

Development and Testing of a New Instrument for Researching on Cancer Treatment Technologies Based on Magnetic Hyperthermia

Oscar García,

Pedro Alou,

Javier Uceda,

Natalia Moreno-Arrones, Andrés Bravo Cuesta, Ana Gutierrez,

, Jesus A. Oliver, José A. Cobos,

Elena Aznar, Ramón Martínez-Mañez, Cristina Sánchez,

Oscar E. Casanova, Jose Javier Serrano, and Francisco del Pozo

Abstract—A power electronics circuit allows the generation of high-frequency magnetic field that can be used to increase the temperature of cancer cells previously invaded with the magnetic nanoparticles. The circuit designed for this purpose is a high-frequency phase-shift inverter implemented with SiC devices and natural zero voltage switching. The inductive load has been optimized to increase as much as possible the magnetic field at the center of it considering the physical restrictions. Into this inductor, an adiabatic probe filled with nanoparticles is placed being the main objective to increase its temperature. The control of the inverter has been designed in such a way that it is easy to try waveforms different from the classical sine waves to see its effect on the temperature of the sample. Although the research is in one of the early stages, the first conclusions about the optimal frequency and field have been obtained showing that this technique could be a real option in the future.

Index Terms—Cancer treatment, magnetic hyperthermia, nanomaterials, PWM Inverter.

I. INTRODUCTION

THERMAL therapies have been used along decades as a mean to help the recovery from several diseases, mainly as a complementary mean to the use of drugs and or mechanical manipulations depending on the specific application [1]. In particular, cancer is a quite well-suited disease to be treated with heat, since cancer cells are more sensitive to heat than healthy ones. In fact, temperature increases over 43 °C for several minutes can seriously damage those cells, which die by apoptotic mechanisms some hours after the treatment, while the rest of the cells survive [2].

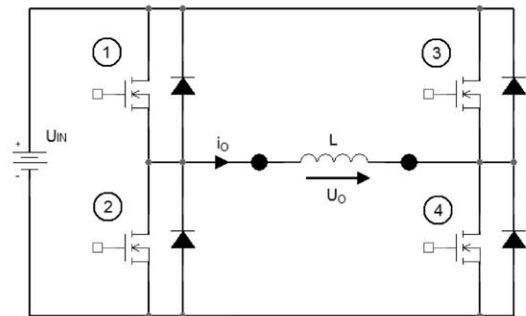


Fig. 1. Power inverter.

Heating is also a well-suited therapy against cancer, since tumors are quite unreceptive to therapeutic molecules for several reasons, and especially in hard-to-access places such as the brain parenchyma [3]. However, using either ultrasounds or different kinds of electromagnetic sources, all conventional techniques suffer from the same drawbacks: 1) not enough spatial resolution; 2) precision in the localization of the volume where to deposit the thermal energy; and 3) the worst, the need for the applied radiation to cross healthy tissues to get to the desired area. These tissues may receive an even larger amount of energy than the targeted ones becoming unnecessary heated as well [4]. Although some efforts are in progress to improve the conventional techniques such as the case of focused ultrasounds, other new ones are being investigated to overcome those limiting performances. They use some intermediate agents previously deployed in place. These agents receive the energy, assuming that it travels throughout the living tissues without affecting them. They convert part of the energy into heat, thus heating their surroundings. This way, each problem is fitted at a different level: spatial resolution and localization is solved by correctly deploying the agents, what is mainly a chemophysiological problem, and the amount of energy and its application is mainly a matter of the energy source.

One of these new techniques is the so-called magnetic hyperthermia [5], [6]. The energy comes from a radio frequency source of some hundreds of kilohertz and consequently, nanoparticles of ferromagnetic materials (some tenths of nanometers) are used as the intermediate

TABLE I
POWER LOSSES ON THE POWER MOSFETs

Device	Manufacturer	Material	Max. Vds (V)	Rdson (mΩ)	Losses (W)
IPA60R125CP	Infineon	Si	600	125	4,25
IPA60R160C6	Infineon	Si	600	160	4,75
STF25NM60ND	ST	Si	600	130	4,33
C2M0080120D	Cree	SiC	1200	98	2,88
CMF10120D	Cree	SiC	1200	200	5,42
TPH3006PS	Transphorm	GaN	600	180	4,83
PGA26A10	Panasonic	GaN	600	150	3,89

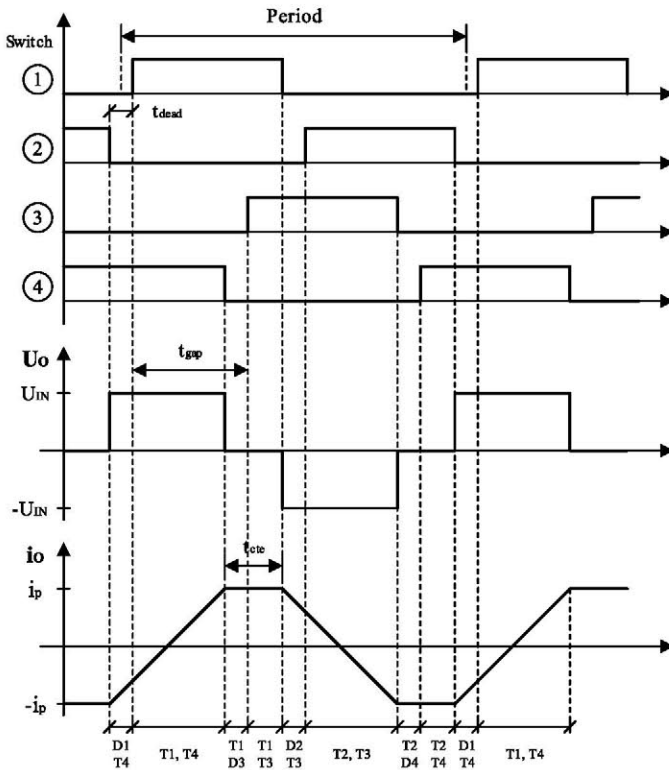


Fig. 2. Gate signals, output voltage, and output current.

agents. Radiofrequency also heats the living tissues due to their conductive character. However, this drawback can be corrected by limiting the power of the source. This inconvenience is largely compensated by the fact that the corresponding wavelength is large enough to bring the energy no matter the place in the body. The particles become magnetized when the radio frequency is present and start vibrating, either their whole body or their inner magnetic momentum, or both. Whatever the mechanism of interaction between particles and radio frequency is, the mechanical energy is transformed into heat.

At this point, one field of research is how to place the particles in place (and what kind of particles) in a safe and effective way, and other is how to excite those particles to maximize the heating. Of course, the goal is to reduce as much as possible the amount of delivered particles and energy, while keeping the therapeutic efficacy. Although both fields are tightly related and the whole approach could be seen as composed of many more faces, there is room to work with some independence in the excitation problem field. At this

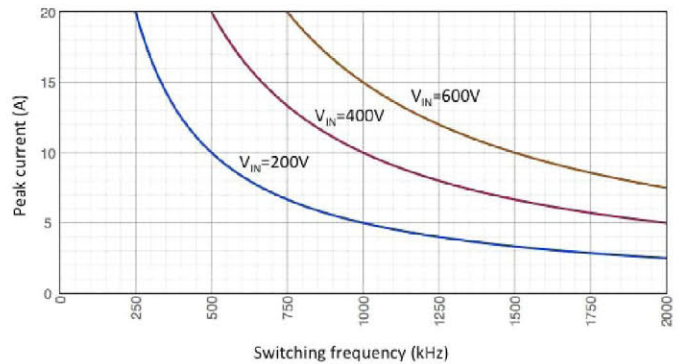


Fig. 3. Maximum peak current as a function of the input voltage and the switching frequency.

point, the state of the art is based on the use of sinusoidal waveforms for the radio frequency emitter, since they are easily obtained at the moderately high power needed from the resonant circuits. Actually, it is not so much a matter of power, as of to heat the particles is rather small, since the amount of particles is not so high. However, the ferromagnetic material when distributed as particles well under a micrometer diameter, to mention a common limit, becomes superparamagnetic. Superparamagnetic materials do not develop remanent magnetic fields and need higher magnetic saturation. The more the magnetization of the particles, the larger the amount of radiated energy converted into heat. Therefore, the issue of the amplitude is of great importance. The resonant circuits have been used as an instrument for this, since they can provide radio frequency power of high amplitude. The amount of power is not high but, in principle, it is not necessary for this purpose.

Few works have been carried on to explore other waveforms, although it has been demonstrated for the ferromagnetic particles that a higher efficiency than the conventional sinusoidal excitation can be achieved [7]. The mechanism converting the radio frequency energy in heat is different in the case of ferromagnetic materials. However, since the size of the particles made of superparamagnetic materials is smaller, they are very useful as intermediate agents in the living tissues for histological reasons.

The question about the use of other waveforms with superparamagnetic particles is open. The interaction of these particles with the liquid environment where they are in suspension is really complex and still rather unknown. However, a previous work, still unpublished, points out to the existence of a dependence of the losses in the particles on the amplitude of the magnetic field different from the

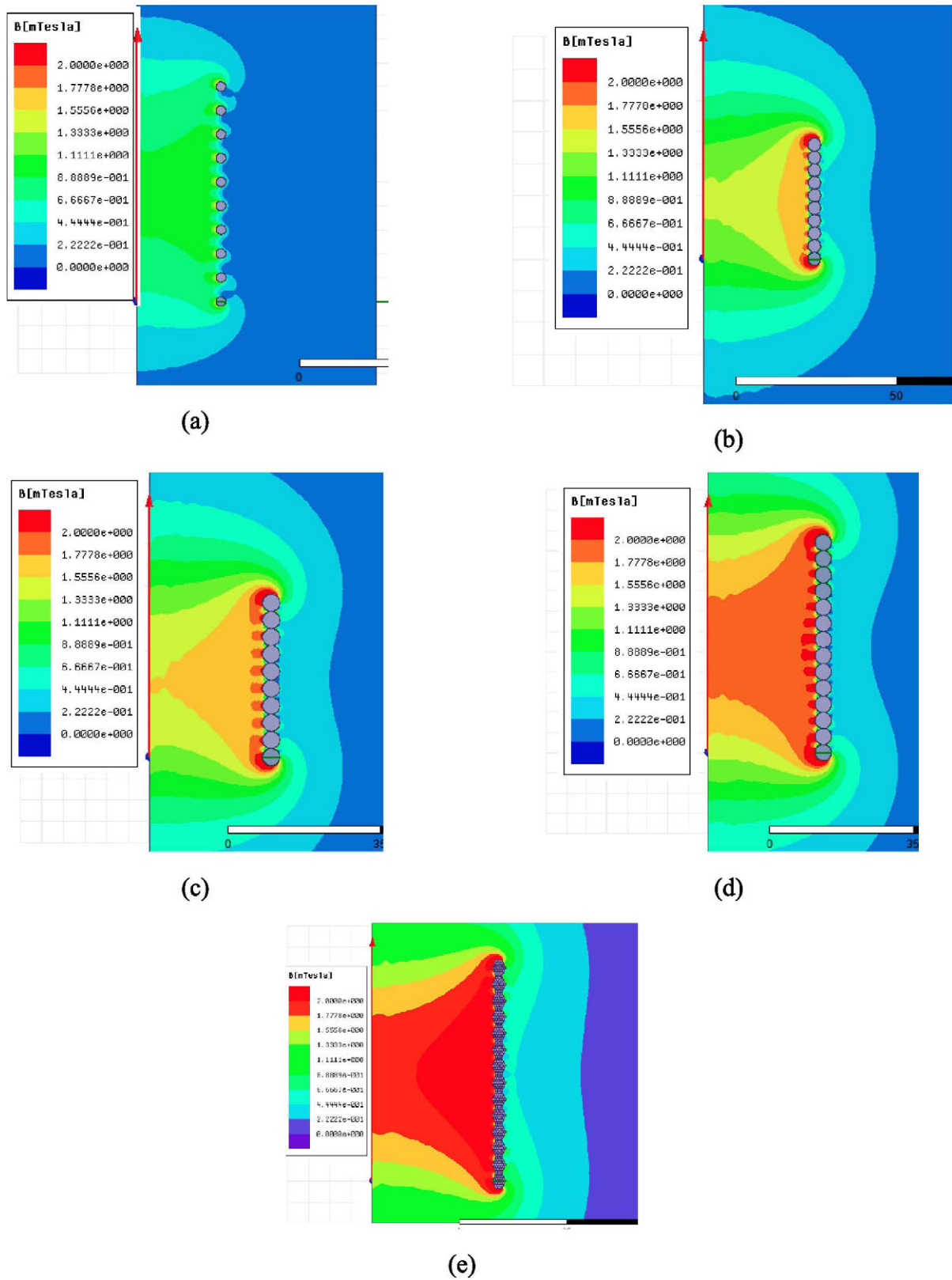


Fig. 4. Flux density simulation obtained from the FEA tool. (a) Original inductor. (b) Design #2. (c) Design #3. (d) Design #4. (e) Design #5.

theoretical one for low fields. At the same time, the stationary movement of the particles, achieved when using harmonic excitation, could tend to reduce the efficacy of the dissipation mechanisms.

To check all these issues in the search for more efficient ways to provide the radio frequency energy for future magnetic hyperthermia-based therapies, we have developed a new instrument that is presented in this paper. Like in other

TABLE II
RESULTS OBTAINED FROM THE SIMULATION WITH THE FEA TOOL

Test	Original	Design #2	Design #3	Design #4	Design #5
Number of turns	10	10	10	14	14
Number of wires x diameter (mm)	1 x 4	1 x 4	1 x 4	1 x 4	30 x 0.55
Radius of the inductor (mm)	35	35	29	29	29
B (mT) at center	0.93	1.35	1.56	1.86	1.95
Rac (mΩ) at 1MHz	60	264	200	339	614

cases [8]–[11], a power electronics circuit helps a lot when it comes to developing a new research for medical purposes. The main contribution of this instrument is that it allows testing with waveforms different from sine waves in an easy way.

The purpose of this paper is to describe this instrument and to perform the first test to investigate the optimal waveform of the magnetic field: the control and power stages of the instrument are explained in Section II. The element that generates the magnetic field is an inductor which is analyzed in Section III. The setup is described in Section IV. Finally, the experimental results and the first practical conclusions about the heating are shown in Section V.

II. POWER INVERTER

The circuit required to generate the alternating magnetic field is a full-bridge inverter (see Fig. 1). Nothing special is required, since a simple phase-shift control is enough to configure the maximum current, the current slope and the switching frequency. From the point of view of the power electronics design, the main challenge is to reduce the power losses when it operates in the megahertz range.

The main specifications of this configurable inverter are as follows:

- 1) *Nominal Switching Frequency*: 800 kHz although it should operate up to 2 MHz;
- 2) *Peak Current*: ± 8 A at 800 kHz but up to 15 A at lower frequencies;
- 3) *Maximum Current Slew Rate*: 50 A/ μ s. This forces to have a small inductor or a high input voltage. Since the inductor will be in the range of 10 μ H, the input voltage should be around 500 V.

Playing with both the input voltage and the phase-shift angle, it is possible to vary the trapezoidal output current (see Fig. 2) to triangular or almost square waveform. The maximum achievable current depends on both input voltage and switching frequency. Assuming that the current is triangular ($t_{cte} = 0$ in Fig. 2) and the inductor is equal to 10 μ H, the maximum peak current is shown in Fig. 3. The converter will work in different operating points to perform experiments with the samples of nanoparticles. In case of using a trapezoidal current, the maximum current will be smaller, since part of the period is used to keep the current constant ($t_{cte} > 0$).

Optimization of the power stage in terms of power losses has been carried out obtaining a circuit that provides the desired current with relatively small losses. Table I shows the power losses analysis on the transistors. Considering the better

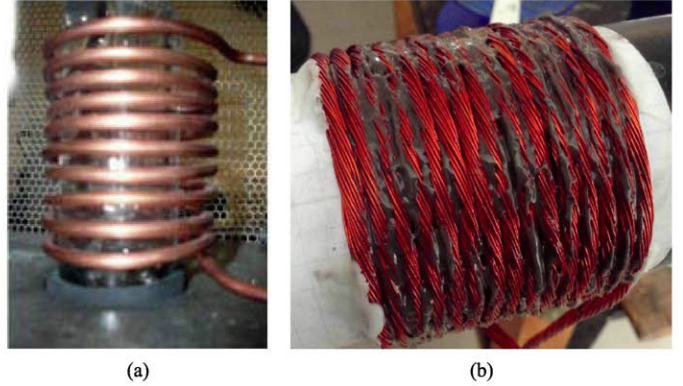


Fig. 5. (a) Picture of the preliminary inductor. (b) Picture of the implemented inductor (design #5).

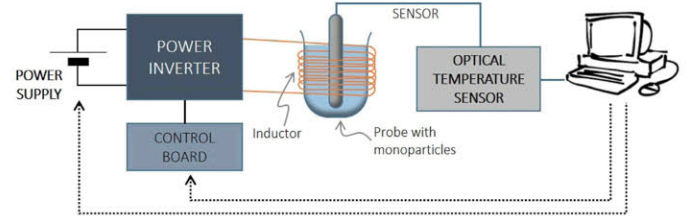


Fig. 6. Experimental setup.

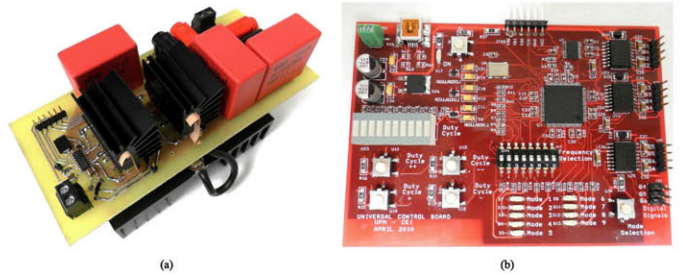


Fig. 7. (a) Power inverter designed for these experiments. (b) Control board of the inverter.

performance in high-frequency switching applications, the best design is obtained using SiC MOSFETs as predicted in [8]. Another advantage of the selected device is reflected in the fact that, if necessary, a higher slew rate could be achieved, since the breakdown voltage is very high (1200 V).

It is important to realize that, since the load is an inductor, it is very easy to achieve zero voltage switching (ZVS) at the turn-ON of the four switches with an appropriate timing of the gate signals [11]–[16]. The dead-time required

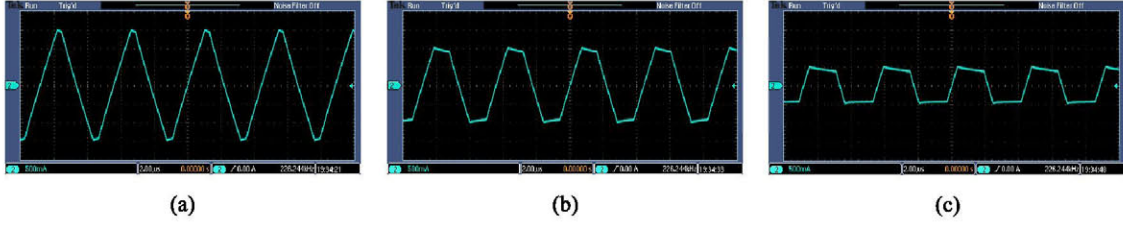


Fig. 8. Capture of the different current shapes. (a) Triangular. (b) Trapezoidal. (c) Almost square.

to achieve ZVS is

$$t_{ZVS} = \frac{2C_{oss} \cdot V_{in}}{I_{L,PEAK}} \quad (1)$$

where C_{oss} is the output capacitance of the power switches. The time required to charge/discharge the parasitic capacitances depends on the inductor current and the input voltage. The selected device has a small output capacitance (80 pF) being possible to obtain ZVS easily. For instance, with an inductor current equal to 8 A and input voltage 400 V, only 16 ns are required to achieve ZVS, which is negligible compared with the switching period.

III. OPTIMIZATION OF THE INDUCTOR

The purpose in this section is to design an inductor with air core that it is able to provide a high electric field in the center of it. It is necessary to remark that the optimization of the inductor is crucial in order to increase the field where the sample is located. Since the objective is to increase the temperature of the nanoparticles, an inductor with big leakages will force to increase the current in the inverter and in the inductor itself to achieve the same field, causing high power losses.

The factors that have been considered for this optimization are: 1) number of turns; 2) wire diameter; 3) radius of the inductor; and 4) separation of the turns. The optimization of the inductor has been carried out using a finite-element analysis (FEA) tool, namely, Maxwell 2-D. This tool has been used in [17] to extract a model of the magnetic component and in [18] to improve the connection of paralleled wires. In this case, the simulation is simpler, since it is a winding with no core and with axisymmetric shape.

The starting point is an inductor that was available from the previous version of the instrument and this inductor was not designed according to high-frequency requirements. It should be considered that there are some physical constrains that limit the degrees of freedom in the design. In particular, the probe with the nanoparticles (explained in the experimental results sections) forces to have a minimum radius of 29 mm.

This inductor was made with 10 turns of 4-mm diameter copper wire. It is 10-cm tall and there is a big separation between turns (~ 1 cm but not homogeneous). With this inductor and with a peak current of 9 A, the flux density in the center is ~ 0.6 mT [this value has been obtained from the FEA simulation and it is shown in Fig. 4(a)]. It is obvious that this inductor has a very high leakage flux due to the separation of the turns and a further optimization is mandatory.

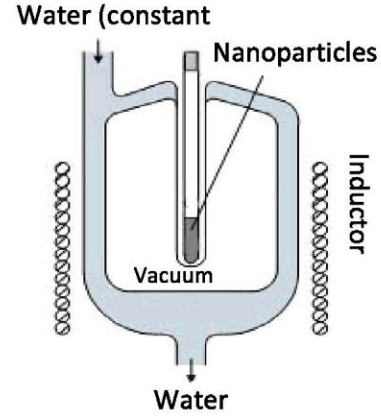


Fig. 9. Description of the probe.

The optimization process has been carried out in several steps as follows:

- 1) reduce the gaps between turns (design #2);
- 2) reduce the radius of the inductor (design #3);
- 3) increase the number of turns (design #4);
- 4) replace single wire by twisted wires (design #5).

Table II shows the main data obtained from these simulations whereas the plots of the flux density for these four cases are shown in Fig. 4.

In design #2, the magnetic field is increased compared with the original design, since there is less leakage; however, proximity effect increases the ac resistance. Design #3 shows a good improvement, since the reduction of the radius increases the flux at the center and reduces the length of the inductor, and thus the resistance. Design #4 has more turns and, therefore, the field is higher; in addition resistance is increased. Finally, the last design shows a slightly higher field but proximity effect is also very high, increasing very much the ac resistance. All these data have been obtained introducing a 800-Hz sine wave with 9-A peak current.

With this last inductor [see Fig. 4(e)], the flux density in the sample is more than three-times higher (1.95 mT) compared with the original and, for this reason, this design has been selected.

Another thing that can be extracted from the simulations is that, the power losses in the inductor increase with every new design. In the last one, the power losses may become very important at high frequency. However, it should be noted that the simulation of design #5 is very sensitive to small changes in distance among wires. The simulation of this design

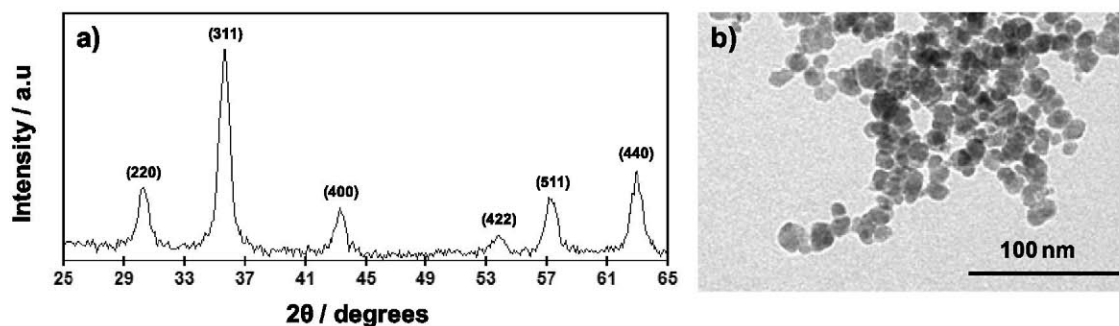


Fig. 10. (a) Powder X-ray diffraction pattern and (b) transmission electron microscopy representative image of synthesized SPION.

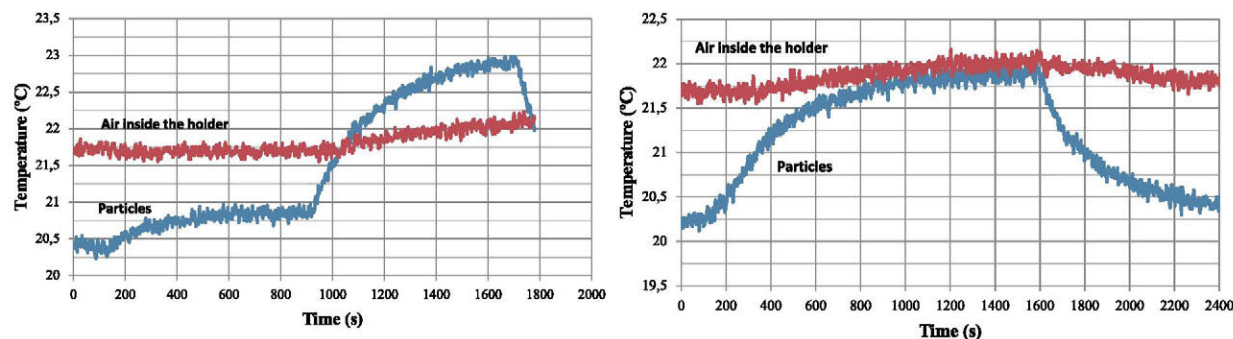


Fig. 11. (a) Experimental temperature increment in test #5. (b) Experimental temperature increment in test #10.

has been repeated including 0.1 mm among wires decreasing the ac resistance to 445 m Ω . Fig. 5 shows picture of the preliminary inductor and design #5.

IV. SETUP DESCRIPTION

Fig. 6 shows a diagram of the instrument and the experimental setup. It has three different parts: 1) power electronics circuit with inductor; 2) probe with nanoparticles; and 3) temperature sensing and recording.

The control board generates the pulses for the power transistors of the inverter. It is based on an FPGA previously configured such that produces different types of pulses. The board contains a simple interface for the user (microswitches, surface mounting devices buttons, and LED indicators) that allows an easy open-loop control of the converter. The inverter is shown in Fig. 7(a) and the control board in Fig. 7(b). The inverter is loaded with an inductor [see Fig. 5(b)]. The measurement of this inductor shows an inductance of 10.7 μ H and the ac resistance of 905 m Ω at 1 MHz.

In this stage of the research, it is possible to operate in an open loop; in a future scenario, it would be necessary to close the loop and be more accurate to obtain a better relation between electric field (i.e., current) and heating. An interface between the PC and the control board is being build now for this purpose [see Fig. 6 (dotted line)].

The parameters that can be controlled with this board are switching frequency, phase delay, and dead-time between transistors. With these parameters and the input voltage of the converter, it is possible to generate different current waveforms on the inductors like the ones in Fig. 8.

The main objective is to design an instrument that generates a configurable magnetic field and to measure its effect on

the temperature of the sample with a particular concentration of nanoparticles. It is very important to assure a very good thermal isolation between the probe and the inductor. For this purpose, the nanoparticles will be in the center of a structure with a vacuum chamber surrounded by a constant temperature water flux. With it, the effects of the power losses on the copper wires of the inductor do not have an impact on the temperature of the nanoparticles. Fig. 9 shows a description of this probe.

Superparamagnetic iron oxide nanoparticles (SPIONs) were synthesized following the method described in [18]. The resulting solid was dried to get a Fe₃O₄ powder. Synthesized SPIONs were characterized by transmission electron microscopy and powder X-ray diffraction. Representative images of the solid show well-defined nanoparticles with an average diameter of 14 nm. Powder X-ray diffraction pattern showed the typical reflections of Fe₃O₄ in the range $25^\circ < 2\theta < 65^\circ$ (see Fig. 10). To perform the hyperthermia experiments, nanoparticles were suspended in an aqueous solution at a concentration of 5 mg/ml.

V. EXPERIMENTAL RESULTS

Several experiments have been carried out to measure the effect of the magnetic field in the sample. Table III summarizes these tests. Experiment #1 is done without nanoparticles, just to confirm that the heat generated in the inductor does not produce any temperature increment in the sample. In the rest of experiments, the sample was made 14 nm Fe₃O₄ nanoparticles.

Fig. 11 shows two experimental data obtained from the tests. The obtained temperature increments could be enough to kill bad cells by inducing localized fever in the patient.

TABLE III
EXPERIMENTS CARRIED OUT USING THE INVERTER AND THE INDUCTOR. THE TEMPERATURE IS MEASURED IN A THERMALLY ISOLATED PROBE WITH NANOPARTICLES LOCATED IN THE CENTER OF THE INDUCTOR

Test	Frequency (kHz)	Shape of field	Voltage (V)	Peak Current (A)	Time (min)	Δ Temperature (°C)
#1	800	Trapezoidal	380	9	40	0 (no nanoparticles)
#2	303	Trapezoidal	195	12	24	1.5
#3	303	Trapezoidal	235	14	10	1.5
#4	510	Trapezoidal	286	10.5	34	1.6
#5	800	Trapezoidal	380	9	35	2.1
#6	800	Trapezoidal	470	11	25	2.1
#7	800	Square	490	6	28	1.3
#8	800	Triangular	205	6	20	2.7
#9	800	Triangular	410	12	13	2.7
#10	1315	Square	500	6	25	1.7
#11	1315	Triangular	370	6	20	2.2
#12	1315	Triangular	500	8.2	10	2.2

TABLE IV
TEMPERATURE INCREMENT COMPARED WITH 800 kHz FREQUENCY USING A VERY HIGH NANOPARTICLE CONCENTRATION

Frequency (kHz)	Temp. increment (°C)
830	+ 1.8
850	+ 4.0
880	+ 1.2
920	+ 0.7

The conclusion that can be extracted is that with this instrument, significant increments of temperature are achieved for nonsinusoidal waveforms, being the first time that this is published. In most of the cases, these tests are useful to see dependence but not to extract the quantitative values. From these first experiments, few preliminary conclusions can be extracted as follows.

- 1) The triangular waveform produces a higher temperature increment than the square. This can be concluded by comparing tests #10 and #12 that have the same input voltage (same slew rate of the current) and frequency. The same conclusion can be obtained comparing tests #7 and #9. In addition, cases #7–#8 and #10–#11 show a small temperature increment for the square waveform with the same frequency and peak current.
- 2) The amplitude of the field (peak current) does not seem crucial in the temperature increment or at least its influence is small. This fact can be checked comparing #2 with #3, #5 with #6, #8 with #9, and #11 with #12.
- 3) The frequency of the field seems dominant against the rest, obtaining a maximum temperature increment at 800 kHz. Since this conclusion about the optimal frequency is very important, an additional test has been done. The described instrument has been used with a much higher concentration of nanoparticles (exceeding by far the previous 5mg/ml) to see better the influence of frequency on the heating. The results are shown in Table IV. Table IV shows increment of temperatures

compared with 800 kHz keeping constant the inductor peak current.

The next steps in this research are as follows:

- 1) to apply the best magnetic field (triangular and 850 kHz) to a sample of nanoparticles with a concentration compatible with the body cells;
- 2) to check the effect of the temperature in a cell culture;
- 3) to obtain percentages of success in killing bad cells.

VI. CONCLUSION

The purpose of this paper is to design a configurable power inverter to induce heating in a sample with nanoparticles, as a first step to improve the magnetic hyperthermia technique. The inverter allows tests with different parameters of the magnetic field such as frequency, intensity, and shape. From the point of view of power electronics, the success is achieved thanks to an optimized design of the full-bridge inverter (ZVS and low losses), and especially to the inductor, that maximizes the field in the position where the sample with nanoparticles is located.

The combination of these three parameters may show the best way to continue the research with this technique. By the moment, temperature increments beyond 2.5 °C have been achieved, being a very promising result, since this is the first time that a nonsinusoidal waveform is used for this purpose. The first sets of experiments have been very useful to identify that the optimal frequency for heating the nanoparticles is ~850 kHz and that the triangular waveform seems better than the rest.

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Oscar García (M'99) was born in Madrid, Spain, in 1968. He received the M.S. and Ph.D. degrees from the Universidad Politécnica de Madrid (UPM), Madrid, in 1992 and 1999, respectively.

He has been involved in more than 80 research projects. He is currently a Full Professor with UPM. He is the Vice Director of Research, Doctoral Studies, and Relations with ETSII-UPM. He has authored over 200 technical papers in conferences and journals and holds eight patents.

Dr. García received the UPM Research and Development Award for faculty less than 35 years in 2003 and the UPM Innovation in Education Award in 2005.



Natalia Moreno-Arrones received the bachelor's degree in industrial engineering from the Universidad Politécnica de Madrid (UPM), Madrid, Spain, in 2014. She is currently working toward the master's degrees in industrial engineering and mechanical engineering or maschinenbau in a double degree program with UPM and the Technische Universität München, Munich, Germany.

During her bachelor's degree, perhaps her most noticeable achievement is having passed her final project with honors.

Andrés Bravo Cuesta received the B.S. degree in industrial technical engineering with a minor in industrial electronics from the Polytechnic University School of Burgos, Burgos, Spain, in 2011, and the M.S. degree in automatics and industrial electronics engineering from the Polytechnic University School of Industrial Engineering, Madrid, Spain, in 2014.

He has authored an article about his work, with reason of its successful and innovative final project conducted with the University of Burgos, Burgos, in 2013.

Ana Gutierrez, photograph and biography not available at the time of publication.



Pedro Alou (M'07) was born in Madrid, Spain, in 1970. He received the M.S. and Ph.D. degrees in electrical engineering from the Universidad Politécnica de Madrid (UPM), Madrid, in 1995 and 2004, respectively.

He has been a Professor with UPM since 1997. He has been involved in power electronics since 1995, participating in more than 40 research and development projects with the industry. His research activity is distributed among industrial, aerospace, and military projects. He has authored or co-authored over 150 technical papers and holds three patents. His current research interests include power supply systems, advanced topologies for efficient energy conversion, modeling of power converters, advanced control techniques for high dynamic response, energy management, and new semiconductor technologies for power electronics.



Jesus A. Oliver, received the master's and Ph.D. degrees in electrical engineering from the Technical University of Madrid (UPM), Madrid, Spain, in 1996 and 2007, respectively.

He became an Assistant Professor in 2001 and an Associate Professor at UPM since 2007. He has been author and co-author in more than 150 scientific papers on journals and conferences and he holds three patents. His research activities include modelling (dc–dc converters, magnetic components, piezoelectric transformers, fuel-cells, and dc distributed power electronic systems), fast control techniques for dc–dc converters for VRM applications and RF amplifiers, three-phase rectifiers for aircraft applications, wireless power transfer, and power systems on chip.

Dr. Oliver has led numerous research projects with private and public funding and he has participated in more than 50 direct R&D projects with companies in Europe, U.S., Australia, and China. He currently serves as an Associate Editor of the *IEEE TRANSACTIONS ON POWER ELECTRONICS*.



José A. Cobos (SM'12) advised 14 Ph.D. dissertations. He has been a Professor with the Universidad Politécnica de Madrid (UPM), Madrid, Spain, since 2001. His contributions are focused on the field of power supply systems for telecom, aerospace, industrial, automotive, and medical applications. He is currently the Director of the Centro de Electrónica Industrial with UPM, a university research center, leading a strong industrial program in power electronics, with technology transfer through direct research and development contracts with more than

20 different companies in Europe, U.S., Australia, and China. He has authored over 200 technical papers and holds six patents. His current research interests include energy efficiency in digital circuits and RF amplifiers, magnetic components, piezoelectric transformers, transcutaneous energy transfer, and dynamic power management.

Dr. Cobos received the UPM Research and Development Award for faculty less than 35 years of age and the Richard Bass Outstanding Young Power Electronics Award of the IEEE in 2000. He received the Semikron Innovation Award for the teamwork on RF Power Amplifier with Increased Efficiency and Bandwidth. He has received one of the ten Google Little Box Challenge awards, to develop the smallest possible inverter, for PV panels and high-density batteries. He has been cooperating with the IEEE and other professional associations (Reviewer, Session Chair, Topic Chair, and Associate Editor). Since 2003, he has served as an Associate Editor (AE) of the *TRANSACTIONS ON POWER ELECTRONICS*. From 2002 to 2005, he served as an AE of the *IEEE POWER ELECTRONICS LETTERS*. He is an AdCom Member of the IEEE Power Electronics Society and a member of the Steering Committee of the IEEE Applied Power Electronics Conference.



Javier Uceda (F'04) received the M.Sc. and Ph.D. degrees in electrical engineering from the Universidad Politécnica de Madrid (UPM), Madrid, Spain, in 1976 and 1979, respectively.

He was appointed as the Vice President for Research and Institutional Relations with UPM in 2000, where he was the President from 2004 to 2012. His research activity has been developed in the field of power electronics, where he has participated in numerous national and international research projects. He is currently a

Full Professor of Electronics with the Electrical and Electronic Engineering Department, UPM. He is an Honorary Doctor with the Universidad Ricardo Palma, Lima, Peru, and the Colegio de Posgraduados, Texcoco, Mexico. He is the General Coordinator of the UPM City of the Future Initiative. His main contributions are in the field of switched-mode power supplies and dc/dc power converters for telecom and aerospace applications. As a result of this activity, he has authored over 250 papers in international journals and conferences and holds several national and international patents.

Dr. Uceda has received several individual and collective awards like the IEEE Third Millennium Medal, the Great Cross to the Military Merit, and the Puig Adán Medal. He has been a member of the Editorial Board of the *European Power Electronics and Drives Journal* and an Associate Editor of the *IEEE TRANSACTIONS ON INDUSTRIAL ELECTRONICS*. He is also a Senior Member of the Administrative Committee of the IEEE Industrial Electronics Society, where he was the Vice President of Technical Activities in 1991. He belongs to the Executive Council of the European Power Electronics and Drives Association, where he was the Vice President. He is a member of the Scientific Advisory Board of the Centre for Power Electronics Systems in USA.



Elena Aznar was born in Valencia, Spain. She received the Ph.D. degree from the Polytechnic University of Valencia, Valencia, in 2011, with a focus on the development of smart materials for advanced controlled release applications with Prof. R. Martínez-Mañez.

She joined Prof. R. Martínez-Mañez's Group, Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, Zaragoza, Spain, as a Post-Doctoral Researcher, where she has been a Permanent Researcher since 2012.

Her current research interests include the design of nanomaterials for advanced applications, such as new nanotherapies and sensing in the biomedical field.



Ramón Martínez-Mañez was born in Valencia, Spain. He received the Ph.D. degree in chemistry from the University of Valencia, Valencia, in 1986.

He was a Post-Doctoral Fellow with Cambridge University, Cambridge, U.K. He is currently a Full Professor with the Department of Chemistry, Universidad Politécnica de Valencia, Valencia, and the Director of the IDM Research Institute. He is a Scientific Director of the Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, Zaragoza, Spain. He has co-authored over 315 research publications and holds nine patents. His current research interests include the design of hybrid materials for biomedical applications, such as sensing, controlled drug delivery, and hyperthermia.



Cristina Sánchez received the M.Eng. degree in telecommunication engineering, the M.Sc. degree in telemedicine and bioengineering, and the Ph.D. degree in biomedical engineering from the Universidad Politécnica de Madrid, Madrid, Spain, in 2009, 2010, and 2013, respectively. She is currently pursuing the Biomedical Engineering degree with the Universidad San Pablo-CEU, Madrid.

She is currently an Associate Professor with the Universidad San Pablo-CEU. Her investigation results have been presented in national and international congresses and have led to several articles in indexed journals. Her current research interests include bioinstrumentation, biosensors, and nanomedicine applications.



Oscar E. Casanova is currently working toward the Ph.D. degree in biomedical engineering with the Universidad Politécnica de Madrid (UPM), Madrid, Spain.

He was an Electronic Engineer and a Teacher and Researcher with the University of Tachira, San Cristóbal, Venezuela, in 2006, where he was involved in the areas of biomedical instrumentation and biomedical digital signal processing from 2008 to 2013. He was a Researcher with the Group of Bioengineering and Applied Biophysics, University Simon Bolívar, Caracas, Venezuela, from 2006 to 2008. He is a Researcher with the Center for Biomedical Technology, UPM. His current research interests include nanomedicine as an alternative therapy for cancer treatment.



Jose Javier Serrano received the Ph.D. degree in telecommunication engineering from the Engineering School on Telecommunication, Universidad Politécnica de Madrid (UPM), Madrid, Spain, in 1996.

He has been involved in several research fields, including superconductor materials characterization and sensor networking. He currently teaches on bioinstrumentation and biosensors with UPM. He is the Head of the Laboratory of Bioinstrumentation and Nanomedicine with the Center for Biomedical Technology, UPM, where he is also the Deputy Director. His current research interests include the application of nanotechnologies to the development of new technologies to help new therapies against cancer.

Francisco del Pozo, photograph and biography not available at the time of publication.