y pacientes con LLA

Hola, mi nombre es _____ y estoy estudiando en la Universidad Popular Autónoma del Estado de Puebla, y/o participando en esta investigación. Actualmente se está llevando a cabo una investigación para saber más acerca de ciertas propiedades dieléctricas de las células de tu enfermedad (leucemia linfoblástica aguda), y para ello queremos pedirte que nos apoyes.

Tu participación en el estudio consistiría en tomar una muestra de tu sangre cuando seas canalizado o te estén tomando una muestra de sangre para otros estudios.

Tu participación en el estudio es voluntaria, es decir, aun cuando tu papá o mamá hayan dicho que puedes participar, si tú no quieres hacerlo puedes decir que no. Es tu decisión si participas o no en el estudio. También es importante que sepas que, si en algún momento ya no quieres continuar en el estudio, no habrá ningún problema, o si no quieres responder a alguna pregunta en particular, tampoco habrá problema.

Esta información será confidencial. Esto quiere decir que no diremos a nadie los resultados de las pruebas que haremos con la muestra que nos proporciones, solo lo sabrán tu cuidador y las personas que forman parte del equipo de este estudio.

Si aceptas participar, te pido que por favor pongas una (✓) en el cuadro de abajo que dice “Si quiero participar” y escribe tu nombre.

Si no quieres participar, no pongas ninguna (✓), ni escribas tu nombre.

☐ Si quiero participar

Nombre:

_____

Nombre y firma de la persona que obtiene el asentimiento:

_____

Observaciones:

_____
_____
_____

Informed Consent Revocation Letter [82]

Fecha: _____/_____/_____

Proyecto:

Análisis de propiedades dieléctricas de sangre. Condiciones normales y pacientes con LLA

Sede donde se realizará el estudio: Una Nueva Esperanza A.B.P.

Nombre del participante: _____

Por este conducto deseo informar mi decisión de retirarme de esta investigación por las siguientes razones: (Este apartado es opcional y puede dejarse en blanco si así lo desea el participante)

_____

_____

_____

_____

Si el participante lo desea, podrá solicitar que le sea entregada toda la información que se haya recabado sobre él, con motivo de su participación en el presente estudio.

_____ _____

Firma del participante Fecha

_____ _____

Nombre y firma del testigo Fecha

Investigator Commitment Letter

Date: _____/_____/_____

To whom it may concern,

In our capacity as representative of the research project: **Blood Dielectric Properties Analysis. Normal Conditions vs ALL Patients**, and through this document we undertake to assume the commitment to respect and enforce the ethical standards of research in human beings, in conjunction with universally proclaimed values and ethical principles. In the same way, I proclaim the obligation to guarantee that the informed consent procedure is carried out in such a way that it promotes the autonomy of the participant, safeguarding their confidential data and making use of their information only for scientific purposes of the research project. Finally, I promise to report any deviation from the project or adverse effects to the research ethics committee, likewise, I will send the results that are achieved through a final written report.

Sincerely,

_____

Jesús Alejandro Martínez Juárez
jesus.martinezaj@gmail.com
Tel. (833) 145 33 74

Student Confidentiality Letter [82]

Puebla, Pue. _____/_____/_____

I, Jesús Alejandro Martínez Juárez, student of the Master of Science in Biomedical Engineering program at the Universidad Popular Autónoma de Puebla, hereby state, in relation to the project entitled: Blood Dielectric Properties Analysis. Normal Conditions vs ALL Patients, that I promise to safeguard, maintain confidentiality and not misuse the documents, files, reports, studies, minutes, resolutions, letters, correspondence, agreements, contracts, agreements, physical and / or electronic files of information collected, statistics or any other records or information related to the aforementioned study, with which I will work to obtain my master's degree. Likewise, I undertake not to disseminate, distribute or commercialize the personal data contained in the information systems developed in the execution of the research.

Being aware that in case of non-compliance, it will proceed according to the civil, criminal or administrative sanctions that proceed in accordance with the provisions of the “Ley Federal de Transparencia y Acceso a la Información Pública Gubernamental”, “Ley Federal de Protección de Datos Personales en Posesión de los Particulares”, “Código Penal del Distrito Federal”, “Ley Federal de Protección de Datos Personales en Posesión de los Particulares”, and other applicable provisions on the matter.

Sincerely,

_____

Jesús Alejandro Martínez Juárez
jesus.martinezaj@gmail.com
Tel. (833) 145 33 74

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Annexes

Information Collection Certificate

Information collection date	
Name of the researcher collecting the information	
Sample collection date	
Name of the researcher collecting the sample	

Blood Dielectric Properties Analysis. Normal Conditions vs ALL Patients	
Participant's name	
Study group (Healthy/LLA)	
Hospital care unit (HNP, HGS, other)	
Age (years y months)	
Ethnicity (Latino, Caucasian, Asian, African-American)	
Place of origin (city and state)	
Do you have a disease other than ALL? Yes / No	
If the previous answer was yes, what disease?	
Treatment stage (No treatment, remission induction, consolidation, maintenance or surveillance)	
Family cancer background (Yes / No)	
If the previous answer was yes, what type of cancer?	
Blood pressure (systolic value / diastolic value mmHg)	
Pulse (beats per minute)	
Body temperature at the time of sampling (°C)	
Blood type	
Actual diagnosis	

Remarks:

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_____

Thesis Authorization

Asunto: Autorización de impresión de tesis
Puebla, Puebla a 21 de noviembre de 2020

Dra. Rosa María Cantón Croda
Decana de Ingenierías
Universidad Popular Autónoma del Estado de Puebla
PRESENTE

Por este conducto notifico a usted que **Jesús Alejandro Martínez Juárez**, estudiante de la maestría en Ciencias de la Ingeniería Biomédica**, con ID 3409446** y **matrícula 19610006**, concluyó satisfactoriamente su trabajo de tesis titulado *Dielectric Spectroscopy Sensor Design. Blood Dielectric Initial Study;* alcanzando el cumplimiento de sus objetivos. Como directora de la tesis, autorizo su impresión.

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Dra. Ma. del Rocío Baños-Lara

Investigadora del Sistema Nacional Conacyt, nivel 1 (SNI-1)
Facultad de Medicina UPAEP, profesora-investigadora.
Centro de Investigación Oncológica Una Nueva Esperanza-UPAEP, directora.
Cel. (+521) 222-577-2596
Email marocio.banos@upaep.mx

c.c.p. Dr. Aurelio Horacio Heredia Jiménez, director del programa.

UPAEP
21 Sur 1103
Barrio de Santiago
Puebla, Pue. México
C.P. 72410

Tel: 01 (222) 229 9400
Fax: 01 (222) 232 5251
01 800 224 2200
www.upaep.mx