Czech Technical University in Prague

Faculty of Electrical Engineering

Department of Electromagnetic Field

Optimization of Hyperthermic Treatment by aid of Ferromagnetic Nanoparticles

Master Thesis

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ABSTRACT

Cancer is one of the diseases with the highest number of deaths worldwide. Thanks to radiotherapy and chemotherapy many people can overcome this disease, in a complementary and innovative way, in certain countries hyperthermia is already used. This is a new body therapy, on which we are going to focus our project, mainly we will study the role of the electromagnetic particles in this new technology.

The first objective of this project includes making a historical context and a more in-depth explanation about what hyperthermia is; the types that exist, the machinery used to apply it in patients, the conditions in which it should be applied and how. In addition, I illustrate the design and function of a waveguide applicator for local hyperthermia, as well as its description and procedures. Its working frequency is 434 MHz and the dimensions of the waveguide are 40 x 80 mm.

In the second objective with the Sim4Life program, a model is created that simulates a part of the human body and the waveguide, in order to obtain simulations and calculations that are as real and accurate as possible; such as the S_{11} and SAR parameters. As we said before, we wanted to study the effect with ferromagnetic particles, so we created two simulation environments; in the first one we obtain the SAR with a replica of the human tissue (phantom agar) and in the second one we add ferromagnetic particles.

The third and last objective includes the most practical part of this project, we carry out the same process, but in an experimental way in the laboratory.

As a conclusion, once the experiments with Sim4Life software and in the laboratory have been performed, a comparison of tissue-specific absorption is made in both cases and with and without nanoparticles. The main objective is to define the effect of ferromagnetic particles in the treatment of hyperthermia.

Keywords: Hyperthermia, SAR, ferromagnetic nanoparticles, waveguide applicators,

STATEMENT

With this statement I certify you that this work is a personal search and obtaining results with the help of my tutors. Everything that has not been obtained by myself is well referenced and in the bibiography described at the end of the page you can clearly see the sources. This applies to literature, software, as well as other people's ideas and results.

ACKNOWLEDGMENTS

After a few long years of graduate and master's degrees, my student days are coming to an end. I have no regrets at all about having chosen this profession, I am proud of it, of being Teleco and of what I have learned during all this time.

Nothing would have been possible without the support of my parents, my sister and my friends and colleagues, they have always been supporting me until the last moment and have trusted me at times that even I did not.

Finally, I would like to thank my prof. Vrba for the opportunity to do my master's thesis in this country and with such an important topic to deal with. On the other hand, I would like to thank Marta for the effort and dedication she has had as a tutor for this work from afar. In the shade you are one of the fundamental pillars in this degree and I am sure that thanks to you everything works better in it. You love your profession and it is something that is transmitted in the classroom, you are an example to follow, Marta.

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CHAPTER 1: STATE OF THE ART

Current problem with cancer and state of the art solutions. Thermotherapy and Hyperthermia. Role of nanotechnology in hyperthermia treatment.

PROBLEMATIC OF CANCER TREATMENT

Today, there are millions of people around the world living with cancer, who have had it or have a family member with the disease. In recent years, the increase in the number of cancer patients is demoralizing. Preventive measures can be taken as part of a healthy lifestyle to reduce the risk of cancer, such as maintaining a diet, physical activity, adapted body weight and avoiding exposure to tobacco smoke and excessive sunshine on our skin.

With the help of professionals to raise awareness of how harmful certain actions such as those mentioned above are to avoid suffering from this disease and despite optimistic statistics that mortality rates in developed countries continue to decline, thanks to studies compiled by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), cancer continues to be one of the leading causes of death in the world.

Certain cancers, such as breast cancer and colon cancer, are available for early detection in order to help diagnose and treat the disease as early as possible. Early diagnosis and initiation of treatment often improves the chances of a good response to cancer treatment and therefore recovery.

Treatment for cancer eradication is multidisciplinary, i.e. different therapeutic techniques are combined in order to establish the most appropriate treatment plan for the cure of this disease. Generally, hospitals follow a series of guidelines or rules established based on scientific experience, which are carried out depending on two very important factors:

- Tumor
    - o Type
    - o Location and size
    - o Affection of other organs

- Patient
    - o Age
    - o Health status
    - o Other diseases

The most common modalities for treating cancer are surgery, radiation therapy, and chemotherapy. A much more recent treatment than these is hyperthermia, one of the most innovative technologies in cancer treatment today and on which this thesis will focus. Taking into account the important advances that have been made in the

treatment of malignant tumours, there is still much to improve and investigate in terms of hyperthermia. It is a treatment that is usually administered together with chemotherapy and radiotherapy for a greater effect.

In order to better understand the role of hyperthermia and how it can help in the treatment of cancer I will explain how cancer occurs.

The body is made up of trillions of cells that normally grow, divide and die in an organized way. Cancer cells originate within normal cells, in which the cell's DNA has been damaged or mutated. This damage can be hereditary, can be triggered by massive exposure to sunlight, to toxins in cigarette smoke... The DNA is the "machinery" in each cell responsible for giving the instructions to be carried out, when the DNA is damaged the cell must be repaired or die.

Cancer is produced when in cancer cells, the damaged DNA is not repaired and the cell does not die either. Because of this, new unusual cells are formed, which begin to grow out of control. Among the characteristics of these cells are that they do not stay together, they do not obey signals from other cells, and they do not stop reproducing when their number has doubled 50 times and they appear immature. Unlike unusual cells, normal cells can reproduce exactly, position themselves and stop reproducing in the right place, are destroyed when these cells are damaged and cannot affect other tissues.

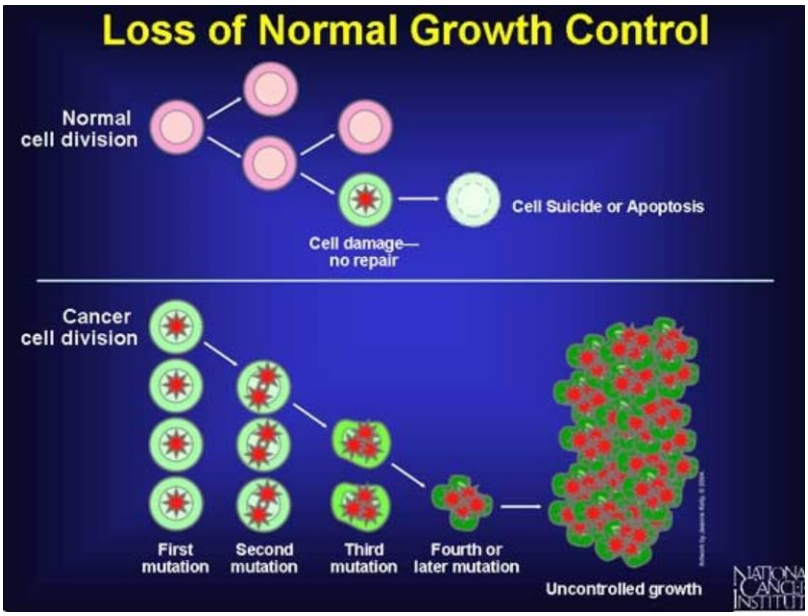


Figure 1: Diffrence between healthy and cancerous cells

WHAT IS HYPERTHERMIA?

Hyperthermia therapy is a type of medical treatment (not yet widely available) for cancer. In oncology, "hyperthermia" refers to the treatment of malignant diseases, which exposes the tumor tissue to high temperatures (up to 45°C). Research has shown that it can damage and destroy cancer cells or make these cells more sensitive to the effects of radiation treatment, usually without damaging normal tissues [1].

HOW IS HYPERTHERMIA USED TO TREAT CANCER?

Hyperthermia is usually applied in addition to two conventional treatments, such as radiotherapy and chemotherapy, for greater effectiveness. These two treatments are usually administered one hour apart. It is a treatment that is currently being studied, it can make some cancer cells more sensitive to radiation or damage other cells that radiation cannot damage, even boosting the effect of certain anti-cancer drugs.

Among other research, they are looking for ways to reach deeper organs and other sites that cannot be treated with hyperthermia at this time, so this treatment is not effective for all cancers.

They have focused on treating cancers of; head and neck, brain, lung, esophagus, breast, bladder, rectum, liver, appendix, cervix and peritoneal lining (mesothelioma), including sarcoma and melanoma. The results of many studies have shown a significant reduction in tumour size when hyperthermia is combined with other treatments. However, not all of these studies have shown increased survival in patients receiving combination treatments.

WHAT ARE THE DIFFERENT METHODS OF HYPERTHERMIA?

Several methods of hyperthermia are currently being investigated, including local, regional, and whole-body hyperthermia, depending on the extent of the body area in which the tumor is located.

When local hyperthermia is used, the heat is applied to a small area, such as a tumor. As mentioned above, very high temperatures are applied to kill the cancer cells and destroy the blood vessels in that part of the tissue. The higher the temperature and the longer the exposure, the greater the effect on the tissue, causing irreversible damage to

the cells [2]. Thermal ablation encompasses this damage, while small increases in temperature constitute mild hyperthermia. To heat the area, heat is applied by different energy sources, which we will discuss in more detail in a later section.

Depending on where the tumour is located, there are various methods for the use of local hyperthermia:

External approaches are used to treat tumors that are in the skin or just under the skin. External applicators are placed around or near the affected region, in order to concentrate the energy on the tumor and raise the temperature of the area.

Intraluminal or endocavity methods are used for tumors that are in or near body cavities, such as the esophagus or rectum. The process involves placing a probe into the cavity, then inserting it into the tumor to apply energy by heating the area directly [1].

Interstitial techniques are used to treat tumors deep in the body, for example, brain tumors. Unlike the other methods, this technique allows the tumor to be treated at even higher temperatures. Needles or probes are inserted into the tumour while the patient is under anaesthesia. The heat source is inserted into the probe. Radiofrequency ablation is a type of interstitial hyperthermia that uses radio waves to heat and destroy cancer cells.

When *regional hyperthermia* is used, a larger part of the body, such as a whole organ, or a limb is heated using different methods of temperature elevation. The reason for using these methods is to weaken the cancer cells so that they are more likely to be destroyed by radiation and chemotherapy drugs.

The same techniques used in the treatment of local hyperthermia or other techniques can be used in this type of hyperthermia, as shown below:

The first is **deep tissue** approaches, used to treat internal cancers, such as cervical or bladder cancer. These work by placing external applicators around the body cavity or organ to be treated, concentrating energy by microwaves or radiofrequency on the affected area to raise the temperature.

Regional perfusion techniques are more specific to treat cancer that has appeared in the arms or legs, such as melanoma, or cancers in some organs such as the liver or lung. The way to apply this technique is by taking blood from the patient, heating it and pumping it (by perfusion) back into the limb or organ. For the duration of the treatment, the patient is given anti-cancer drugs.

The latest technique used in regional hyperthermia is called **continuous hypertermic peritoneal perfusion (CHPP)**. It is used in difficult-to-treat cancers such as those located

in the peritoneal cavity, that is, the inner space of the abdomen where the intestines, stomach, and liver meet. In the surgical process, heated anti-cancer drugs flow from the temperature-raising device into the peritoneal cavity to kill the cancer cells. This achieves temperatures of 106-108ºF, about 41.1-42.2ºC.

The last type of hyperthermia is **full-body**, used for metastatic cancers that have spread throughout the body. This technique can be performed by raising the body temperature to 107-108°F (41.6-42.2°C), such as with the use of thermal chambers (similar to large incubators) or hot water bottles.

The effectiveness of the treatment of hyperthermia is modified by factors such as the temperature reached during the treatment, the duration of the treatment and the characteristics of the cells and damaged tissue. Excessive temperature is undesirable, as side effects can be aggravated. To ensure that the desired temperature is reached and not exceeded, the temperature of the tumor and tissue is monitored during treatment of hyperthermia [1].

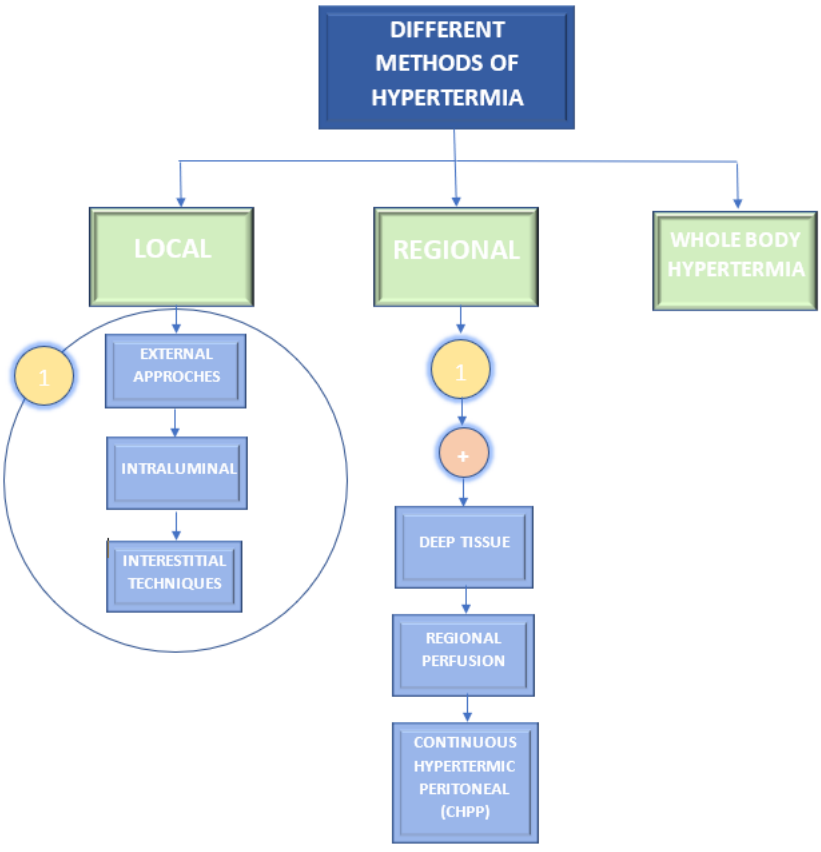


Figure 2. Summary of different methods of hyperthermia

HOW IS THE HEAT APPLIED?

Ablative therapies are taking a major role in the treatment of cancer. They are of a non-invasive nature and their technical success has increased their clinical relevance.

The term ¨ablación¨ refers to tissue destruction through the application of energy. The primary goal of thermal ablative therapy is to destroy tumor cells by using heat to kill the malignant cells without damaging adjacent vital structures.

Radio Frequency Ablation (RFA): is one of the most widely used types of thermal ablation. This particular type uses high-energy radio waves for treatment. In the process performed for local anesthesia, the doctor inserts a thin, needle-like probe into the tumor for a short period of time, between 10 and 30 minutes. The probe is placed by ultrasound, MRI or CT scan, always making sure it is in the correct position. The end of the probe releases energy, thus emitting a high frequency current, which creates a high heat and removes cells from a particular area.

This type of technology is primarily used to remove tumors that cannot be removed by surgery or for patients who cannot undergo surgery. It is usually performed on an outpatient basis and may be repeated for tumors that recur or are growing. This process can be combined with treatments such as surgery, radiation therapy, chemotherapy, hepatic artery infusion therapy, etc.

RFA is used to treat tumors up to 5 cm in diameter. It is mostly used for the treatment of tumors of the liver, kidneys and lungs. In addition, its use for other areas of the body is being studied. The results are not yet fully known, but are encouraging [2].

WHAT ARE THE ENERGY SOURCES USED FOR THESE TECHNIQUES?

The main sources of energy used by these techniques are radiofrequency, microwaves and infrared electro-magnetisation, ultrasound and, finally, high-frequency magnetic fields.

In the 1990s it was discovered that, under the action of alternating magnetic fields, magnetic nanoparticles absorbed a great deal of energy. This discovery led to what is known as magnetic hyperthermia, an experimental cancer therapy that uses a combination of alternating magnetic fields and magnetic nanoparticles that are placed in tumours and become a source of heat.

The aim of magnetic hyperthermia is to increase the temperature of the region affected by the tumour. This increase is achieved by means of the magnetic losses of

nanoparticles subjected to an alternating magnetic field, since the nanoparticles emit in the form of heat the energy they absorb from this magnetic field applied from the outside, doing so without damaging the surrounding healthy tissue.

As for the loss of energy in the magnetic material, there are two possible results:

1.- The magnetic losses caused by domain wall displacements (Néel losses)
2.- Loss of mechanical rotation energy of the particles (Brown losses)

In both cases it is energy lost, therefore, they are added up and converted into heat. According to the physicist Eneko Garai, from the University of the Basque Country (Spain), this system offers several advantages: "On the one hand, the magnetic fields used are not harmful to the organism, that is, they do not produce heat, so they do not affect healthy areas of the body. On the other hand, the nanoparticles can be surrounded by ligands. The particles are usually made of iron oxide, while the ligand consists of a layer made of organic molecules. Thanks to this system, nanoparticles can adhere to tumour cells, without affecting healthy cells.

Another advantage present in magnetic hyperthermia by means of super-paramagnetic nanoparticles is that the heating of these can be located with greater precision by concentrating the magnetic particles in the vicinity of the tumour cells to be necrosed.

In summary, there are several methods to raise the temperature, according to which hyperthermia treatments are classified. In radiofrequency hyperthermia, as I have already explained, electrical currents induced by electromagnetic waves are used to increase the temperature of the tumors, and antennas are used to concentrate the heat on the tumors. The placement of these antennas next to the tumors is done by surgery.

In ultrasound hyperthermia, the heating is done by means of vibrations; in laser hyperthermia, on the other hand, the gold or silver nanoparticles that are placed next to the tumours are excited by means of an infrared laser to heat the tumour cells.

ADVANTAGES AND SIDE EFFECTS OF HYPERTHERMIA.

Local hyperthermia, such as RFA, has multiple advantages. The main one is that it is able to destroy tumors without the need for surgery. Research and scientific studies have shown that this type of hyperthermia is more effective working within a very precise

and specific temperature range. This is the point where complications arise, since it is complicated to obtain the exact temperature inside a tumor, and therefore to maintain this temperature during a certain time without damaging the other tissues that surround it.

In addition, not all tissues in the body have the same response when subjected to a high temperature, some have a higher sensitivity rate than others. For example, the brain is very sensitive to heat.

Specialists are continually working to find more specific ways to control the temperature in the treated area. One solution is to place small thermometers at the ends of the probes in the treatment areas to ensure the desired temperature range. MRI is a new way of controlling temperature without the need for probes.

In regional and whole-body hyperthermia the main advantage is that it seems to help other forms of cancer treatment work better. Raising the temperature of affected cells higher than normal makes it easier to destroy them by using radiation and chemotherapy drugs. But careful temperature control is essential in any type of hyperthermia.

The possible side effects of hyperthermia depend on the technique used, the part of the body being treated, and the temperature rise. Most side effects do not last long, but some can be serious.

The side effects of local hyperthermia can cause pain at the affected site, infection, bleeding, blood clots, swelling, burns, blisters, and damage to the skin, muscles, and nerves near the treated area.

Regional and total body hyperthermia can cause nausea, vomiting and diarrhea. More serious, but much less common, side effects may include problems with the heart, blood vessels, and other organs.

Because regional and whole-body hyperthermia is often given along with other cancer treatments, such as chemotherapy and radiation, the side effects of these treatments may be seen at that time or at a later time.

With the help of certain factors, such as improved technology, experience has decreased the side effects caused by hyperthermia treatment. Generally, the effects are not great.

HYPERTHERMIA EQUIPMENT

Hyperthermia can now be categorized as the fourth mainstay in the treatment of cancer after standard treatments such as surgery, radiation and chemotherapy. Because of this, there is a great variety of hyperthermia devices on the market, each one of them has a specific function for the different types of existing hyperthermia.

Looking for information about this type of equipment I have found the PYREXAR hyperthermia (HT) systems, these systems provide therapeutic heat through non-invasive radio frequency (RF) energy in a established frequency range, this is 75-140 MHz (the BSD-500 supplies at a fixed frequency of 915 MHz). During treatment with HT PYREXAR; the cancerous tumor is gently heated to 40˚-45˚C (104˚-113˚F) destroying the malignant cells while preserving healthy tissue. High temperatures damage cells that are hypoxic (less oxygen present) and have a low pH level, a characteristic that is only present in cells affected by cancer [3].

BSD-500 Superficial/Interstitial RF Hyperthermia System

Figure 3. BSD-500 Superficial/Interstitial RF Hyperthermia System

In Figure 2 we can see the BSD-500 Surface, this is a versatile and fully autonomous treatment system in a mobile configuration for maximum flexibility in treating surface tumors (within 1 inch of the skin surface). It has the following feature

BSD-500

- Generator: 915 MHz / 0-400 Watts total power and 0-60 Watts per channel / 8 Channels (no RF shielding required)
- Waveguides: Three (3) external waveguide applicators for direct energy application to solid surface tumors (MA-120, MA-151, MA-100), including the adjustable upper suspension arm system
- Thermometry: Eight (8) thermistor type sensor ports, sensor simulator and thermal probe calibration well.
- Workstation: Integrated PC with treatment planning software and touch screen monitor.

On the other hand, interstitial hyperthermia delivers heat directly to a tumor using arrays of up to 24 independent flexible dipole antenna cables energized with eight (8) independent power channels. To learn more about the operation of the equipment, the steps followed are detailed below:

RF generator for the BSD-500

The generator develops a high-frequency electrical power output from a conventional single-phase 115/220Vac source with independent multi-channel amplitude and phase adjustment capability. An integrated computer controls forward and reflected power, phase and power level on each channel. Frequency 915MHz.

BSD-500 Waveguides

Using an electrical signal from the generator, the waveguide creates and projects the RF energy beam to the treatment area. The absorption of this energy beam by the tissue causes heating by the excitation of the tissue.

Treatment Control Workstation

Treatments are planned and administered on a PC workstation. The closed-loop feedback system provides automatic monitoring and control of treatment parameters, including output power, frequency (the BSD-500 is set to 915MHz), amplitude and phase, tissue temperatures, core temperature and treatment time.

BSD-2000 Deep Regional RF Hyperthermia System

The BSD-2000 series systems use up to 8 dipole antennas with ring phase array configuration to focus the thermal energy on the affected area, aiming to reach deep into the pelvis, abdomen, extremities or chest.

Figure 4. BSD-2000 3D and BSD-2000 3D/MRI

As we can see in the previous images, there are two types of BSD-2000 3D, one of them is more complete since it uses MRI (Magnetic Resonance imaging). The characteristics for these are the following [3]:

BSD-2000 3D

- Generator: 75 – 140 MHz / 0–150 Watts per channel / 12 Channels (RF shielding required).
- Sigma Eye Applicator with 24 dipole antenna (8 dipoles per annular ring x 3 rings) to provide 3D electronic focus steering. Options allow for use with the other phased array applicators.
- Thermometry: Eight (8) ports for thermistor type sensors, motorized thermal mapping, sensor simulator, and thermal probe calibration bath.

BSD-2000 3D/MRI

- Pyrexar BSD-2000 3D/MR Hyperthermia System docked in a MRI
- Integration with 1.5 Tesla MR system
- Generator: 100 MHz / 0–150 Watts per channel / 12 Channels (RF shielding required).
- Sigma Eye/MR 12 channel applicator with 24 dipole antenna (8 dipoles per annular ring x 3 rings) to provide 3D electronic focus steering
- MR image-guided real-time non-invasive thermometry
- External Water Heating/Chilling/ Circulation System
- Thermometry: Eight (8) ports for thermistor type sensors, motorized thermal mapping, sensor simulator, and thermal probe calibration well.

The system of operation is decisive compared to the BSD-500, since, each one of them is used for a different type of hyperthermia, this case is for types of regional or deep hyperthermia. All the components, with their functionalities described below make the application of hyperthermia possible:

RF shielding

Ringed ultrasonic waveguides always use frequencies that are not within the ISM band and therefore require RF shielding. On the other hand, Single Source and Interstitial Cable waveguides use the Industrial, Scientific and Medical (ISM) radio band which operates at a frequency of 915 MHz and does not require RF shielding.

Water Module

The water-filled bolus on the surface of the waveguide provides dielectric charge and an energy-containment medium.

- Modes: Fill, drain, circulate, heat and cool.
- Temperature range: 25°C to 40°C

Sigma Base (BSD-2000)

The Sigma treatment base provides a comfortable patient position and location possibilities for the opening of the chest to finger matrix.

- Hydraulic elevation/tilting of the patient
- Dielectric isolation of the patient
- Integrated hot and cold water tanks with quick drainage capability

Thermometry

With this type of machine, the affected biological tissue is monitored throughout the treatment exposure with temperature probes, which are placed in interestitial catheters and/or body cavities located near the affected area. In particular, the PYREXAR HT systems use a maximum of 8 stable TMP110 thermistor-type sensors, i.e. they do not create instabilities and are electromagnetically insensitive.

- The sensor diameter is approximately 1.1 mm (0.4 in.) and is located at one end of a 33 cm (13 in.) cable.
- Accuracy: +/- 0.2˚C in the range of 25 to 52˚C.
- The automated positioning system with the BSD-2000 allows thermal mapping along the length of the catheter to measure and monitor the temperature profile in all tumor tissue.
- An integrated probe calibration system has an accuracy of +/- 0.05˚C in the range of 0 to 60˚C is provided with the BSD-2000, and an integral thermal well is provided with the BSD-500.

The BSD-2000 3D/MRI employs non-invasive, real-time MRI-guided thermometry that uses proton resonance frequency shift measurements, with an accuracy of +/- 0.5˚C.

Treatment Control Workstation

The operation of this machine in terms of treatments, planning and administration is done on a PC. The closed loop feedback system provides automatic monitoring and control of the parameters used in the treatment being applied to the person, including output power, frequency, amplitude, phase, tissue temperature, core and time.

Below, I show a table with the summary of all the properties and data given above [3]:

	BSD-500	**BSD-2000**	**BSD-2000 3D**
Generator	915 MHz/0-400 Watts total power and 0.60 Watts per channel/8 channels	75-140 MHz/0-325 or 0-450 Watts per channel/ 4 channels	75-140 MHz/0-150 Watts per channel/ 12 channels (RF shielding required)
Wave Guides	Three external waveguide applicators (MA-120, MA-151, MA-100)	Phase array applicators: sigma ellipse and sigma 60. Sigma base: comfortably positions and supports the patient on sling inside phased array aperture	Sigma Eye Applicator with 24 dipole antenna to provide 3D electronic focus steering
Thermometry	Eight ports for termistor type, sensors, sensor simulator…	Eight ports for termistor type sensor, motorized termal mapping, sensor simulator	Eight ports for thermistor type sensors, motorized thermal mapping, sensor simulator…
Workstation	Integrated PC with treatment planning software and touch screen monitor	PC with treatment planning software and touch screen monitor	PC with treatment planning software and touch screen monitor

Table 1 Summary of characteristics between differents BSD

CHAPTER 2: ELECTROMAGNETIC PROPERTIES AND FERROMAGNETIC NANOPARTICLES IN THERMOTHERAPHY.

Microwave influence on biological tissue and describe the role of ferromagnetic nanoparticles in microwave thermotherapy

BIOLOGICAL EFFECTS OF MICROWAVE

Before talking about the biological effects of microwaves, it is necessary to get context of the electromagnetic spectrum, it is known as "the energy distribution of the electromagnetic wave array", it ranges from the shortest wavelength (e.g. gamma rays) to the longest wavelength, like radio waves.

The electromagnetic spectrum is divided into bands, the cut-off frequencies overlap and the sections are differentiated from each other apart from the name, by the behaviour of their waves during emission, transmission and absorption. The frequencies of the spectrum range from less than one Hz to more than 1025 Hz.

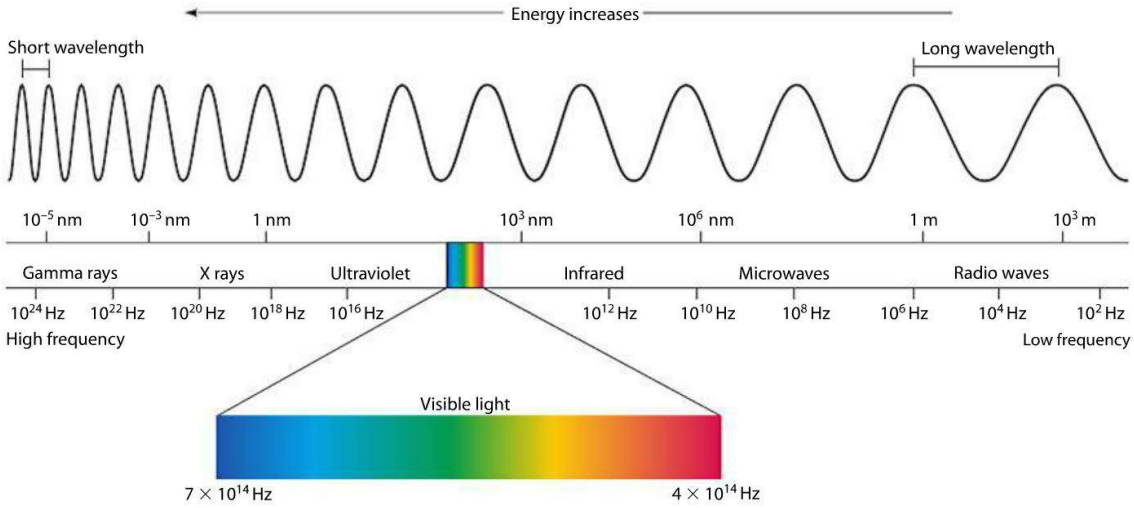


Figure 5. Electromagnetic spectrum

Today the world is driven by new technologies, they are present in many fields such as industry, communication, navigation and of course medicine. These devices emit electromagnetic waves, so the increase in electromagnetic pollution and its possible impact on human health has raised concern in society. On the opposite, it is important to know the real impact that microwaves can have on tissue. If we are talking about the field of medicine, specifically oncology, these microwaves are killing cancer cells located in the human body with their exposure to high temperatures. For this reason, there are currently many professionals in the field working on the study of the interaction of electromagnetic waves with living beings and their behaviour.

The effect of electromagnetic waves on biological systems is determined by the intensity of the field and the amount of energy contained in each photon (is a small group of energy through which an electromagnetic wave is formed). There are low frequency electromagnetic waves "electromagnetic fields" and very high frequency

"electromagnetic radiation", depending on their energy and frequency there are two types of effects: thermal and non-thermal.
When the thermal effect is applied - the intensity of the exposure produces the heating of the tissues due to the absorption of the energy that leads to an increase of the temperature in the tissue [4]. The amount of absorbed energy changes depending on the frequency of radiation and the size of the body.

Microwaves (MO) and radio frequencies (RF) are part of the non-thermal effect and are located in the electromagnetic spectrum in the region of non-ionising radiation, in the range of the spectrum with the lowest energy power. The frequencies of microwaves and radio frequencies do not have sufficient energetic power to ionize the matter that is in contact with the biological system[5].

As we can see, the difference between these two effects is quite difficult to understand. To be more precise in the definition, it is better to use the terms "low/high level electromagnetic field effects".

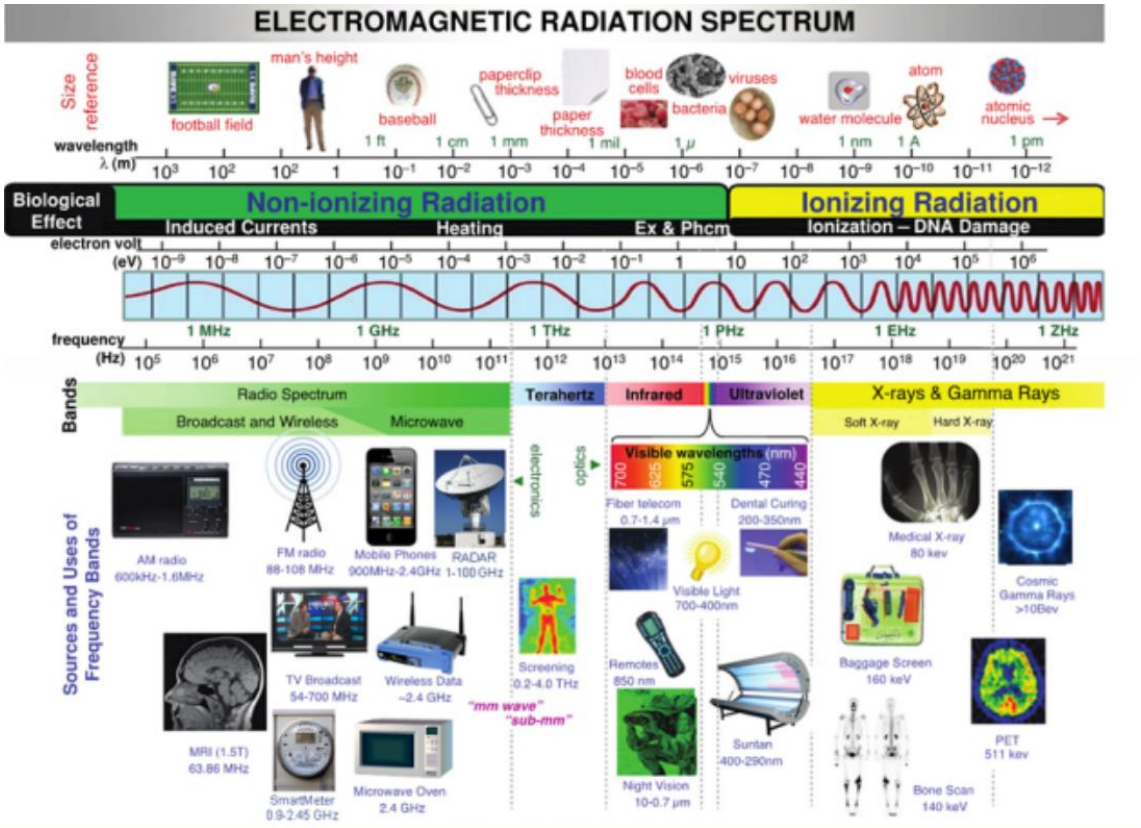


Figure 6. Ionizing and non-ionizing radiation

INTERACTION OF ELECTROMAGNETIC WAVES WITH BIOLOGICAL TISSUES.

The purpose of this section is to understand deeper the interaction of electromagnetic waves with human tissues. To do this, it is essential to know the physical bases of this interaction.

High-frequency electromagnetic waves penetrate the tissues of the human body. When this penetration occurs, the biological tissue acts as a dielectric with losses, so the electromagnetic energy generated in the body is absorbed and transformed into heat. One of the characteristics of this type of wave is that the parameters of the medium can change when the frequency is modified, therefore, biological tissues are non-homogeneous media with dispersive properties. The values of permittivity and electrical conductivity change considerably with frequency and with the type of tissue [3]. As an approximation, these tissues are considered linear and isotropic media, i.e. their characteristics do not change with the value of the electromagnetic fields and with their direction of propagation.

If we want to analyse the influence of electromagnetic radiation on the body's tissues, we must firstly determine how the electromagnetic field is distributed in the affected area in order to determine the spatial distribution and secondly the amount of energy absorbed by the tissue. The fundamental basis of any calculation that has to do with the electromagnetic field can be obtained with Maxwell's equations. These equations can be expressed as integral, vector or tensor equations[6].:

$$\nabla \cdot \vec{\mathrm{E}} = \frac{\rho}{\varepsilon_0} \tag{1}$$

$$\nabla \cdot \vec{\mathrm{E}} + \frac{\partial \vec{\mathrm{B}}}{\partial t} = 0 \tag{2}$$

$$\nabla \cdot \vec{\mathrm{B}} = 0 \tag{3}$$

$$\nabla \cdot \vec{\mathrm{B}} - \frac{1}{c^2}\frac{\partial \vec{E}}{\partial t} = \mu_0 \vec{\mathrm{J}} \tag{4}$$

Respectively these are Gauss' Law for the electric field, Faraday-Lenz' Law, Gauss' Law for the magnetic field and Ampère-Maxwell's Law. Gauss was the first to mathematically create the explanation of the forces of gravity, electricity and magnetism. Starting in 1871, Maxwell managed to translate Faraday's concepts into mathematical equations and to perfect the Gauss equations. He created these four equations that synthesize the

entire physical theory of electromagnetism, which together with the Lorentz force law constitute the foundation of classical electrodynamics.

To better understanding the above equations, they are written according to the traditional convention, the fields to be determined (the effect) are located on the left side of the equation and the specified sources (the cause) are located on the right side. Among the elements that compose them where $\mu_0\varepsilon_0 = {}^{1}/_{c^2}$; $\vec{E}$ is the electric field; $\vec{B}$ the magnetic field; ρ is the charge density (scalar function); and $\vec{J}$ the current density (vector function), where c is the speed of light [5].

MICROWAVE PROPAGATION IN A LOSSY ENVIRONMENT.

As we have said before, tissues are dispersive in frequency, which causes undesired effects when the signal propagates through them, therefore, it influences the properties of any tissue and affects its propagation speed, wavelength, penetration depth... and some more that we are going to describe next.

In human tissues it is not possible to neglect the shift currents, these are usually much higher than the conduction ones, that is why we say that tissue can behave like a dielectric. Neither can conduction currents be completely neglected; they are necessary in order to know some information about the effect of their losses. We must take into account that the medium has a conductivity σ, the current density $\vec{J}$ and the flux density $\vec{D}$, can be expressed:

$$\vec{J} = \sigma\vec{E} \quad (5)$$

$$\vec{D} = \varepsilon_0\varepsilon_r\vec{E} \quad (6)$$

We must also take into account the dielectric permittivity ε to determine the complex dielectric constant. However, to make the measurements simpler and taking into account the variation of dielectric properties with frequency it is more common to formulate:

$$\varepsilon = \varepsilon' - j\varepsilon'' \quad (7)$$

$$\mu = \mu' - j\mu'' \quad (8)$$

Where:

ε' : is the product between the relative permittivity of the medium and the permittivity of the free space and μ′ is the same but with the permeability and are measured in ${}^{F}/_{m}$ y ${}^{H}/_{m}$.

ε'', μ'': dielectric and magnetic losses respectively
ε , μ: complex permittivity and permeability

The value of μ'' is zero for this case because it corresponds to the value of magnetic losses and human tissues are not. The physical explanation for permittivity and permeability is that there is a phase shift between the medium and the field, due to which the field delivers energy, thus indicating that the medium has losses.
Knowing that:

$$\varepsilon'' = \frac{\sigma}{\omega\varepsilon_0} = \frac{36\pi\sigma}{\omega \cdot 10^{-9}} \tag{9}$$

Using equations (5) and (6), Maxwell's equation in its differential form for $\vec{H}$, we can express the **complex permittivity** as:

$$\varepsilon = \varepsilon_0 \left(\varepsilon_r - j\frac{\sigma}{\omega\varepsilon_0}\right) \tag{10}$$

Where σ is the conductivity in Siemens by Metro and ω the angular frequency. The division of $\varepsilon''/\varepsilon'$ is commonly used as a reference parameter in tables and graphs and directly expresses the ratio of the conduction current to the shift current in the dielectric, it is known as the **loss tangent:**

$$tan\delta = \frac{\varepsilon''}{\varepsilon'} = \frac{\sigma}{\omega\varepsilon_r\varepsilon_0} = \frac{\sigma}{\omega\varepsilon} \tag{11}$$

Applying Maxwell's differential equation for the electric field, assuming that the medium is source-free the **wave number** in a lossy medium can be represented as follows:

$$k = \omega\sqrt{\mu_0\varepsilon_0\left[\varepsilon_r - j\frac{\sigma}{\omega\varepsilon_0}\right]} \tag{12}$$

Once the wave number is obtained, the **propagation constant** for the medium is:

$$\gamma = \alpha + j\beta = j\omega\sqrt{\mu_0\varepsilon_0[\varepsilon_r - j\frac{\sigma}{\omega\varepsilon_0}]} \tag{13}$$

One of the differences between uniform plane waves in lossless and lossy media is that the imaginary part of the propagation constant is non-zero, so it is divided into two. Separating the real and imaginary part of this equation, with α and β being the **propagation constant and phase** measured in [Np/m] and [rad/m] respectively, we would obtain:

$$\alpha = \frac{\omega}{c_0} = \sqrt{\frac{\varepsilon_r}{2}\left[\sqrt{1+\left(\frac{\sigma}{\omega\varepsilon_0\varepsilon_r}\right)^2}-1\right]} \tag{14}$$

$$\beta = \frac{\omega}{c_0} = \sqrt{\frac{\varepsilon_r}{2}\left[\sqrt{1+\left(\frac{\sigma}{\omega\varepsilon_0\varepsilon_r}\right)^2}-1\right]} \tag{15}$$

Wavelength

The wavelength is a magnitude applicable to any type of periodic wave. It is the distance a periodic disturbance travels through a medium in a cycle [6]. It is the inverse of the frequency and is commonly determined as the distance between two consecutive maximum points on a wave. In a lossy medium it is:

$$\lambda_m = \frac{2\pi}{\beta} = \frac{2\pi c_0}{\omega\sqrt{\frac{\varepsilon_r}{2}\left[\sqrt{1+\left(\frac{\sigma}{\omega\varepsilon_0\varepsilon_r}\right)^2}-1\right]}} \tag{16}$$

Attenuation

Attenuation is the loss of power incurred in an electromagnetic signal as it propagates through any transmission medium [7]. Assuming that the waves are propagated in the +Z direction, the attenuation is defined:

$$D_a = \frac{|E(z)|}{|E(0)|} = \frac{|E(0)\cdot e^{-\alpha z}|}{|E(0)|} = e^{-\alpha z} \tag{17}$$

Penetration Depth

The radio frequency electromagnetic field penetrates the materials depending basically on the value of their conductivity σ . As we have said before, the human body is a good conductor in the range of RF and microwave frequencies, therefore, the conductivity σ is much higher than the unit. From there the term "penetration by skin effect" is defined represented by δ_p, it is the distance that a wave travels through a medium with losses until its amplitude decreases in $1/e$ (being e=2.71) with respect to its initial value. It can be described as:

$$\delta_p = \frac{1}{\alpha} = \frac{c_0}{\omega\sqrt{\frac{\varepsilon_r}{2}\left[\sqrt{1+\left(\frac{\sigma}{\omega\varepsilon_0\varepsilon_r}\right)^2}-1\right]}} \tag{18}$$

From the above expression we can obtain the relationship between conductivity and frequency. The extent to which a field penetrates decreases with conductivity and frequency.

At low frequencies, the electric and magnetic field exist separately and the penetration of the electric field in the body is almost non-existent. In radio frequency, when greater is the frequency smaller is the penetration of the electromagnetic field of the weave and will have greater concentration in the surface.

DIELECTRIC PROPERTIES OF HUMAN TISSUES

For studies on the biological effects of RF and microwave waves, information on the dielectric properties of tissues is important. These properties describe the level of interaction of electromagnetic waves with human tissue molecules, at the microscopic level, reflecting the molecular field mechanisms underlying the absorption of electromagnetic energy by tissue [9]. It is one of the fundamental properties in the development and design of antennas in biological projects, since it contributes to the study of the propagation of EM waves in tissues, to obtain the specific absorption rate (SAR) and so on.

The dielectric properties of human tissues depend on the frequency. When a tissue is under the action of an electric field, it is subjected to forces that act on it due to the dispersion of the atoms. The response of biological tissue to this fact is strongly affected by changes in its structures and dipoles, apart from its ability to form and orient itself [10].

The dielectric spectrum range of biological tissues is between the frequency range of Hertz to GigaHertz. In the different regions of the biological tissue three main relaxation or dispersion factors related to the response of the tissue to current and frequency can be distinguished, they are called as $\alpha, \beta\ y\ \gamma$. The scattering for low frequencies (below hundreds of KHz) α is associated with the processes of ionic diffusion at the membrane cell site [11]. As I said before, the dielectric properties of tissues are affected by changes in the structure and composition of the tissues, in this case the changes that occur after death affect the ionic environment of the cells and with it, the dielectric spectrum in the frequency range of KHz [12], the relative permittivity of the tissue reaches very high values being more present in the conductivity than in the permittivity.

The dispersion β is between 0.1 MHz and 10 MHz, is mainly due to the polarization of the cell membrane, will have negligible impedance and the current that circulates through the cellular medium will be reflected in the permittivity and conductivity. The

spectrum is affected by the physical state of the cell membrane, if this is destroyed the dispersion β will suffer a great change [12].

Finally, at microwave frequencies (≈1 GHz) the tissues present the dispersion γ for which the capacities of the membrane are short-circuited, this making the membranes electrically "dumb". The decrease in conductivity (and therefore the increase in permitivity) at frequencies higher than 1 GHz can be related to the polar properties of the tissue free water molecules. We can see the explanation in the following image [13]:

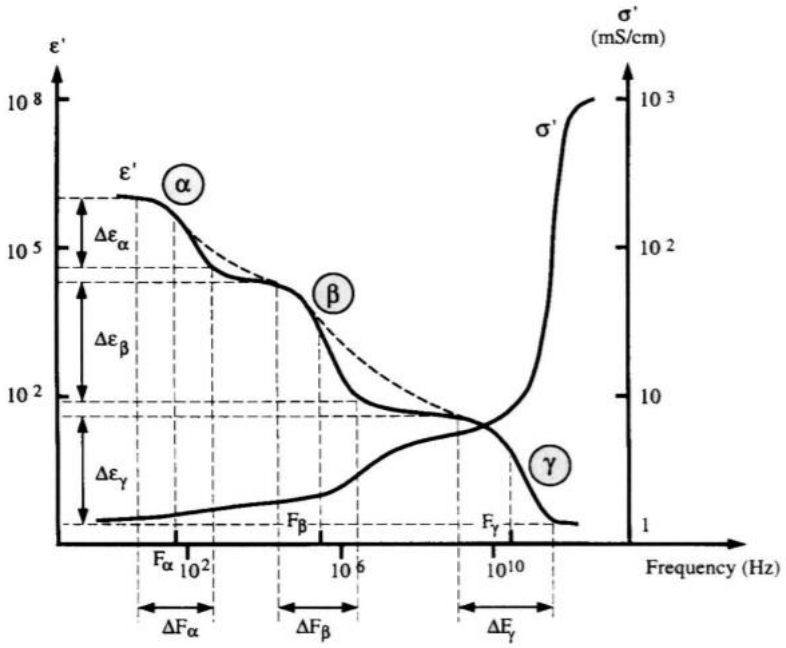


Figure 7: Ideal representation of permittivity and conductivity of biological tissue as a función of frequency.

Mathematically speaking, the frequency dispersion of dielectric properties can be described by the Debye equation [7]:

$$\varepsilon = \varepsilon_0 \left(\varepsilon_r - j \frac{\sigma}{\omega \varepsilon_0} \right) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + j\omega\tau'} \tag{19}$$

Where ε_∞ and ε_s are the permittivity when $\omega \rightarrow \infty$ (high frequency) or in case of a very rapidly changing field and $\omega \rightarrow 0$ (low frequency). The symbol τ' is the relaxation time, i.e. the time required for a stimulated dipole to return to its original state.

In practice, the above equation does not make it possible to model heterogeneous media such as biological tissues well since the dielectric relaxation of most of the biological substances is more complicated and involves several time constants. As we have seen above, the dielectric behavior of tissues can be separated into several regions of dispersion. A large number of empirical relaxation functions were proposed to improve the Deybe equation, the most used being the one proposed by Cole, which is based on a distribution of relaxation time constants, thus obtaining the dielectric

behavior of tissues [13]. These terms predict frequency dependence within each region of dispersion:

$$\varepsilon(\omega) = \varepsilon_0\left(\varepsilon_r - j\frac{\sigma}{\omega\varepsilon_0}\right) = \varepsilon_\infty + \sum_n \frac{\Delta\varepsilon_n}{1+(j\omega\tau')^{(1-\alpha_n)}} + \frac{\sigma_i}{j\omega\varepsilon_0} \quad (20)$$

Where α_n is the width of the spread, n indicates which of the 4 regions of spread it is, $\Delta\varepsilon_n$ represents the magnitude of the dispersion and σ_i the static ionic conductivity.

ELECTROMAGNETIC CHARACTERISTICS OF HUMAN TISSUES

The electromagnetic properties of biological tissues depend mainly on the type of tissue and the frequency. These properties affect the propagation, reflection, attenuation of the tissues, on the other hand, temperature and blood perfusion also affect this type of tissues, but with less importance. Within the electromagnetic characteristics of human tissues, relative permittivity and conductivity are studied. Magnetic permeability can be neglected in human tissue calculations since its value is approximately the same as that of free space ≈1.

When a dielectric is exposed to an electric field, chemical and physical processes are generated in it. The electrical representation of this behavior can be described by two main properties the electrical conductivity (σ) and the electrical permittivity (ε). The electrical conductivity and permittivity are tensor quantities, but they can be considered in isotropic mediums and with an independent response of time, which leads to simplify them as frequency-dependent scalar values that can be expressed as a complex number [13].

It is important to know that all tissues in the human body can be divided into two groups according to their water content. The water content is largely responsible for the different levels of energy absorption under the same conditions of exposure to electromagnetic waves. Some examples of tissues with high water content are skin, muscles and internal organs, which have low dielectric constant and reduced losses, therefore, their energy absorption and temperature increase will be higher [3]; while bones and fatty tissues have low water content as opposed to the other type of tissues which have high dielectric constant and high losses.

SAR

The most important aspect to consider before starting any treatment is hygiene standards. This is a standard that protects the human being from any undesired effect, it contains the calculations and specifications of the amount of exposure or under what conditions it is acceptable to subject a human being to do no damages. So far we have described various effects of EM radiation on biological tissues such as: power density *p* [W/m^2], SAR [W/kg] (Specific Absorption Rate), electric field intensity E [V/m]. All these values have a regulation, in which their maximum admissible values are stated.

In this thesis we will go into more detail to talk about the specific absorption rate (SAR), this allows to measure the effect of electromagnetic waves (EM) in the human body, that is, it indicates the amount of electromagnetic energy absorbed by biological tissues. In the limit values established at European level by the ICNIRP, International Commission on Non-Ionizing Radiation Protection [14] and with ANSI, American National Standard Institute, the limit of the SAR value is 4 W/kg. It may seem easy to obtain this measurement with phantoms but in real application on human tissue it is very difficult, for this, in addition to using SAR to measure the amount of energy absorbed, we use power density. As defined by ANSI (American National Standard Institute):

$$SAR = \frac{\delta}{\delta t}\left(\frac{\delta W}{\delta m}\right) = \frac{\delta}{\delta t}\left(\frac{\delta W}{\rho \delta V}\right) = \frac{\delta P}{\delta m} = \frac{\delta P}{\rho \delta V} \tag{21}$$

The SI unit is $\left[{}^{W}/_{Kg}\right]$. Where $\frac{\delta}{\delta t}$ is the temporary derivative of the increase of electromagnetic energy δW, absorbed by an increase of mass δm contained in a volume element δV given by a density ρ.

According to IEEE, International Committee on Electromagnetic Safety [15], SAR can be related to two methods:

- *Electric field*

$$SAR = \frac{\sigma |E|^2}{\rho} \tag{22}$$

where σ is the conductivity of tissue (S/m), ρ is the mass density of tissue (Kg/m^3) and E is rms electric field strength in tissue (V/m).

- *Temperature field*

$$SAR = \frac{c\Delta T}{\Delta t}|_{t=0} \quad (23)$$

where ΔT is the temperature change measured in (ºC), Δt is the duration of exposure measured in (s) and finally c is the specific heat capacity measured in ($^{J}/_{Kg^{o}C}$).

PERSPECTIVES ON ELECTROMAGNETIC HYPERTHERMIA.

As we have described so far, electromagnetism with human tissues has a deep field of study, therefore, researches in the field of hyperthermia continue to be carried out and call the attention of the most experts in the field. Currently, many teams of researchers continue to work on the development of this technology with the aim of increasing the improvement in the methods of heating and in the study of the interaction of electromagnetic waves with living beings, as well as their mechanisms of action.

This research focuses on three main guidelines for the application of local hyperthermia [16]:

- The use of ferromagnetic materials, these are used with the aim of making the magnetic field intervene and achieve a rise in temperature and the location of this heating.
- The design of applicators to locate the heating zone more accurately.
- The creation of medical programs, based on a studied treatment planning that allows to forecast the temperature distribution in the patient. It is studied that taking into account multiplier systems, the change of phase and amplitude would allow the localization of heat in the tumor [16].

In this thesis we will focus on the possibilities of using ferromagnetic nanoparticles in microwave thermotherapy.

THE ROLE OF NANOTECHNOLOGY IN THE TREATMENT OF HYPERTHERMIA.

Nanotechnology is used to exclusively define sciences and techniques dedicated to the study, design, creation... of materials and functional systems at the nanoscale, one millionth of a millimeter [8].

Within nanotechnology we could distinguish several areas, depending on this work the two most important are the area referred to "Medical devices and health" and "Electronics, information and communications". The greatest amount of research is focused on the field of medicine and biology, specifically on how to apply nanotechnology to medicine in order to prevent, diagnose, examine and treat diseases. It is a reality that there are advances in applying nanomedicine, there are certain fields that are more attractive than others such as: image monitoring, tissue repair, control of the evolution of diseases, defense and improvement of human biological systems and so on.

As we have explained on several occasions before, hyperthermia is a treatment that they want to complement along with traditional cancer treatments such as radiotherapy and chemotherapy, but it has limitations. This technique is capable of raising the temperature and killing the cancer cells; on the other hand, undesirable effects such as radiation or lack of precision in terms of exposure to laser and microwave waves can occur, this affecting the healthy tissues around it. Therefore, due to the location of the tumor or the patient's condition it is difficult to apply this treatment [9].

This is where magnetic hyperthermia plays a fundamental role. This treatment not only overcomes the obstacles present in classic hyperthermia, but also attempts to solve the problem of heat location by combining magnetic fields and nanoparticles responsible for generating the temperature increase. After this, the problems regarding the location of the cancer cells and the patient's condition are solved since these nanoparticles are located in the areas affected by the tumor, these particles move through the blood looking for this type of areas distinguishing them by their morphology. Once they are located, they are heated by exposing the external magnetic field of the tumour region without damaging the surrounding ones.

As we have said before, thanks to the fact that nanotechnology works at this scale it is possible to create completely new and unique phenomena and properties in matter, making possible procedures that are essential for producing magnetic nanoparticles. These are coated by polymers or vesicles with surfaces specifically designed to interact only with a cell or tissue, in our case against cells and tissue affected by cancer [10]. For the implementation of this technique as a treatment for cancer, the functionality in which the particles only interact with a cell or tissue must endure over time, especially biochemically and physiologically.

Nanoparticles have a size between 1 and 100 nanometers and are in continuous scientific research due to their potential application in several fields; biomedical, optical... When we talk about biological applications it is important to know that these

nanoparticles are encapsulated in a surface in order to protect the biological tissue from the metallic material they contain. Normally the nanoparticles are designed to be directed to specific sites within the human body, depending on the design they will follow organelles within a cell, proteins or individual molecules, these are linked or coupled to the coating of biological molecules that do the function of direction or guidance.

There are nanoparticles of various types; Cobalt (Co), Iron (Fe) or combinations of these two [11]. The most used for magnetic hyperthermia are those formed with iron oxide, one of their main characteristics is that they are biocompatible and stable to oxidation, in addition they are those that have the greatest interaction with the applied magnetic field since they are more magnetic. Not all are advantages, in this type of particles there are also problems, the first of them is its protection against oxidation and the toxicity that can generate in the human body, to reduce the interaction is of vital importance the polymer coating of the particles.

The main challenge for researchers for future progress in the viability of this technique is the characterization of nanoparticles, to study them further and to be able to establish with determination and accuracy their effects on biological tissues [12]. It is also a challenge to study the competent magnetic field that originates the best response of the nanoparticles and the design, with the aim of being as selective as possible so that the highest percentage of them reaches the desired cells and reduces losses in other tissues [13] .

CHAPTER 3: WAVEGUIDE AND ITS FUNCTION FOR MICROWAVE HYPERTHERMIA TREATMENT.

Brief description and the important role of waveguides in the treatment of hyperthermia.

WAVEGUIDES AND WAVEGUIDE APPLICATORS FOR MICROWAVE HYPERTHERMIA.

There are different ways to radiate biological tissue. The choice of this factor depends on the frequency, the required power density, the duration of exposure (SAR) and its distribution. The radiation can be from a specific part of the body or radiation from the whole body, the dimensions and characteristics of the tumour to be treated depend on this.

There is a wide variety of applicators used in different types of hyperthermia, depending on accessibility and the particular requirements of the treatment to be used. In this project we want to radiate a specific area of the human body, therefore one of the main technologies used for partial body radiation is the microwave applicator. Specifically in this case I will focus on the waveguide applicator as a means of transmitting the electromagnetic energy coming from a microwave generator to the affected area. This type of applicator is used because it is most appropriate in cases where the tumor is close to the surface. For any frequency and size of opening, a waveguide applicator allows the greatest depth of penetration, because in the central part of the applicator opening, the distribution of the magnetic field is very similar to the distribution of a flat wave field.

A waveguide is a structure that guides waves, can be electromagnetic waves or sound[14]. There are different types of waveguides for different types of waves, the most common is a special type of tranmission line that consist of a segment of metal pipe used to carry high frequency radiowaves, more specifically, microwaves. The fundamental comfort of the waveguide are the simple production, minimal losses, capacity to transfer the greatest power, particularly wide frequency bandwidth and limited emittance of energy into the surroundings.

To sum up, the main function of the waveguide is carrying electromagnetic waves from one place to another without significant losses in intensity. The walls of the guide are conductive and therefore reflect electromagnetic energy from the surface. In a waveguide, the conduction of energy does not occur in the walls of the waveguide but through the dielectric within the waveguide[15]. The transmisión of energy occurs when the mode is induced by a frequency greater than the cut-off frequency, if not the mode is exponentially attenuated along the waveguide.

The cross-sectional dimensions are selected in such a way that the waves are propagated within the guide. It has any form of cross-section, closed on one side but the most commonly type of waveguide are of rectangular cross section using TE_{10} and

circular TE_{11} as a fundamental mode respectively. The modes are superpositions of plane waves; electromagnetic waves that are not guided in free space, or in a bulk isotropic dielectric can be described as such. Can be classified as follow [16]:

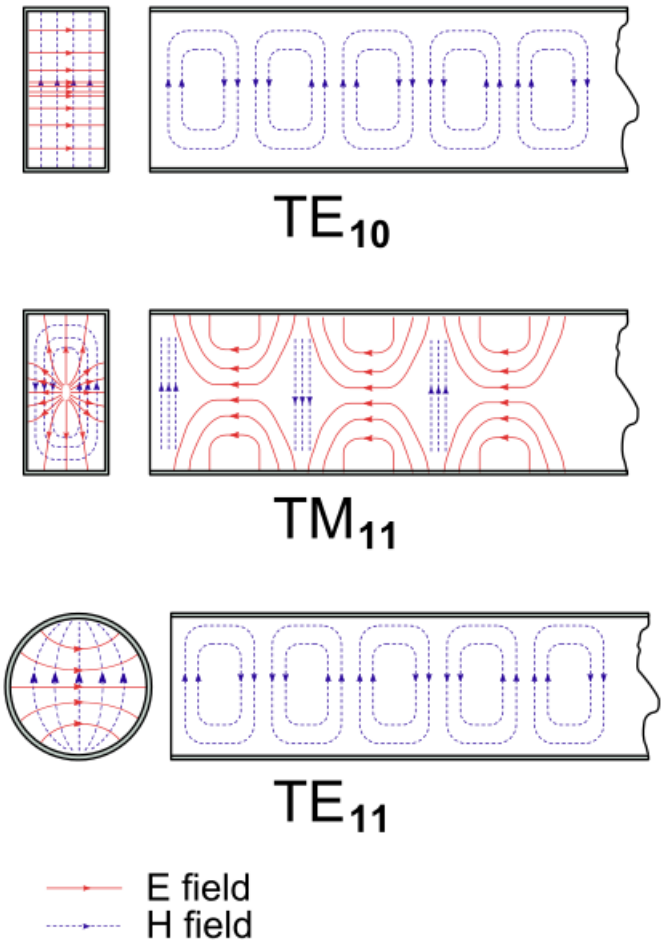


Figure 8: Field patterns of some commonly used waveguide modes.

In rectangular waveguides, rectangular mode numbers are desginated by two suffix numbers attached to the mode type, such as TE_{mn} or TM_{mn}, where m is the number of half-wave patterns across the width of the waveguide and n is the same but across the height of the waveguide. In circular waveguides, circular modes exist and here m is the number of full-wave patterns along the circumference and n along the diameter[16].

Hollow metallic waveguides filled with a homogeneous, isotropic material support TE (Transverse electric modes – No electric field in the direction of propagation) and TM modes (Transverse magnetic modes – No magnetic field in the direction of propagation) but not the TEM mode (Neither electric nor magnetic field in the direction of propagation).

The geometry of a waveguide reflects its function; the frequency of the transmitted wave also dictates the size of a waveguide: each waveguide has a cutoff wavelength determined by its size[14]. The cutoff frequency is given by:

$$f_{c_{mn}} = \frac{c}{2\sqrt{\varepsilon_r \mu_r}} \sqrt{\left(\frac{m}{a}\right)^2 + \left(\frac{n}{b}\right)^2} \quad [Hz] \tag{24}$$

Where c is the speed of light in vacuum and m and n indicate the modes, a is the longer side of the waveguide and b is the shorter [17].

In order to reduce the cut-off frequency, waveguides may contain various types of dielectrics. The simplest and most widely used solution, which will be used in this project, is to introduce distilled water, the dielectric properties of which are very similar to those of biological tissue.

WAVEGUIDE APPLICATOR

If we talk more specifically about waveguide applicators in medicine, the waves are propagated from the outside as a convergent cylindrical or elliptical shape towards the inside of the patient's body. One of the settings to be considered is the frequency of the wave, it must be directed centrally in the affected area. In addition, it is important that the settings of the wave applicator are correctly configured, since there is a risk of hot spots in this area.

Due to the serious consequences that using an applicator in hyperthermia can have on humans, it is tested and studied previously on phantoms and experimental animals. To test the applicators, the biological tissue is replaced by phantoms with similar dielectric properties, they are not the same but the difference is minimal and to predict behavior is a good substitute. Regarding the measurements to be made, the two most important parameters would be; the S_{11} parameters in charge of measuring the adaptation in the waveguide and the specific absorption rate (SAR).

The design to be carried out in this thesis is shown below:

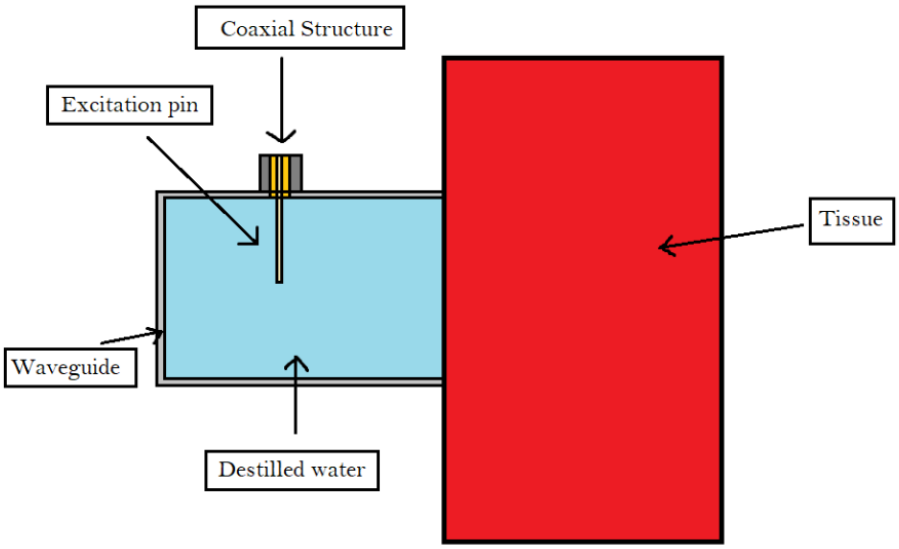


Figure 9: Representation of the proposed waveguide applicator

It is important to note that between the waveguide and the human tissue a material can be placed, for example water, this material helps to create a transition between the two media, as there is an abrupt difference between the permittivity of water and the permittivity of human tissue, it is introduced in order to minimize the reflection of the waves.

Another reason for placing the water bolus is to eliminate the risk of creating hot spots with high density at the edges of the waveguide. The presence of water bolus eliminates the risk of hot spots in the treated area.

And the last reason is that the amplitude decreases exponentially following the temperature distribution, to keep the high temperatures longer without the presence of the water bolus the human tissue can be damaged.

In local hyperthermia the temperature is set at a level of about 40 degrees Celsius. For whole body hyperthermia, the average temperature set would be 10 degrees Celsius.

It has not been included because computation time was high in this type of program, but in future experiments one can think of including a water bolus between these two structures to make a gradual or softer transition.

CHAPTER 4: SIMULATION IN SIM4LIFE

The second aim is to consider and simulate local microwave applicator operating at frequency 434 MHz and radiating into the agar phantom of the treated area with added ferromagnetic nanoparticles.

HYPERTHERMIA TREATMENT PLANNING

Hyperthermia is an innovative treatment and current research; due to this it has different planning systems to expose the treatment and with it a great variety of applications. These applications are used with the purpose of optimizing the healing process to individual patients, to characterize systems that apply hyperthermia, to ensure quality assurance and finally, we are working on creating new antenna systems.

Treatment planning in hyperthermia is a two-step process; the first is the calculation of the specific absorption rate (SAR) and the second is the distribution of temperature measurements in the human body using computer models.

As you can imagine, working under real conditions to determine SAR distribution when body tissues are not homogeneous and blood flow is undefined is a challenge. Therefore, it is necessary to first do experiments and calculations to determine the distribution of heat that will be induced into the body with a certain high electromagnetic frequency.

Thanks to advances in computer technology and development in electromagnetic and thermal 3D systems, the integration of clinical treatment planning is now a reality [15].

The main objective of hyperthermia treatment planning is to adapt the electromagnetic energy deposited in the clinical device to the human body by heating a particular area, avoiding the exposure of those hot spots in the tissue not affected by the cancer cells.

The advantages present in the application of this treatment are: the adaptation effects of the heating technique can be tested in advance, on the other hand, the number of temperature measurement points is limited, the beneficial part is that the predictions of the models provide an additional insight into the hot spots and the measurement of SAR in a patient.

In addition to the treatment planning process being effectively applied in the patient's routine, physicians need to know for certain that predictions differ from reality. Therefore, the predicted SAR results from an electromagnetic (EM) model of a hyperthermia applicator are critical in the process of developing a treatment planning system. It is very important that the difference between the measured and the predicted SAR distribution is low, i.e. that the coincidence is of quality and that the model evaluation obtains clear criteria and is scientifically supported [15].

SAR MODELING

As explained above, SAR is one of the fundamental parameters for the treatment of hyperthermia.

There are two ways to model it, the first is empirically based modeling, this consists of measuring the distribution of heat or electromagnetic field within a tissue phantom. Between these two measurements it is more sensible to use the results obtained from the heat distribution, these include the measurement of the electromagnetic field and in addition, the heat distribution field that it carries. This type of modelling is very effective in phantoms but is not clinically suitable. The number of needle sensors that can be inserted is limited and, as we have said on several occasions, biological tissues are not homogeneous.

On the other hand, there is mathematical modeling. It is necessary to mathematically calculate the heat distribution caused by the exposure of human tissues to electromagnetic energy. To do so, it is essential to solve a partial differential equation, but equally, obtaining this calculation is variable and complicated, since there is variation in the blood flow and once again it is influenced by the fact that the tissue is not homogeneous. This modeling could only be applied to a small number of models.

In order to overcome the limitations of classical methods, numerical methods were developed[18]. Among the most used methods are:

- Finite difference time domain method (FDTD) – is a numerical analysis technique used for modeling computation electrodynamics.
- Method of moments (MoM) – is a method of assessing population parameters.
- Finite element method (FEM) – generic method used for approximation of complex partial differential equations.
- Integral equation methods (Volume integral and surface integral) – methods including differential equations, are those in which a function appears under an integral sign.

There is a difference in the way of working in these four methods. The FDTD and FEM methods focus the field values on discrete points in the affected area. In contrast, the other two perform the work globally, that is, the field is calculated in one volume. To carry out this thesis we have used the program SIM4LIFE and we have carried out the simulations with the FDTD method, which we will explain in more detail below.

FINITE DIFFERENCE TIME DOMAIN METHOD (FDTD).

The finite difference time domain method, abbreviated as FDTD is an application of the difference method, is commonly used and is the most direct way to solve differential equations, this obtaining Maxwell's equations. The basic algorithm of FDTD was first proposed by K.S. Yee in 1966.

This method uses central difference approximations in order to evaluate the spatial and temporal axis. Each element of the network is characterized by its dielectric parameters, there are three for the electric field (E field) and three for the magnetic field (H field) and these are discretized in both space and time in the form of a staggered grid of a Cartesian coordinate system [16]. The space is divided into small portions called cells and on the surface of each one, there are points assigned in order to satisfy Maxwell's equations, this way the electromagnetic waves propagate in the numerical space, as they occur in reality. This method is common in the analysis of electromagnetic phenomena at radio and microwave frequencies.

Next, we can clearly see the components of the electric and magnetic field that we talked about in the previous paragraph, it is the scheme on which the FDTD space network is based. If we look at these two fields, both the network belonging to the magnetic field in space and time is displaced from the electric[19].

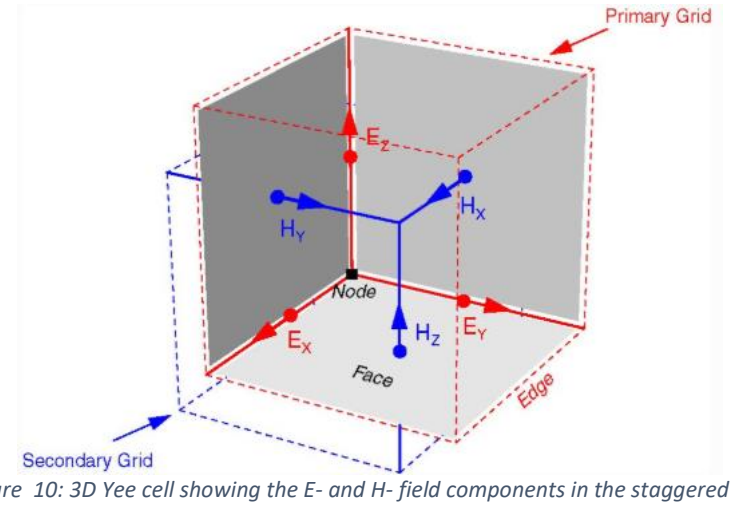


Figure 10: 3D Yee cell showing the E- and H- field components in the staggered grid.

SIMULATION IN SIM4LIFE

From this section we will focus more on the practical part of this thesis. The main objective is to consider and similar a microwave applicator operating at the frequency of 434 MHz, this will radiate within an agar phantom in the treated area. A study of the results of the simulations obtained with and without nanoparticles will be carried out. As measurement tools we will use SAR and temperature calculations using an electromagnetic field simulator. To do this, we will use the SIM4LIFE program, especially the "Sim4life Light Limited Student Edition".

The program was totally unknown to me but thanks to the tutorials incorporated in it and the help of Prof.Ondrej I gradually understood how to make the proposed simulations.

I will now write up the progress according to the three different parts into which the program is divided.

➢ PROGRAM OPERATING ENVIRONMENTS

○ MODEL

This is the section of the program where you must create the model you have to examine. From the basic tools of the program, i.e. solid structures or plots, you can build different shapes to represent the structure of the model to be analyzed later. In this project, the model is as follows:

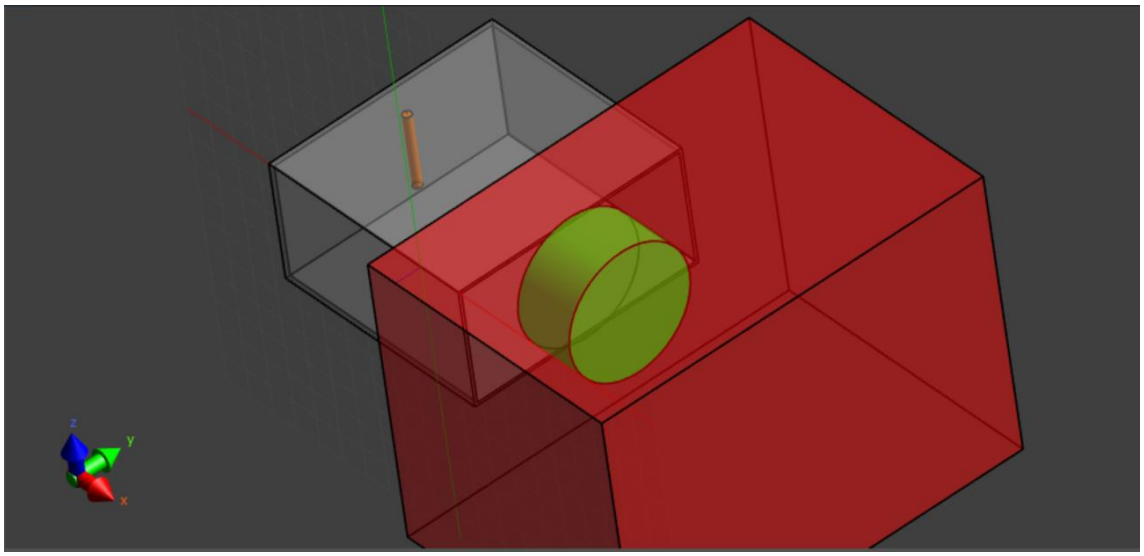


Figure 11: General model in Sim4Life

In the image above we can see several differentiated blocks with different colors. Each piece represents a fundamental part in the model to be examined, with the help of the following figure we will identify what each figure symbolizes:

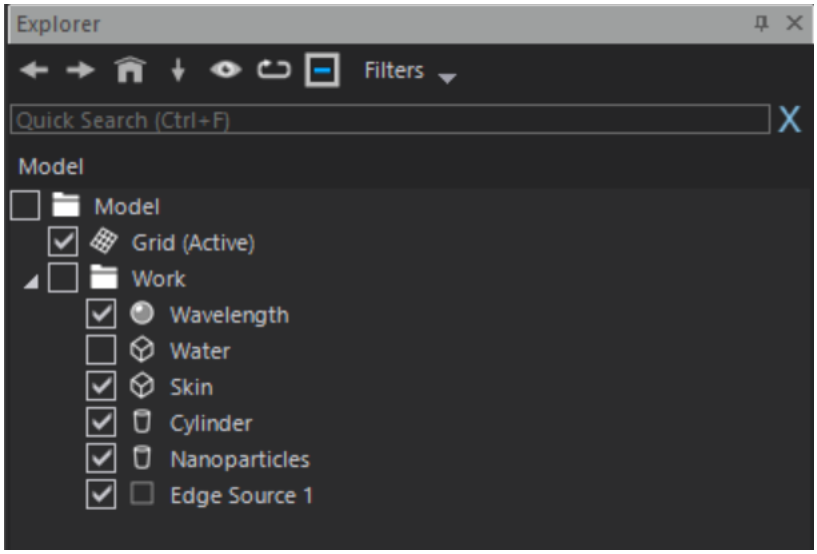


Figure 12: Different parts of the model

The most important part is the waveguide applicator for local hyperthermia represented in grey, it works at a frequency of 434 MHz with dimensions 40x80 mm.

This is a waveguide model to be excited with the standard method, which is composed of an edge source connected to a probe excitation. The orange cylinder that can be seen inside the waveguide would be the probe, on top of this there is a very small red metal wire that is the edge source.

The green cylinder is the agar phantom, which contains a different permittivity and loss tangent for the different cases of simulations, regular microwave hyperthermia and hyperthermia using ferromagnetic nanoparticles. The data will be detailed in the following sections.

Following the assignment of the model to reality, the larger red square simulates the patient's skin. Finally, if you have contrasted the image of the Sim4Life explorer window with the elements of the image there is an undescribed element. For this, I added the same image as before but with a clear difference, the waveguide is filled with distilled water. The distilled water as mentioned above is introduced into the waveguide in order to more accurately reproduce the biological tissue as they have very similar dielectric properties.

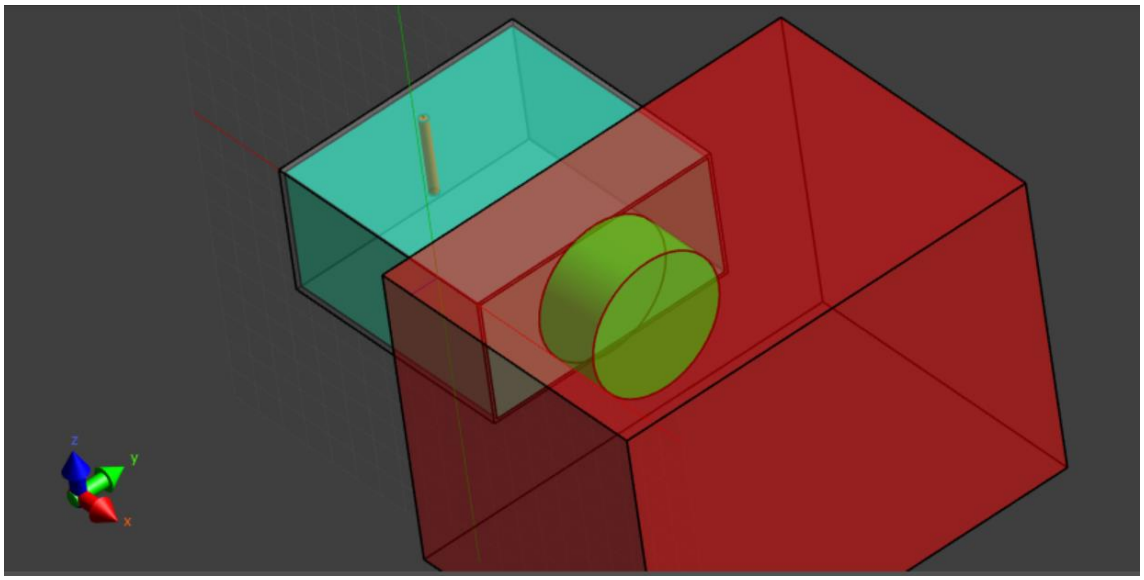


Figure 13: General Model in Sim4Life by adding distilled water to the waveguide

○ SIMULATION

The part of the simulation includes the most important part of the practice and is the slowest because the simulation process takes too long when you have the student version as in my case.

From the same project I have created three different simulations, which allow to calculate and compare different configurations; in the first one the S_{11}parameters are simulated, the second one is performed to obtain the SAR results without nanoparticles and finally, with them. There is a slight difference between these simulations, but I will mention them throughout this section.

The first thing to do is to create a new simulation, in this case Electromagnetic based on the finite difference time domain method, abbreviated as EM FDTD. Within the simulation, it has several properties to change depending on what you are going to simulate. Below, I show a breakdown of the drop-down menu:

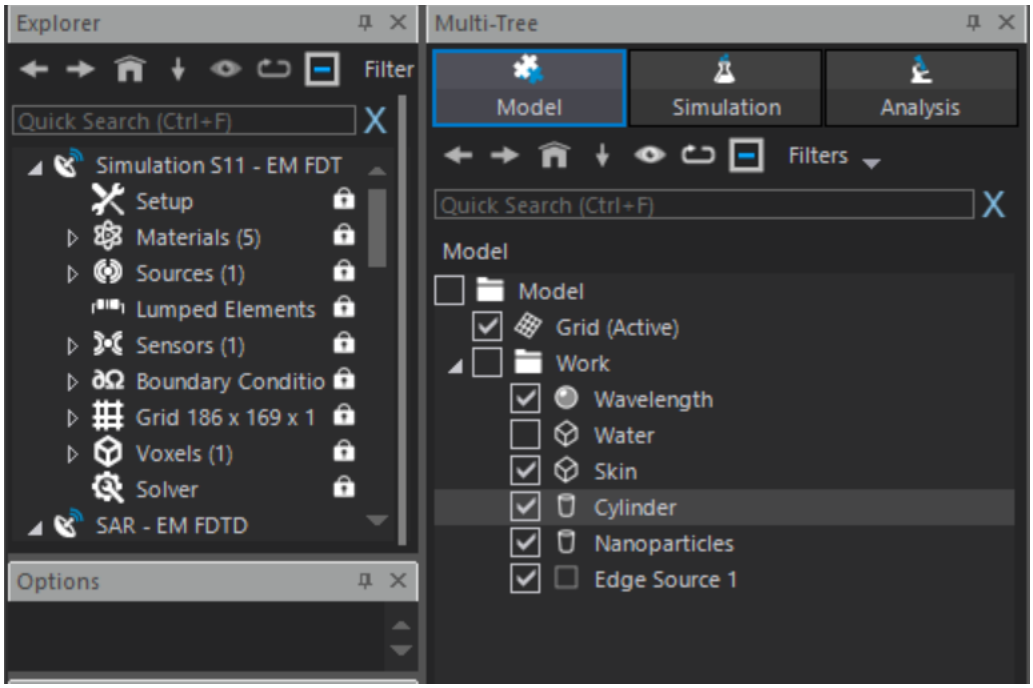


Figure 14: Simulation part of Sim4Life

First, we must assign to the different parts that we have created in the model the materials that correspond to each one of them:

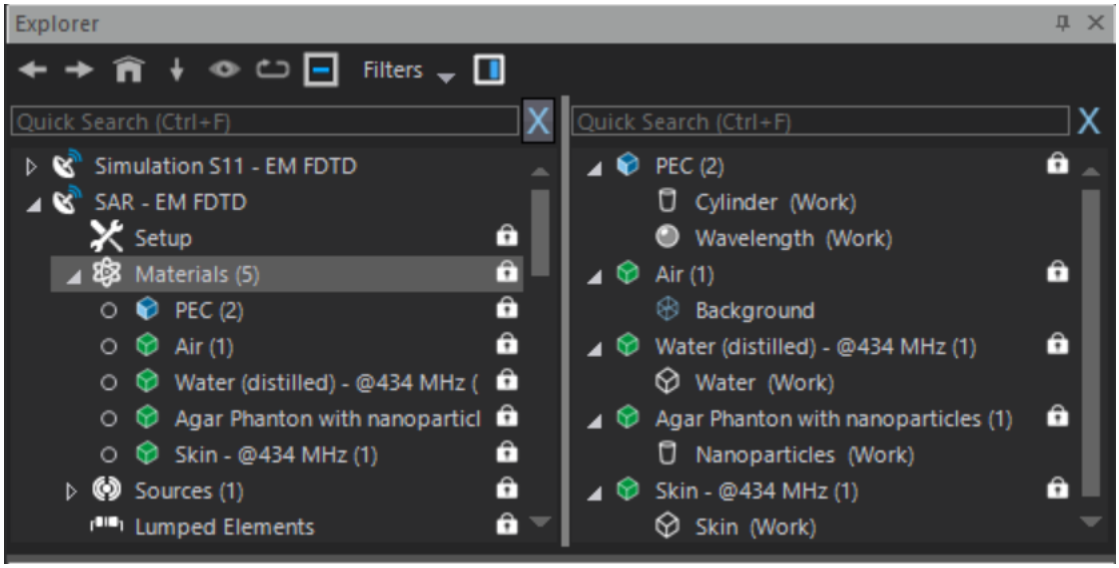


Figure 15: Allocation of materials to each part of the model

The program has a database of materials already created, which we have used for skin, distilled water and so on, also gives you the option to create the material with the properties you need.

In this case, I have created two types of new materials, agar phantom with nanoparticles with the data from the following images:

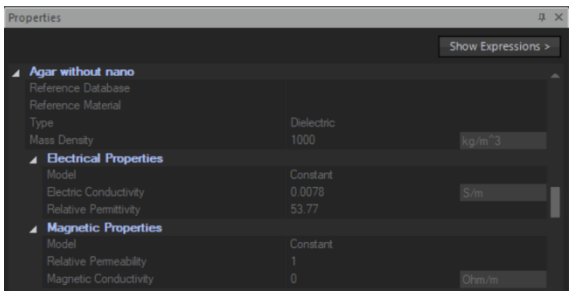


Figure 17: Properties Agar without nanoparticles

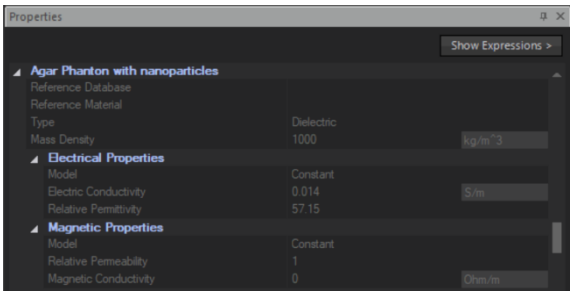


Figure 16: Properties Agar with nanoparticles

If we go back to the image of the properties inside each simulation, the next one is the Source, this is the "Edge source" type as I said before. In the settings of these we change the excitation of the signal to Gaussian. We center the frequency in 434 MHz and a 1e9 Hz bandwidth. We will excite our waveguide with the following source:

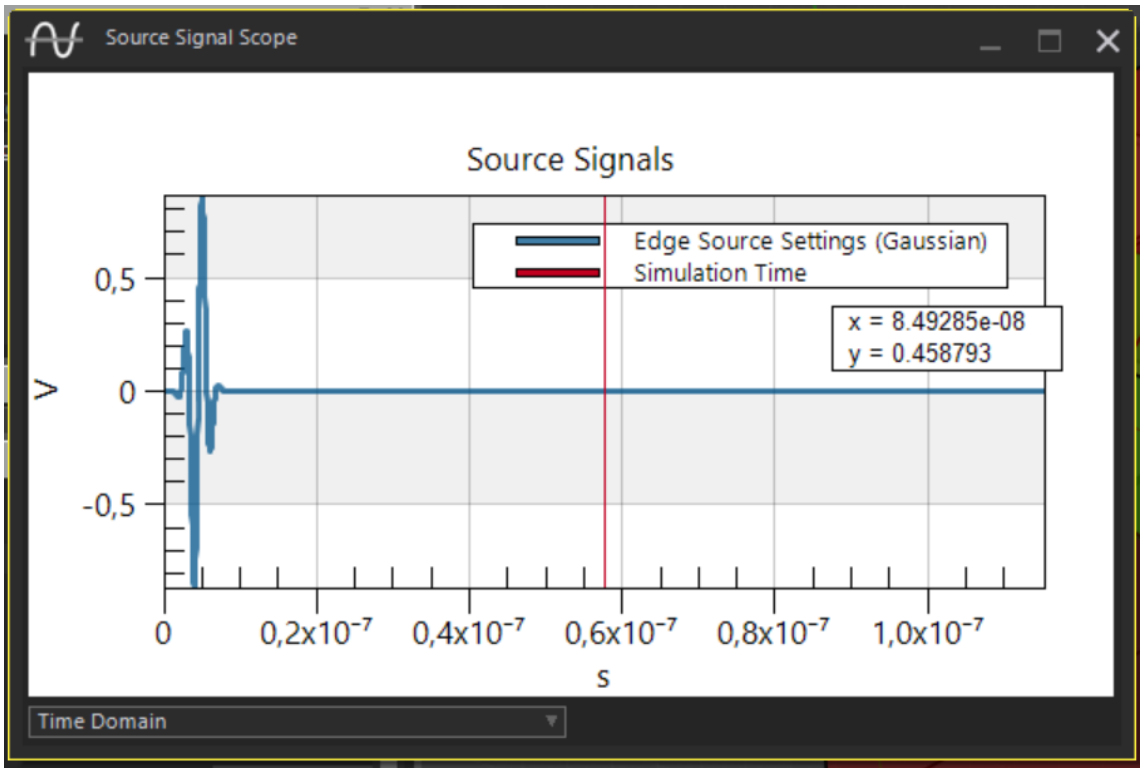


Figure 18: Gaussian signal source

The next property is sensors and depending on what we are going to simulate we will only have the sensor "Edge source" to obtain the parameters S_{11} and to simulate the SAR we will have this sensor added of "Field sensor" which contains inside Overall field. With the parameter S_{11} we measure the point where you are impacting the waveguide. To measure fields, as we do not fear a port where to take a data we have to generate a

field and there I make a reading of the electric field, due to this it is necessary to introduce a new sensor to measure the SAR.

Another difference in simulation with or without nanoparticles is the properties of Sim4Life's grid and voxels. In the case of simulation without nanoparticles we must not introduce the nanoparticles into the voxel, in the following screenshots we can see the difference:

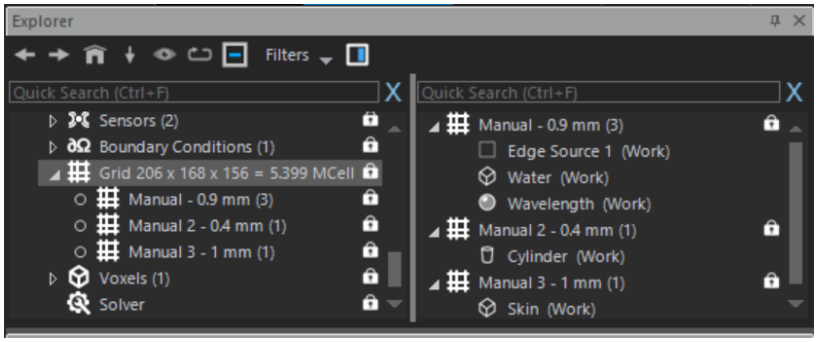


Figure 19: Grid without nanoparticles

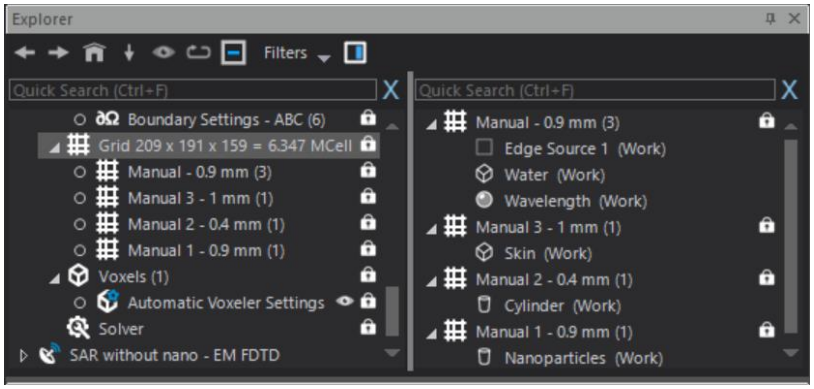


Figure 20: Grid with nanoparticles

The values in mm attached to the different grid sections have been changed according to the 3D representation that I could see in Sim4Life in order to create an optimal setting to obtain the representation of the S_{11} and SAR parameters (measures the energy absorbed by the biological tissues).

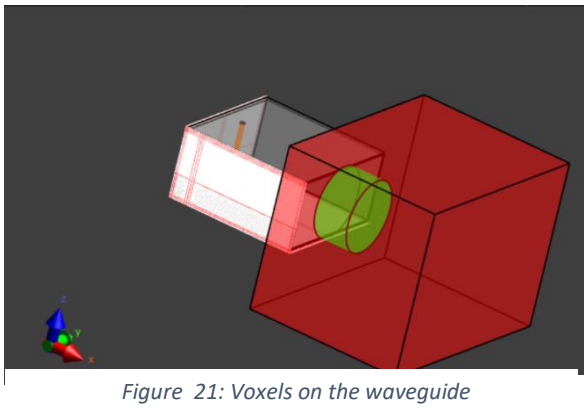


Figure 21: Voxels on the waveguide

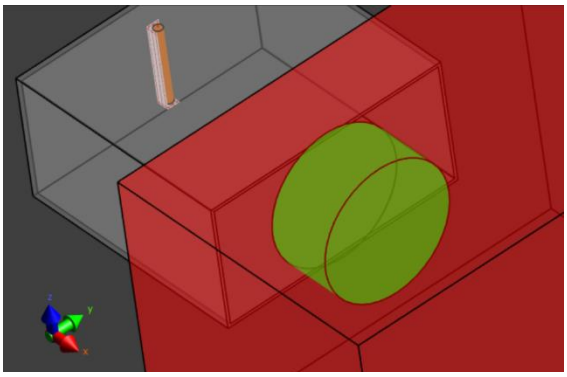


Figure 22: Voxels on the probe

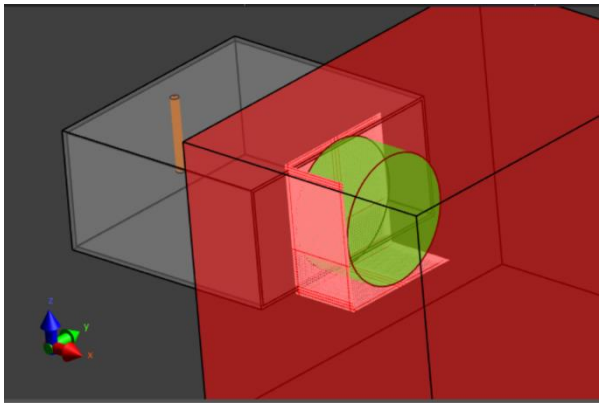


Figure 24: Voxels on the nanoparticles

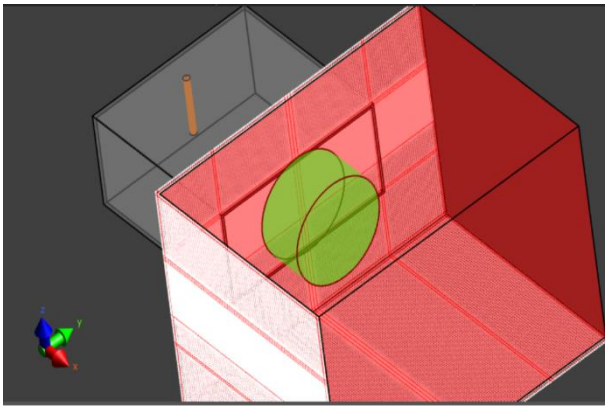


Figure 23: Voxels on the skin

Once we have created the voxels in the simulation, we click on Run to start simulating. The time that the simulation will take depends on the type of computer and the version of Sim4Life used. If you want to see the simulation status click on the button at the bottom right of the screen and you can see the bar in % of the progress of the simulation.

○ ANALYSIS

The Analysis part is the last one before obtaining the corresponding graphs and results.

As I said before, we have carried out several simulations of the same project, so there will also be several analyses. The way to proceed to obtain them is different, it is not the same process to obtain the S_{11} parameters as the SAR.

Parameters S_{11} are commonly used in electrical engineering and are used to complement the basic behavior of electrical networks that are subjected to permanent small signal stimulus regimes [18]. In this case, with parameters S_{11} we want to measure the adaptation between the waveguide excited by a Gaussian source and the biological tissue of the human.

Click on the Analysis section and the results of the simulations carried out in the explorer windows will be available. In the view output view window select the Source and, in the ribbon, click "Sensor Extractor". Automatically a subfolder is generated and then we select the simulation that we want to obtain, in this case, first we plot EM-Reflection coefficient(f).

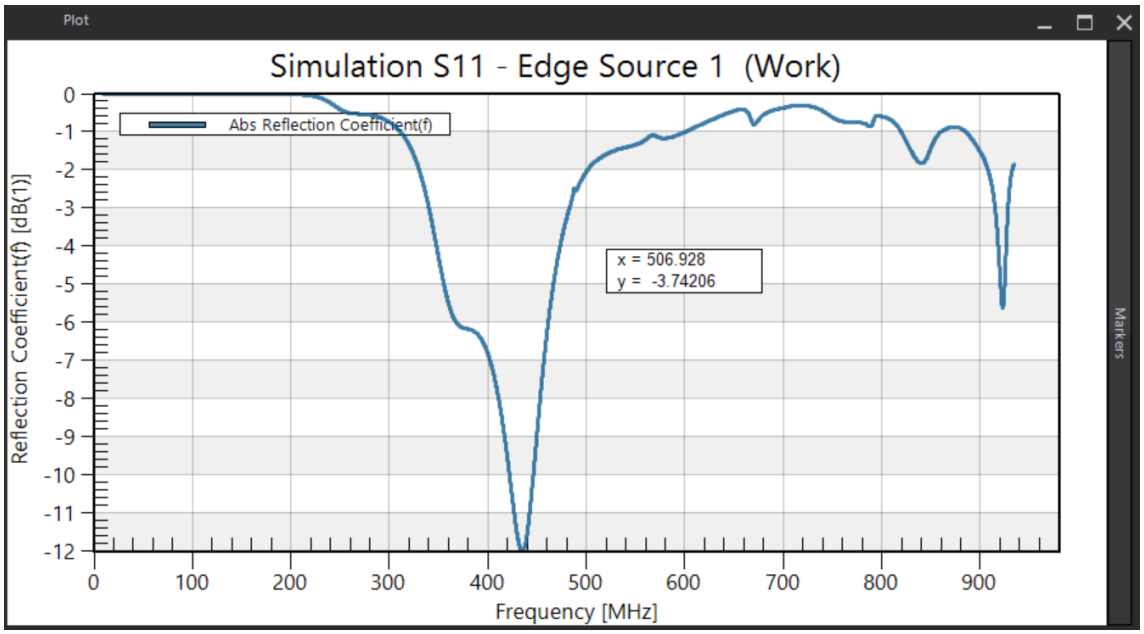


Figure 25: EM-Reflection coefficient (f)

As I said before with the parameter S_{11} we measure the point where you are impacting the waveguide, it is a voltage reading and the current at the power point, therefore, voltage between current is the ohm law and we obtain the impedance (Z) of the port. With it and with an input impedance of 50 ohms we calculate the reflection coefficient S_{11}which is the amount of reflected power.

To be sure that the guide is getting the power through the cable we need to check the reflection coefficient in logarithmic units, S_{11}. When the S_{11} is less than -10 dB, the antenna is adapted, as we see in the previous picture the result of our S_{11} is -12 dB, which means that the antenna is well adapted with the port because it is less than the reflected power.

Finally, to extract the SAR value from the system, we click on the main simulation folder in the Explorer window, and then on the "Overall Field" object in the "Output View" window. And we click as in obtaining the parametersS_{11} to sensor Extractor.

We follow the instructions of the examples that are present in the tutorial of the program itself. We can obtain the SAR as recommended by the IEEE/IEC62704-1 standard or not, change the view of the results, the planes in which we want to analyze the simulation...

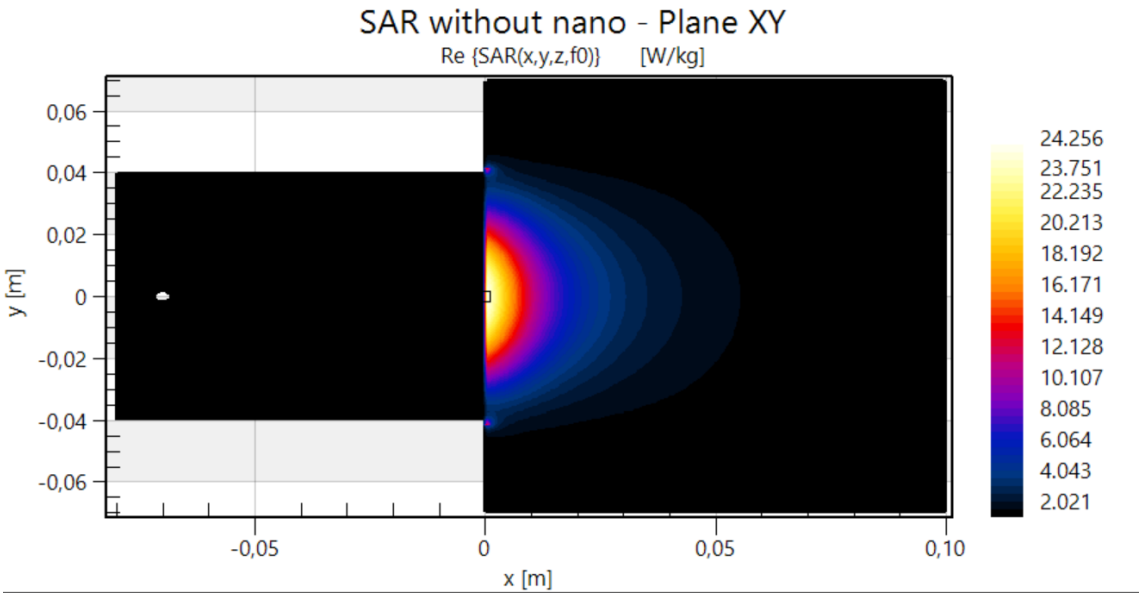
➢ TESTING SAR DISTRIBUTION WITH AND WITHOUT NANOPARTICLES.

In order to measure the effectiveness of microwaves in the treatment of hyperthermia with nanoparticles, I have made different graphs with the Sim4Life program. As you have seen in the model shown in *figure 11* for example, the nanoparticles are represented in green, they are located 5mm from the surface of human tissue and the diameter of the container that contains them is 40 mm.

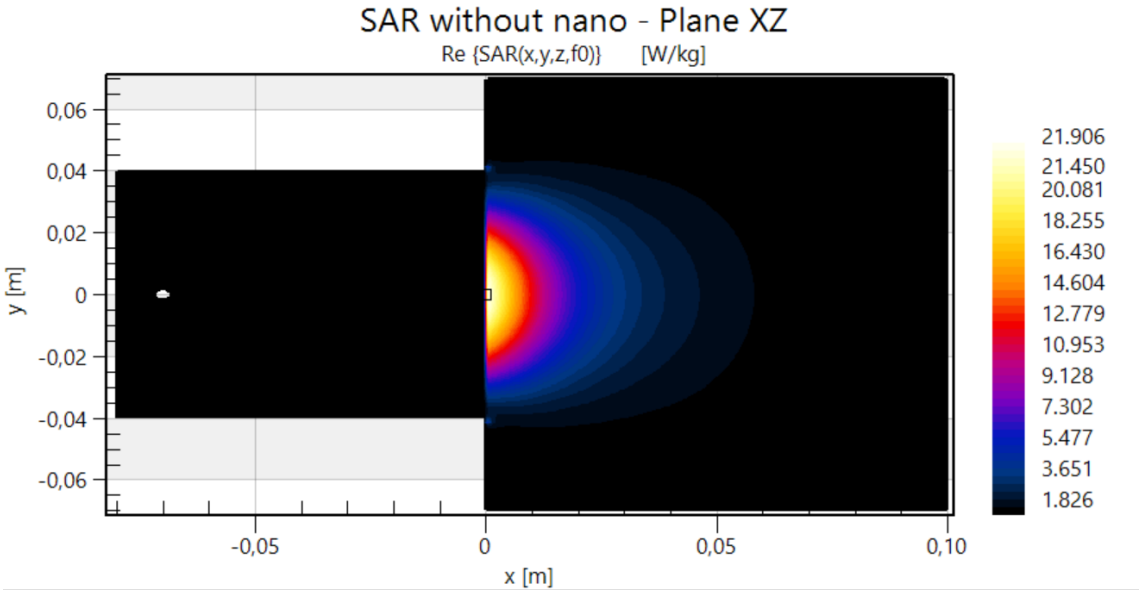
Having said that, we will show the results obtained by first measuring SAR without nanoparticles and then introducing them. To finish, we will make a comparison of several planes with and without nanoparticles, to be able to see a more appreciable difference.

○ RESULTS OF SIMULATING LOCAL MICROWAVE APPLICATOR RADIATING INTO THE AGAR PHANTOM OF THE TREATED AREA.

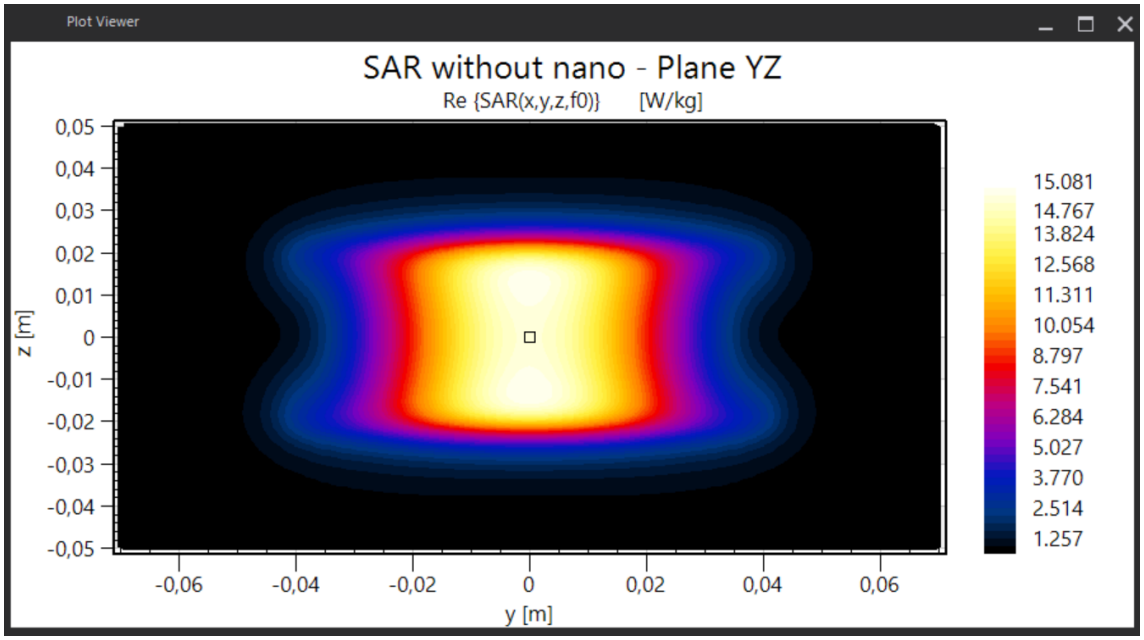
Distribution of SAR in the X-Y plane



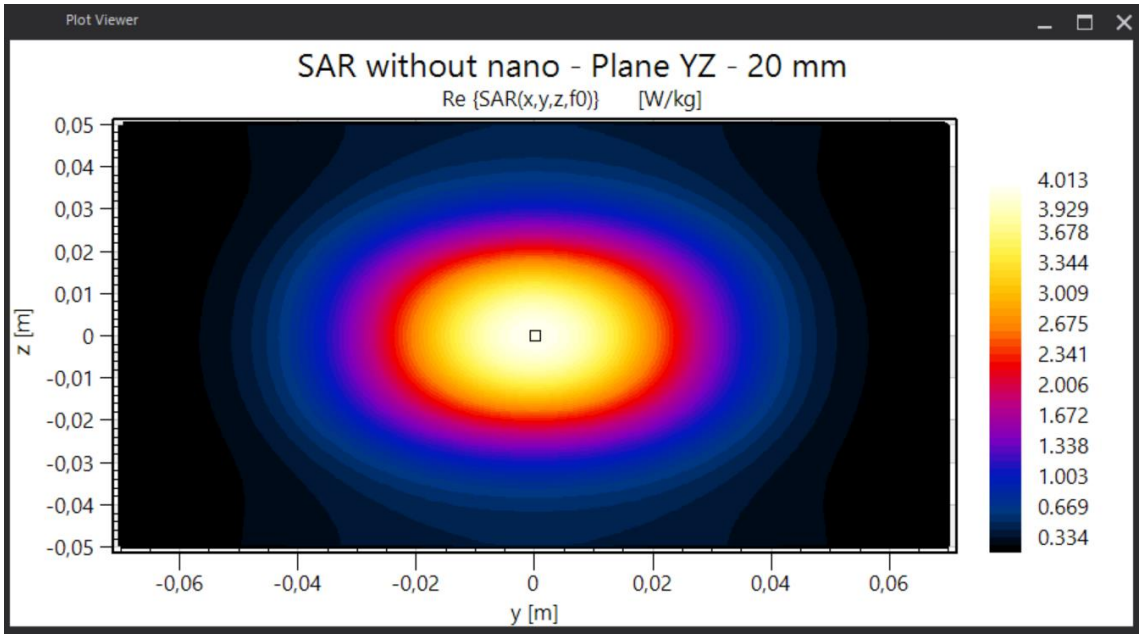
SAR distribution in the X-Z plane



In the case of the Y-Z plane we will measure the distribution of the penetration in different depths, in order to visualize in more detail, the behavior of the SAR. In this case, shown below, we measure at 5 mm depth in the human tissue.



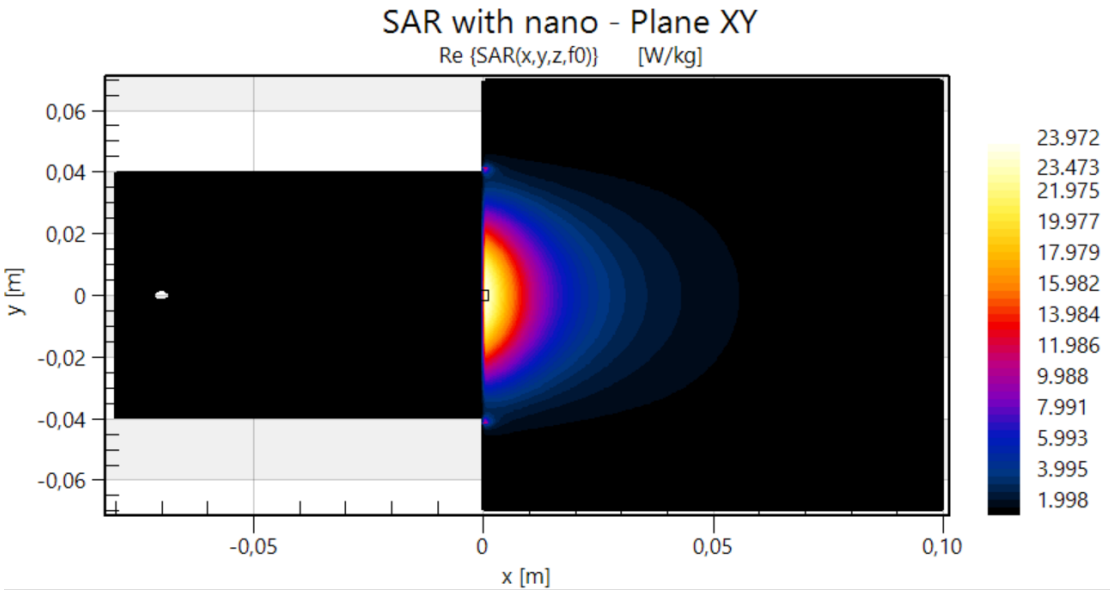
SAR distribution in the same plane, Y-Z, but 20 mm deep:



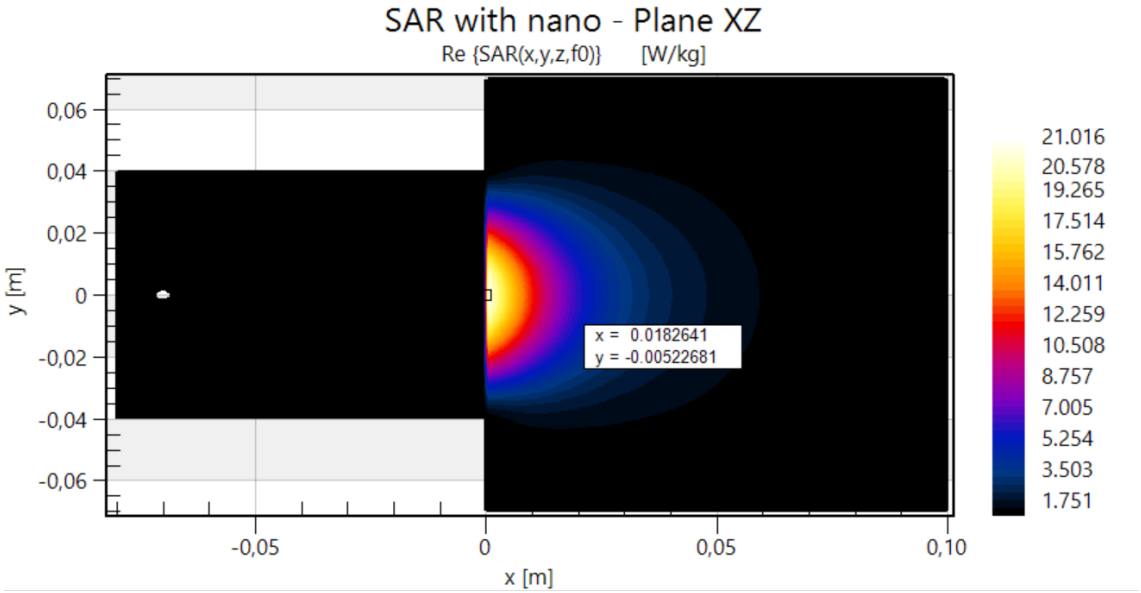
As you can see in the images, the form of representation changes and the scale of the legend also changes, reflecting that at greater depths the penetration decreases slightly due to the reduction of the field intensity.

- RESULTS OF SIMULATING LOCAL MICROWAVE APPLICATOR RADIATING INTO THE AGAR PHANTOM OF THE TREATED AREA WITH ADDED FERROMAGNETIC NANOPARTICLES.

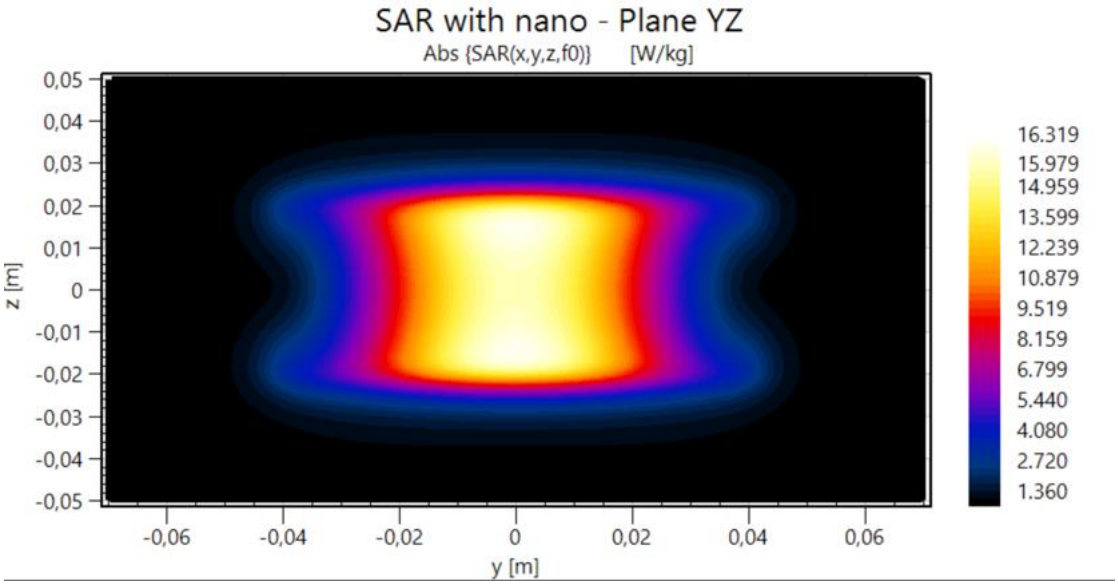
Distribution of SAR in the X-Y plane with added nanoparticles:



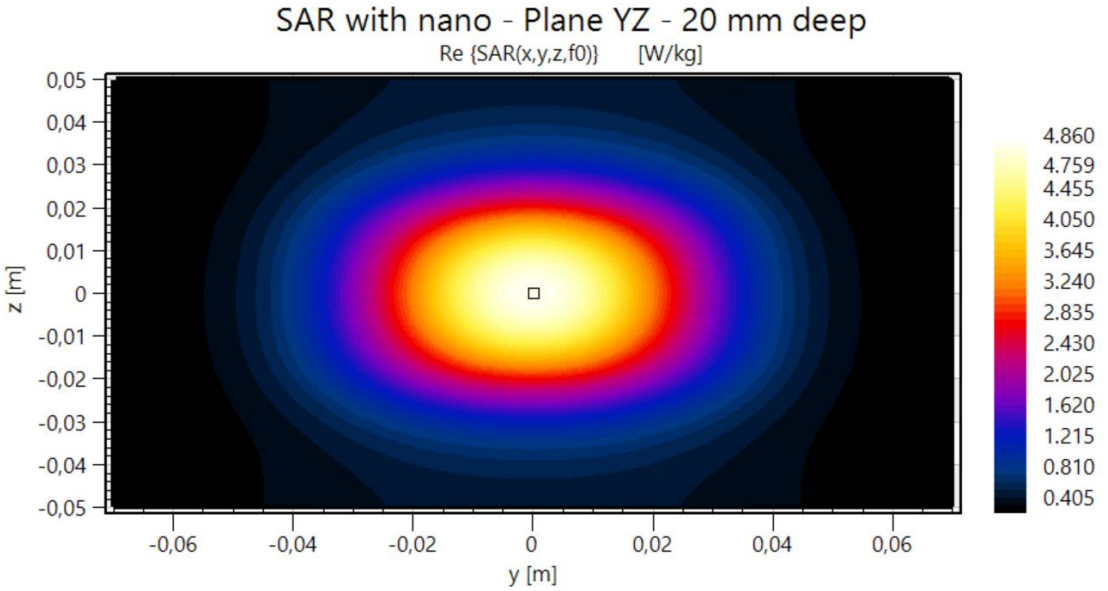
SAR distribution in the X-Z plane with added nanoparticles



As I mentioned before, in the Y-Z plane we are going to measure in different depths, the image we see below is measured at a penetration distance of 5mm:



Same plane to measure the distribution, but at different depths, this time at 20 mm.



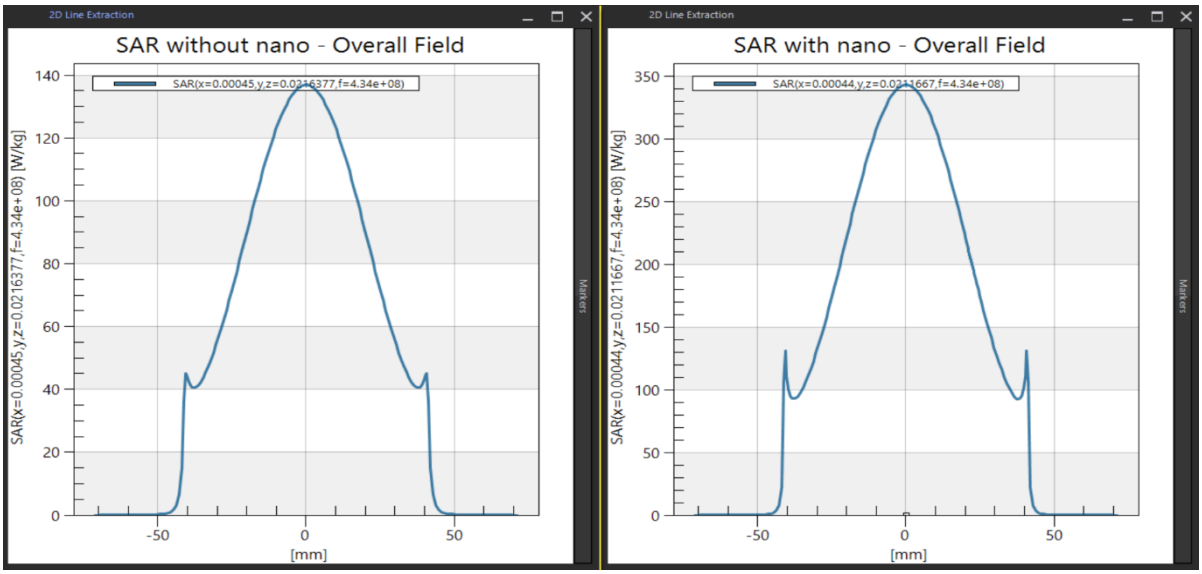
We can see the same difference in the shape and values of the color table represented in the image.

When analyzing the results, in this type of visualization there is not much difference in the shape or colors represented in the images when comparing the same plane with or without nanoparticles. If we look at the numerical colour scale of the legend the difference is more noticeable, in the images captured with the presence of nanoparticles, the depth and focus is greater.
Once I gained more fluency with the Sim4Life program I found a more optimal 2D representation form, in which the results with and without nanoparticles can be seen more clearly.

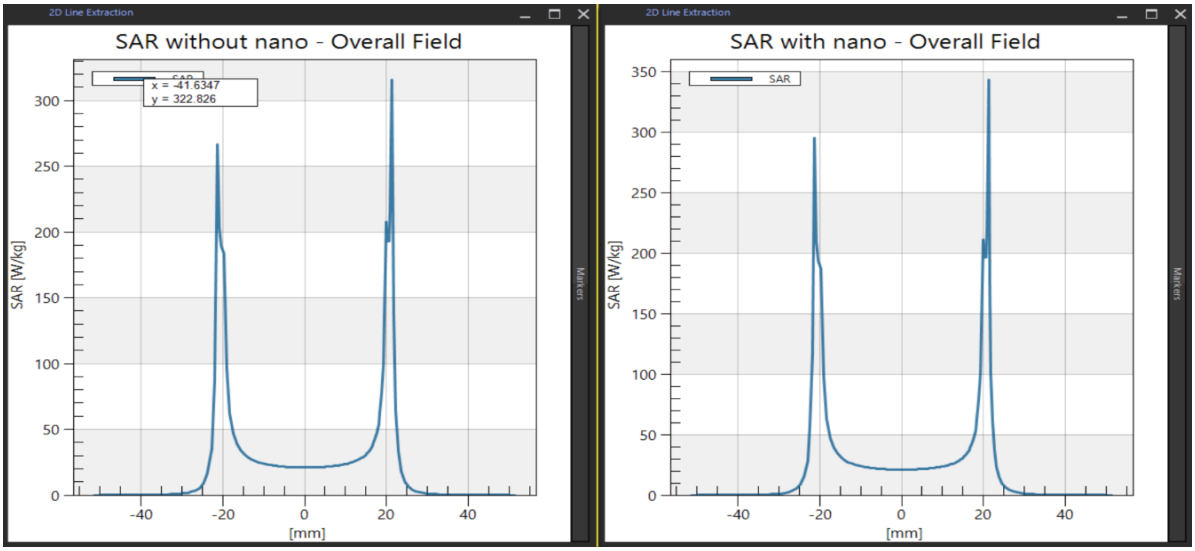
○ COMPARISION WITH/WITHOUT NANOPARTICLES

After several tests with different types of visualizations I have come to the conclusion that the extraction of a 2D line is where the differences are most noticeable. Next, you can see the comparative images, on the left we have the graph extracted from the model without the presence of nanoparticles and on the right with the inclusion of these.

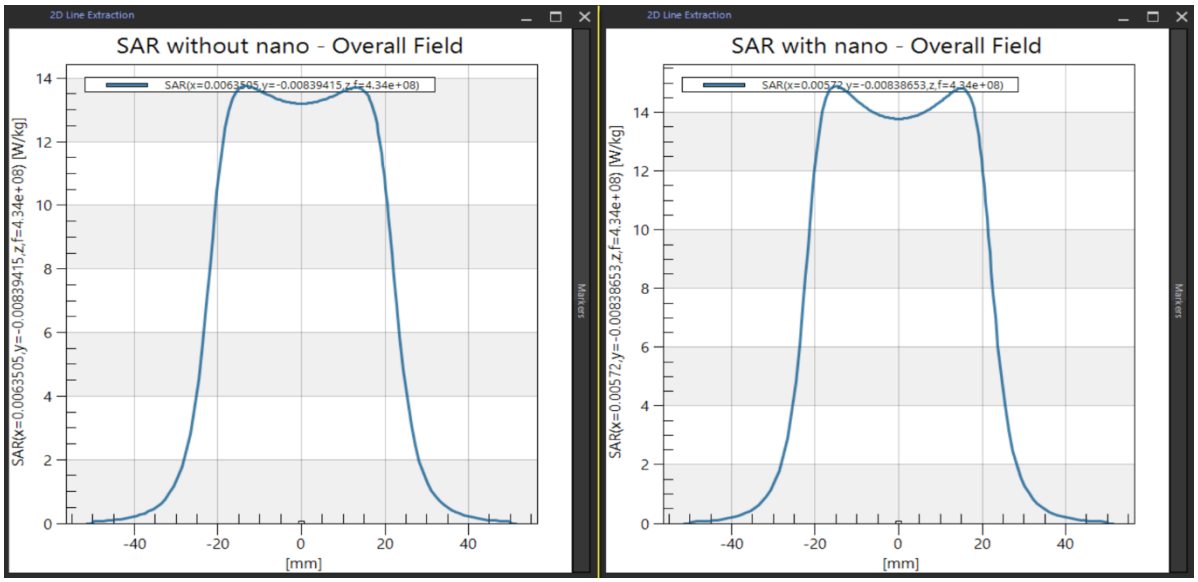
X-Y plane comparison of SAR distribution:



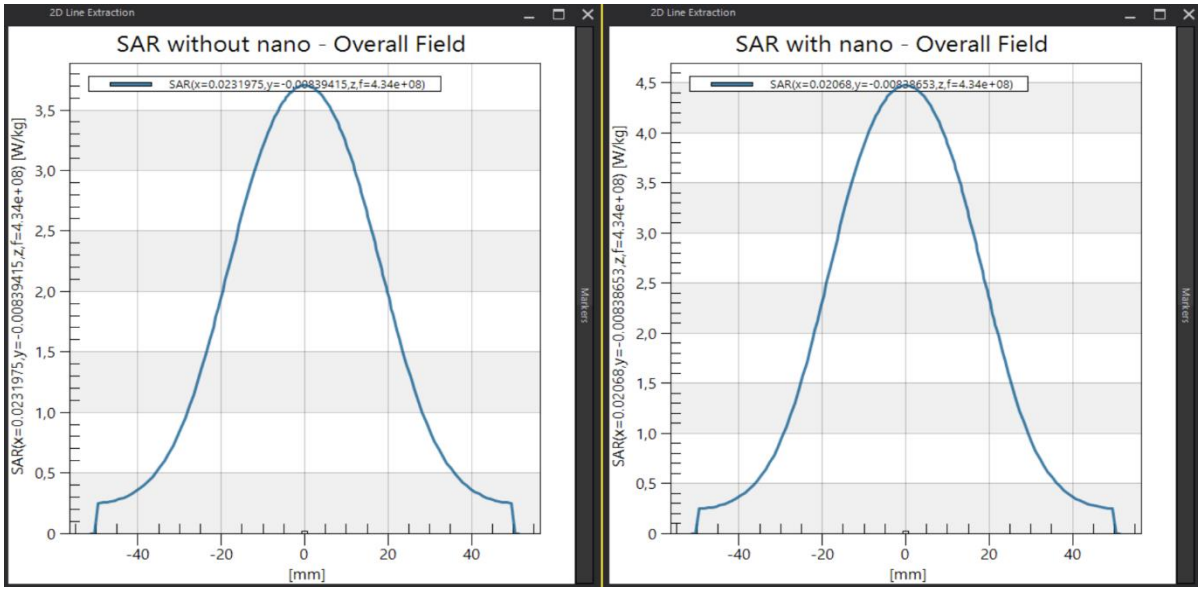
X-Z plane comparison of SAR distribution



Y-Z plane comparison of SAR distribution with a depth of 5 mm:



Y-Z plane comparison of SAR distribution with a depth of 20 mm



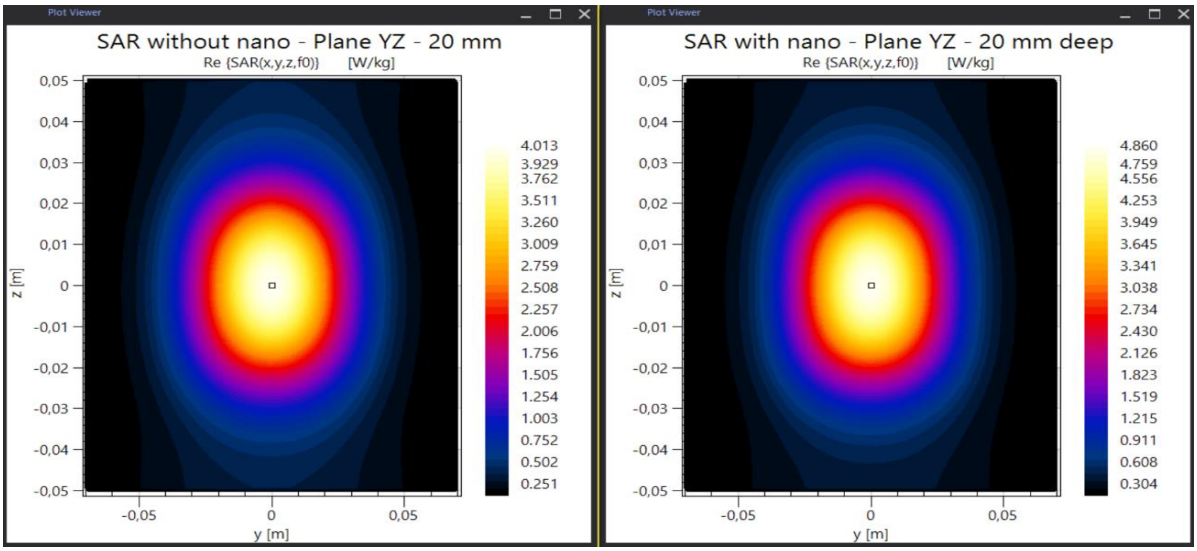


Figure 26: Comparision SAR with/without nano

Analyzing the different representations in a general way, we can see that in all cases with the presence of nanoparticles the field intensity is higher.

In the case of comparison between different depths in the same plane, we have previously concluded that the field strength decreases as the distance from the surface increases. The presence of nanoparticles makes it possible to increase the field intensity and depth; this behaviour is due to the reaction of the composition of which they are created when an electromagnetic field exists.

CHAPTER 5: CREATE A LOCAL MICROWAVE APPLICATOR AND THE AGAR PHANTOM DONATED BY FERROMAGNETIC PARTICLES.

Empirical results of the experiment using agar phantom as a biological tissue

EXPERIMENTAL PART

In order to validate the simulations that I have done with the Sim4Life program, we are going to do almost the same simulation but experimentally. To do this, the settings and configuration must be as precise as possible. The first objective is to perform the phantom (a mixture of agar with water and salt) to simulate human tissue.

As a general rule, the most commonly used material to simulate this tissue is agar. This is a kind of gelatine that solidifies from 32 ˚C to 40 ˚C merging at 85 ˚C, agar is widely used in scientific experiments and has a specific concentration. Normally, the composition contains 96% water, 3.6% power agar and 0.4% salt.

In our case, we have created 3 phantoms made with 2.5 liters of water, 90 grams of powder agar and 10 grams of salt, providing the latter conductivity. This mixture creates the real part of a complex permittivity and the salt increases the conductivity to obtain the closest to the biological tissue. Below, we can see the type of agar used:

Figure 27: Agar phantom characteristics

Figure 28: Agar phantom powder

The result of the composition I mentioned earlier is as follows:

Figure 29: Block agar Phantom I

Figure 30: Block agar Phantom II

The next step was to make a phantom but with a container in which the center was open by a hole with a certain measure to introduce in it the mixture of agar resolution with nanoparticles. This composition has been impossible to carry out due to the situation that has been experienced with this pandemic.

Likewise, with the three phantoms shown above we can start the experiment:

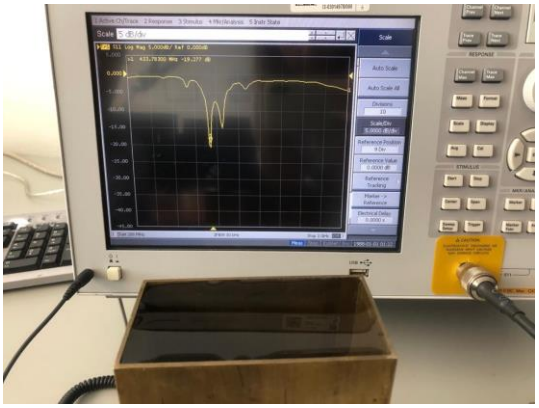


Figure 31: Impedance matching using the network analyzer and wveguide

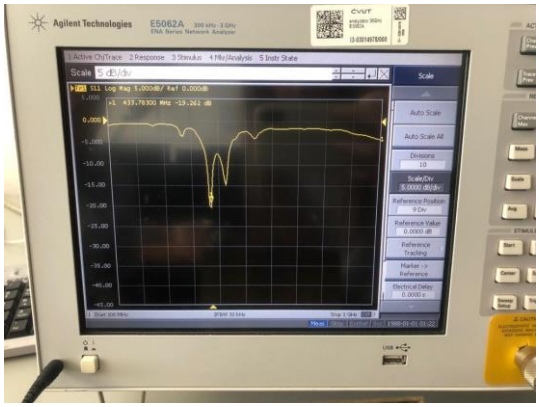


Figure 32: Impedance matching using the network analyzer

The first step to do it is to find the matching of the input impedance for our rectangle waveguide to the desired frequency, in our case at 434 MHz, that is, to measure the parameter S_{11} that I have talked about several times before. To do this in the frame of experiments, we used the microwave vector network analyzer (Agilent Technologies E5062A) that we can see in the image above.

If we put on the aperture of the applicator agar phantom, mimicking the muscel tissue, as shown in the following picture, the measured value of parameter S_{11} in dB is -16,524 dB. As I explained this is an acceptable value since the minimum required is -10 dB or less.

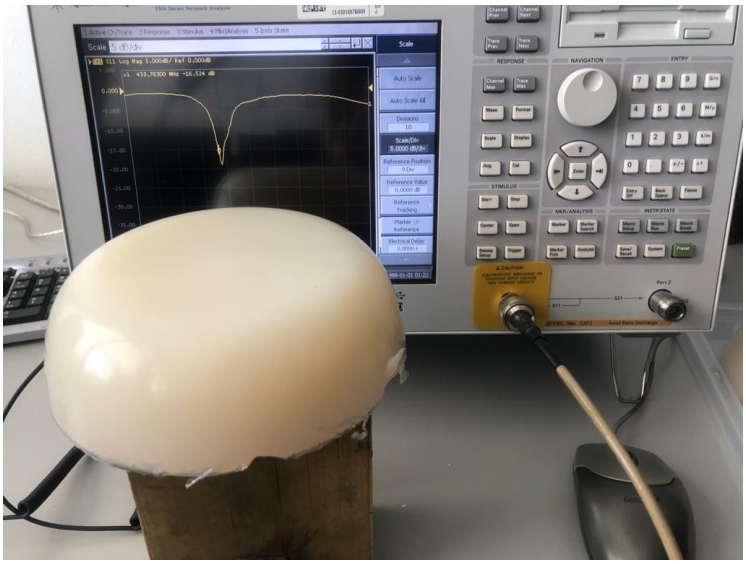


Figure 33: Impedance matching with the agar phantom

The next step is to heat the phantom agar using a power generator, in our case we were going to use the Alba Hypertermia System as the one attached in the image located on the left, due to problems with the adapter we had to replace it and use an older microwave power generator instead, the UHF-POWER-GENERATOR (PG 70 150 2) which we can see in the image located on the right.

Figure 34: Alba Hyperthermia System

Figure 35: UHF-POWER-GENERATOR (PG 70 150 2)

We heated the agar phantom using the power generator for 5 minutes as shown in the following figure. Then, we used the infrared camera (Flir Therma CAM P25) in order to observe the distribution inside the created phantom. To make good measurements (i.e. easily readable thermograms) we should have the optimal environmental conditions (i.e. air-conditioned room with stabilized temperature). In our case the temperature of

the laboratory table (i.e. background for thermograms) was 26 ˚C, i.e. 8 ˚C higher than temperature of the phanroms. To match these temperatures we created a surface with wet cloths for better results.

Below, you can see different photos of thermograms obtained in experiments with 3 different phantoms. The first of them was exposed to a power of 50 W (65 W forward and 15 W reflected), in the second and third case exposed to a power of 40 W (50 W forward and 10 W reflected).

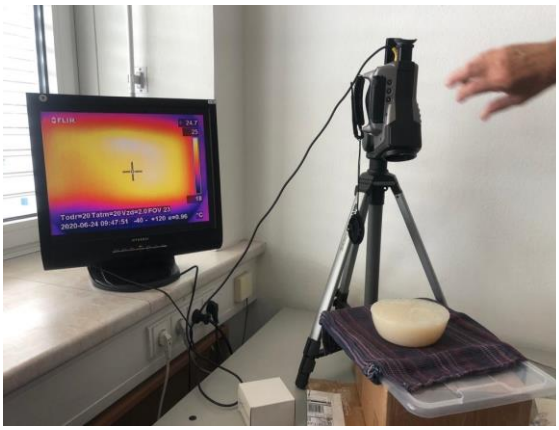


Figure 36: Infrared image of the radiated Phantom I

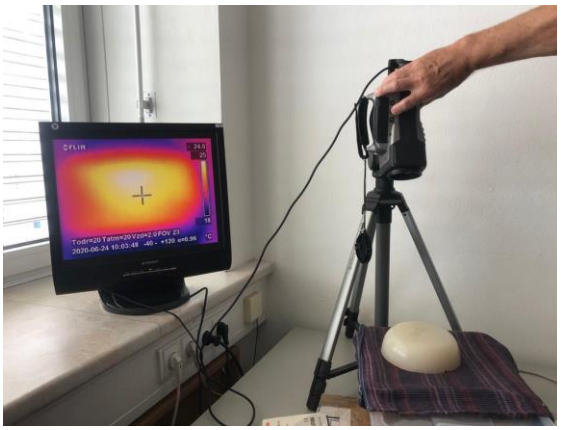


Figure 37: Infrared image of the radiated Phantom II

In order to analyze the temperature profile under the surface of the phantom and with the main purpose of seeing the temperature distribution within the phantom agar, we made a cut in the middle of the composition as shown in the figure on the left. In the other image, it can be seen from the infrared camera that the highest temperature is in the center which very well corresponds to results of simulations, see e.g. picture on page 55.

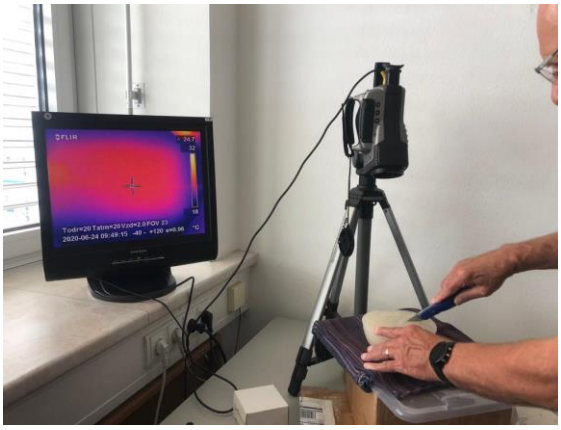


Figure 38: Side cut of agar phantom

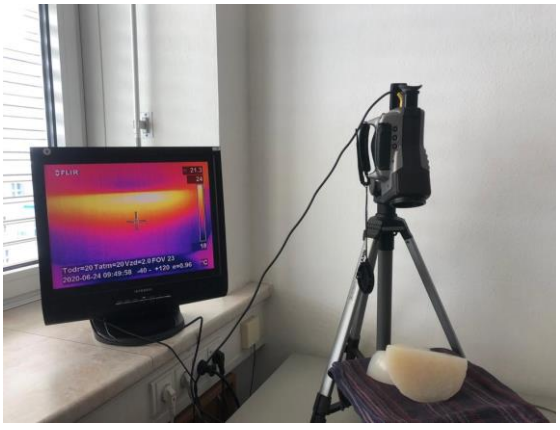


Figure 39: Side cut of agar phantom viewed through infrared camera

CHAPTER 6: CONLUSIONS AND FUTURE LINES

As a conclusion we will analyze the results obtained throughout the project in the simulated and experimental part and we will talk about future lines of hyperthermia treatment.

CONCLUSIONS AND FUTURE LINES

At this point in the project, it is necessary to compile everything that has been analysed and learned during its implementation. We will use this section to do so, as well as to open up a path for continued future study on the treatment of hyperthermia. This will mean an extension of the documentation and improvement following the same line of research.

➢ CONCLUSIONS

As conclusions, in this project we have firstly put hyperthermia into context, what it is, what types of hyperthermia exist, how it is applied, what the objective is and so on. Another important point is to situate the role of ferromagnetic nanoparticles in this treatment. After studying the theoretical function of these particles, we analyze the influence on the properties of human tissues in which electromagnetic fields are applied.

For this, the second objective was to consider and simulate a microwave applicator operating at the frequency of 434 MHz and radiating the microwave power into phantoms with and without nanoparticles. For these simulations, we used the Sim4Life program (EM Field Simulator) and as conclusions we can obtain that injecting this type of particles in human tissues the effectiveness of the hyperthermia treatment is greater, since there is a deeper penetration in the human body and it is more focused, thus allowing to reach more easily areas to be treated, even if they are positioned deeper in the human body.

As a last objective, thanks to the laboratory equipment that my tutor has in the university laboratory, I have made the simulations experimentally. We filled the waveguide with water and placed the phantom agar over the aperture of the waveguide, heated it with a microwave power generator for five minutes and then scan the agar by an infrared camera to see the temperature distribution on the surface. In addition, we made a cut through the middle to be able to analyze the 3D temperature distribution and came to the conclusion that the highest temperatures are located in the middle of the phantom.

➢ FUTURE LINES

Electromagnetism with human tissues has a wide field of study, so research will continue in the field of hyperthermia as it attracts much attention from experts in the field.

Many researchers are still working on the development of this technology with the aim of further improving heating methods and studying the interaction of electromagnetic waves with living beings.

Mainly, the improvements in the application of local hyperthermia have defined guidelines, these are [11] :

- The use of ferromagnetic materials
- The design of applicators to locate the heating zone more precisely
- The creation of medical programs, based on a studied treatment planning for the patient

A possible improvement of the project carried out so far would be e.g. to change the rectangular waveguide for a horn type one, this would focus more and with the insertion of the nanoparticles the results would be more focused and could be analyzed more deeply in the human tissue.

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