EUROPEAN COOPERATION
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COST Office
Avenue Louise 149
1050 Brussels, Belgium
t: +32 (0)2 533 3800
f: +32 (0)2 533 3890
office@cost.eu

www.cost.eu

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Subject | Core expertise and draft working strategy

COST Action TD1402 - Multifunctional Nanoparticles for Magnetic Hyperthermia and Indirect Radiation Therapy (RADIOMAG)

Working Group 2 - Physical aspects of hyperthermia: standardisation and testing

by Daniel Ortega

PART I - Draft working strategy

Background

According to the description and objectives set for this working group in the action strategy and roadmap document, there are certain priority issues to be addressed regarding the physics behind magnetic hyperthermia. This document is a brief description of the main issues, which are based on excerpts from the original RADIOMAG proposal. The first three ones can be encompassed under the milestone *establishing a standard procedure for estimating the thermal/radiation dose safety standards, and the investigation of particle-particle and particle- tissue interactions*. Of course, the balance between theoretical and experimental work varies for each objective. For example, developing a more comprehensive theory of magnetic hyperthermia mainly entails improving the existing theoretical models of heat transfer at the nanoscale, even though this also demands validating the candidate models through data gathered from purpose designed experiments. Only by addressing all these points will it be possible to design combination therapies (radiation + hyperthermia) that start from a more solid physical foundation (Fig. 1).

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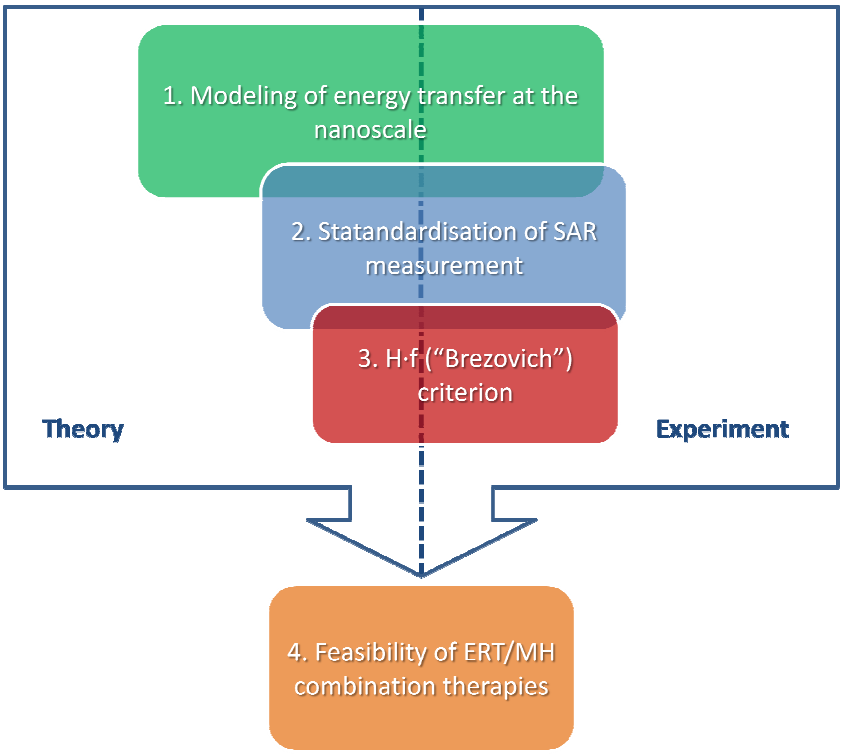

Fig. 1 Scheme representing the overall WG2 working strategy, with indication of the main challenges. ERT stands for external radiation therapies.

1. Modelling energy transfer

The magnetic-thermal energy transfer process upon which magnetic hyperthermia is based may be considered at three different levels.

Single particle & single cell heating. Most of the studies done about how heat is generated and dissipated by a single nanoparticle—in other words, nanoscale heating effects—have used a theoretical approach. A good example is the paper by Rabin (Y. Rabin, *International Journal of Hyperthermia* 18 (2002) 194) about intracellular/extracellular hyperthermia or whether or not a single cell can be effectively heated. At present, nanoscale heating is yet to be accurately measured, and in this sense, there is a long way ahead. Innovative experimental approaches, like the decomposition of thermal-sensitive molecular probes attached to the surface of nanoparticles, have been devised and tested, but our knowledge of the physical phenomena behind nanoscale heating is rather limited. Advances in this field will definitely help in explaining unexpected experimental observations like "cold" hyperthermia, i.e. induced cell death upon AC field exposure without an apparent temperature rise.

Many-particle heating. The heat released by a system of magnetic nanoparticles depends not only on their intrinsic properties, but also on the interaction between individual particles. The latter is an important issue intimately related to the efficiency of magnetic hyperthermia agents that has not been properly addressed in the past years. In a fluid containing superparamagnetic nanoparticles (i.e., no magnetic hysteresis), the collective behaviour is different from that of isolated particles when a magnetic field is applied. For larger particles, near the superparamagnetic/stable single domain size threshold, dipolar interactions between nanoparticles are even stronger and play a role in the relaxation process. The

degree of dipolar interaction depends also on the coating thickness which that separates the individual particles. A better knowledge about magnetic particle interactions in living tissue is of importance for a better understanding and determination of the intrinsic loss parameter (ILP) *in vivo* and for modelling the transfer of heat inside tumours.

Bio-heating. In order to optimise a magnetic hyperthermia treatment in vivo, it is necessary to predict the expected temperature distribution in and around the tumour as a function of the intensity and application time of the external magnetic field. In addition, the cooling effect of blood circulation has to be also taken into account. These predictions are usually done by mathematical modelling, and more specifically, by solving the *bio-heat transfer equation*. Currently, macroscopic heat transfer analysis is used to assess the energy distribution in and around a tumour. This theoretical concept is not the best for treatment planning, because there seems to be no advantage to deliver heat using nanoparticles. Instead, recent experimental data have shown that nanoscale thermal effects exist due to energy dissipation when nanoparticles are exposed to alternating fields. On such nanoscale, the existing macroscopic heat transfer analysis is no more appropriate for modelling temperature rises, which explains contradictions between experimental and model data according to investigations of several research groups.

2. Standardisation of SAR measurement

This is a shared objective with WG4 to a good extent. Its purpose is to bring together theoretical and experimental scientists in order to work out a common standard protocol for determining the energy absorbed in biological tissues, being supported by a new theoretical concept taking into account nanoscale thermal effects. Our motivation for this objective stems from:

- differences in experimental equipment and measurement procedures that are used in distinct universities and research centres across the world;
- the need for an agreement about standard procedures for experimental validation of the heat distribution in tumours, which is required for the advancement of magnetic hyperthermia as an anti-cancer treatment, by taking into account the strong dependence on the type of tumour, the location of the xenograft, and scaling small animal tumour models to human cancer treatment;
- different perceptions of the concept of electromagnetic energy absorption by living organisms used in magnetic hyperthermia by individual research groups.

A common standardisation in procedures of parameter definition and experimental practice will allow for a better comparison of the heating performance of ferrofluids developed, based on the same criteria of evaluation on a European level. It will also help in furthering advancement in magnetic hyperthermia as a cancer treatment, and accelerating clinical transfer of results.

3. Safety/tolerance levels or the "Brezovich" criterion

Another example underlining the demand for discussions and exchange concerns the upper limits of magnetic field intensity and frequency range. These values have to be consistent with the EU directive (2013/35/EU) on the minimum health and safety requirements regarding the risks upon exposure of workers to electromagnetic fields. For example, current pre-clinical experiments use a ten times higher field intensity × frequency product (per unit area exposed) than that suggested by the EU directive. There is neither a common agreement on safety limits of magnetic hyperthermia nor it is clear which way is best to quantify MH induced cytotoxicity. A first step towards common exposure criteria is revisiting the experimental evidences so far and planning further assays in the light of the current knowledge in the area.
An example of the problem in the determination of safety/tolerance levels is illustrated in the following. One of the very few clinical tolerance tests performed to date is that reported by Atkinson et al using a single-turn induction coil placed around the thorax of healthy volunteers. The outcomes showed that field intensities up to 35.8 A·turns/m at a frequency of 13.56 MHz could be thermally tolerated for extended periods of time. These data have been progressively transformed into the so-called "Brezovich criterion",

which states that the field intensity-frequency product should not exceed the value 4.85 $\times$ 10^8 A m^{-1} s^{-1} for a 30 cm coil. The main problem with this definition lies within the experimental conditions under which this alleged limit was measured, which do not meet the envisaged clinical scenario for magnetic hyperthermia. For example, as an eminently local technique, the current practice usually implies smaller coils with different field geometries. Another point of discussion is that the study is based on the subjective perception of discomfort of the participants. Consequently, moving forward from the present knowledge about the safety/toxicological aspects of magnetic hyperthermia implies redesigning and re-measuring the tolerance to the treatment in a more accurate way, adapted to the current practice of the technique.

4. Feasibility of external radiation therapies (ERT)-magnetic hyperthermia combination therapies

The synergetic effect of ionising radiation and hyperthermia in killing cancer cells is well known since cancer cells resistant to radiation but sensitive to hyperthermic conditions were discovered. Notwithstanding, thermo- and irradiation sensitivity of cancer cell types depends on the stage of cancer growth. Combining both therapy concepts, one expects an increased efficiency of the radiation treatment by prior application of moderate MH. It may also be possible to decrease the delivered radiation dose or to enhance the radiation effect on cellular hypoxia by increasing the local energy deposition related to the interaction between the radiation beam and magnetic nanoparticles. The radiosensitiser effect of nanoparticles related to the enhancement of the photon absorption, which is proportional to the cubic electron density (Z) was previously proposed for gold and gadolinium oxide. Despite the lower Z value of the iron and iron oxide, it is argued that this effect will also enhance the cell damaging power of the ERT in tumour cells, thus improving the survival rate of cancer patients with poor prognosis.

5. Conclusions and future directions

The above-defined objectives are only four of a multitude of other research topics that could be covered by our working group. We will concentrate first on these objectives, which were originally proposed for our action, before considering further directions. Our initial step was to "classify" the broad range of expertise available in WG2. To this aim, we asked every participant (i.e., institutions/groups, not individuals) to choose a specific objective/s on which to concentrate efforts, exploiting their expertise and/or instrumental capacities more efficiently. A succinct description of each objective and a tentative list of tasks is included in Table 1, which was distributed among participants to help them in making a sensible choice. Along with other details, the results from this survey and the main conclusions are described in the next part of this report.

Table 1 Proposed objectives for the tentative working strategy of WG2.

Objective	Tentative tasks	Observations
1	• Hysteresis loop modelling (hysteretic losses). Experiment design to validate proposed models • Modelling spatial heat distribution at the nanoscale. Experiment design for measuring heat dissipation at the nanoscale (improvement) • Establishing a protocol for characterising static and dynamic magnetic properties of nanoparticles through DC & AC magnetometry measurements. Comparison with theoretical models	Requires collaboration with WG4 to gather experimental data from standard samples (already started in the past Lisbon meeting)
2,3	• Survey/revision of the existing energy absorption parameters: amendments and/or	Requires collaboration with WG1 for sample selection and WG4 for

	proposition of new ones • Data analysis and interpretation from calorimetry measurements • Establishing a protocol for characterising static and dynamic magnetic properties of nanoparticles through DC & AC magnetometry measurements. Comparison with theoretical models	experiment/instrument design and gathering experimental data from standard samples
1	• Simulation of temperature distribution in cells and tissues (bio-heat equation) • Experiment design (field application & thermometry) for clinical MH sessions in humans. Data processing and interpretation	Requires collaboration with WGs 3 & 4 for experiment design and data processing
4	• Simulation of the penetration depth of radiation in cells and tissues from either independent radioactive sources or combined with magnetic nanoparticles • Experiment design for conducting combined ERT & MH treatments in humans. Suitability of simultaneous sessions	Requires collaboration with all the WGs 3 & 4 for experiment/instrument design and analysis of experimental data

For convenience, the objectives above will be referenced in the foregoing by using a short, representative expression, namely:

— **Objective 1**: *modelling & characterisation*
— **Objective 2**: *standardisation*
— **Objective 3**: *in vivo MH*
— **Objective 4**: *radiation & combination therapy*

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PART II - CORE EXPERTISE OF THE WORKING GROUP

6. Geographical spread and basic figures

The WG2 research group members come from 15 different countries, and the majority of them are located at western Europe (Fig. 2).[1] Denmark, Belgium, Spain and UK are the countries with the highest presence. At the time of writing, there are additional groups from eastern countries in the process of joining the action, like Belarus or Ukraine. An international partner from the United States (leaded by Jon Dobson at University of Florida) acts as observer to our group/action. Out of a total **46** researchers, there are **35** holding a primary affiliation to WG2 (see Annex II), whereas the rest holds a secondary affiliation.

Other basic figures of WG2 as of 15th of March 2016:

- Number of early stage researchers: **6**
- Number of researchers coming from SMEs/industry: **5**
- Number of researchers coming from inclusiveness target countries (ITCs)[2]: **10**

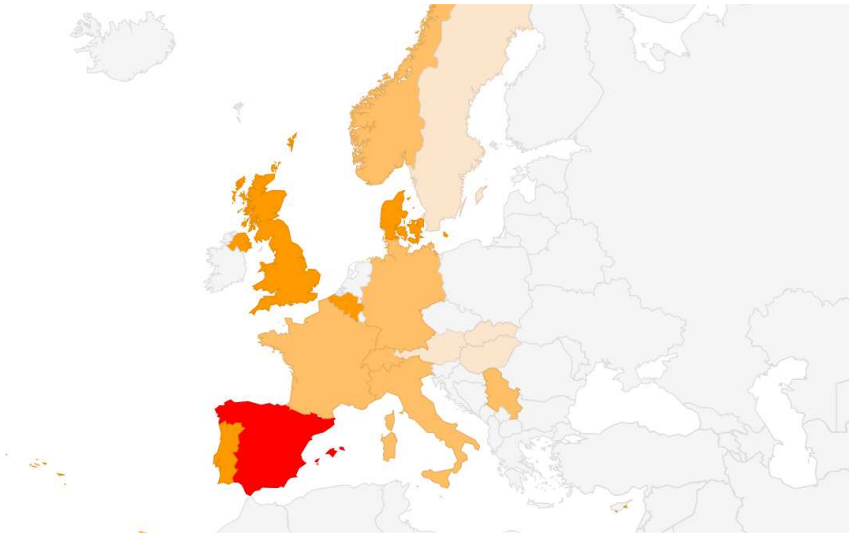

Fig. 2 Geographical distribution of the participant countries in WG2. To build this map, only those participants with primary affiliation to WG2 have been considered. Legend: the stronger the colour intensity the higher the participation of the member country.

[1] *It has to be borne in* mind *that in this version of the report there are still groups - from Switzerland, Hungary, Slovakia - that have not completed the survey.*

[2] *Bosnia-Herzegovina, Bulgaria, Cyprus, Czech Republic, Estonia, Croatia, Hungary, Lithuania, Latvia, Luxembourg, Malta, Montenegro, Poland, Portugal, Romania, Slovenia, Slovakia, the former Yugoslav Republic of Macedonia, Republic of Serbia and Turkey. Visit www.cost.eu for more information.*

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7. Type of research

The roadmap for WG2 includes a set of objectives requiring different scientific approaches (heat transfer models, formulation of new physical parameters, physical characterisation of samples, etc.) and therefore researchers with different expertise. In terms of the type of research carried out by WG2 members, only 30.8% develops theoretical models or makes use of these models to theoretically predict physical properties or behaviours in sub-areas of magnetism and radiation physics relevant to magnetic hyperthermia. Only 3.8% of these groups focus categorises their research activities as purely theoretical (Fig. 3). On the other hand, the majority of the members (65.4%) define their work as experimental.

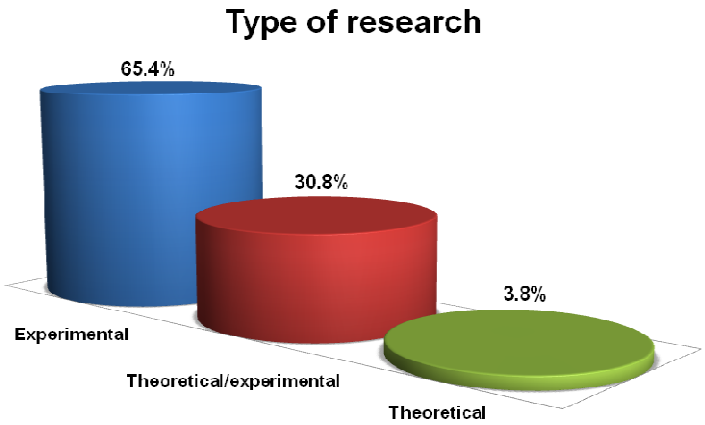


Fig. 3 Type of research conducted by the members of WG2.

8. Available equipment

One of the added values of networking originally proposed for this particular COST action concerns with "*a more efficient exploitation of human and instrumental research resources available, shortening experimentation times and making possible the realisation of complex/coordinated experiments otherwise impossible to carry out*". In this spirit, the available equipment throughout WG2 has been surveyed[3] to make easier the interaction between members when it comes to the establishment of research collaborations, preparation of short-term scientific missions (STSMs), or even identification of potential partners for the submission of project proposals to either national or trans-national schemes. The techniques here featured mostly concerns with magnetic characterisation - with particular emphasis on the quantification of magnetic heating in nanoparticles - but many other dealing with structural characterisation and measurement of other physical properties are also included.

Table 2 Instrumentation available at each of the participants premises in WG2. See page 13 for a list of abbreviations use in this table.

Representative/s of the group/unit	Available techniques/instrumentation
Vladan Kusigerski	SQUID magnetometry (Quantum Design MPMS system, DC and AC measurements) Complete nB (Nanoscale Biomagnetics) hyperthermia setup DM100 (all three applicators: ferrofluids, in vitro and in vivo experiments) Mossbauer spectroscopy

[3] *See the survey in Annex I (page 14).*

	Gamma counter
Francisco J. Terán/Daniel Ortega	DLS, micro-Raman, NMR, nanoparticle (chemical) synthesis Singular equipment: Calorimetric set up for measuring SAR values of colloids dispersed in aqueous media under AC magnetic fields in a frequency range up to 500 kHz and field intensities up to 90 mT AC inductive magnetometer for measuring hysteresis loops of colloids dispersed in aqueous media under AC magnetic fields (up to 300 kHz and 40 mT) AC magneto-optical magnetometer for measuring the evolution of hysteresis loops of colloids dispersed in water media under AC magnetic fields (up to 300 kHz and 50 mT)
Quentin Pankhurst	MFH, SQUID VSM, TEM, Mössbauer, A4F, XRD, cell line studies Singular equipment: Live cell imaging with MFH
Olga Kazakova	NA
Simo Spassov	AC-susceptometry DC-magnetometry Remanence-vector magnetometry FORC analysis
Jon Dobson	MH (nanoTherics & Ambrell), SQUID magnetometry, DLS, electron microscopy
Jesús M. de la Fuente	TEM and HR-TEM, SEM FE, SQUID, VSM, AFM, MFM, AMF (solution, cells, and small animals), NMR, cell culture facilities, animal facilities
Kenneth Knudsen	Neutron techniques (SANS, diffraction), X-ray techniques
Mikkel F. Hansen/Cathrine Frandsen	*Mikkel Fougt Hansen*: DC magnetometry *Cathrine Frandsen*: Mossbauer spectroscopy, DLS, TEM, scattering techniques, nanoparticle synthesis
Angel Millán	AC susceptometry, DC magnetometry, DLS, neutron techniques, SAR measurements in nanoparticle dispersions Singular equipment: AC electromagnet coupled to a fluorescence microscope for in-cell hyperthermia. The instrument has also a system for luminescence temperature mapping
Claudio Sangregorio	AC susceptometry, DC magnetometry, DLS, XRD, TE, AFM, chemical synthesis of magnetic nanoparticles, calorimetric set up for SAR evaluation
Uwe Steinhoff	Numerical simulations of hysteresis, AC susceptometry, DC magnetometry, DLS, MR-spectroscopy, magnetorelaxometry, nonlinear susceptibility, magnetic measurements in flowing liquids, Mössbauer spectroscopy, MPI
Eva Natividad	My present expertise is the accurate characterizaton of SAR in adiabatic conditions, in function of the alternating magnetic field amplitude and frequency, and also in function of the temperature. My lab has two adiabatic magnetothermal setups which are, as far as I know, unique setups
Luc Dupre	SAR measurement equipment
Julian Carrey	Modelisation of hysteresis loops (hysteretic losses). Experiment design to validate proposed models. DC & AC magnetometry measurements. Comparison with theoretical models
Fernando Plazaola	AC susceptometry, DC magnetometry, Mössbauer spectroscopy
Liliana P. Ferreira	DC SQUID magnetometry, AC susceptibility, Calorimetric magnetic hyperthermia, Mossbauer spectroscopy
Aristides Bakandritsos	SQUID, SAR measuring setup, magnetophoresis, DLS, TGA
Christer Johansson	AC susceptometry, DC magnetometry

Silvio Dutz	SAR measuring setup, DC magnetometry
Gerardo F. Goya	numerical simulations of sar, AC susceptometry, DC magnetometry, dynamic light scattering, TEM, SEM, DB, power sources
Oscar Iglesias	Monte Carlo simulations, numerical methods, micromagnetics, AC susceptometry, DC magnetometry, synthesis of Fe and Co based oxide and spinel nanoparticles, TEM and X-ray structural characterization
Beata Kalska-Szostko	TGA, DLS, TEM, SEM, AFM, BET, XRD, IR, Raman spectroscopy
Claire Wilhelm	SAR measurement equipment: (a) home-made, 1 cm coil, 300-900kHz, 0-25 mT; (b) nanoScale Biomagnetics, 100-470kHz, 0-20 mT; (c) NanoTherics, 100-300 kHz, 0-12 mT
Alessandro Lascialfari	NMR relaxometer, DC SQUID magnetometer, MUSR, simulation of field distribution
José Mariano	AC susceptometry, DC magnetometry, dynamic light scattering, SEM, TEM, zero feild NMR, XRD, Mossbauer, FTIR

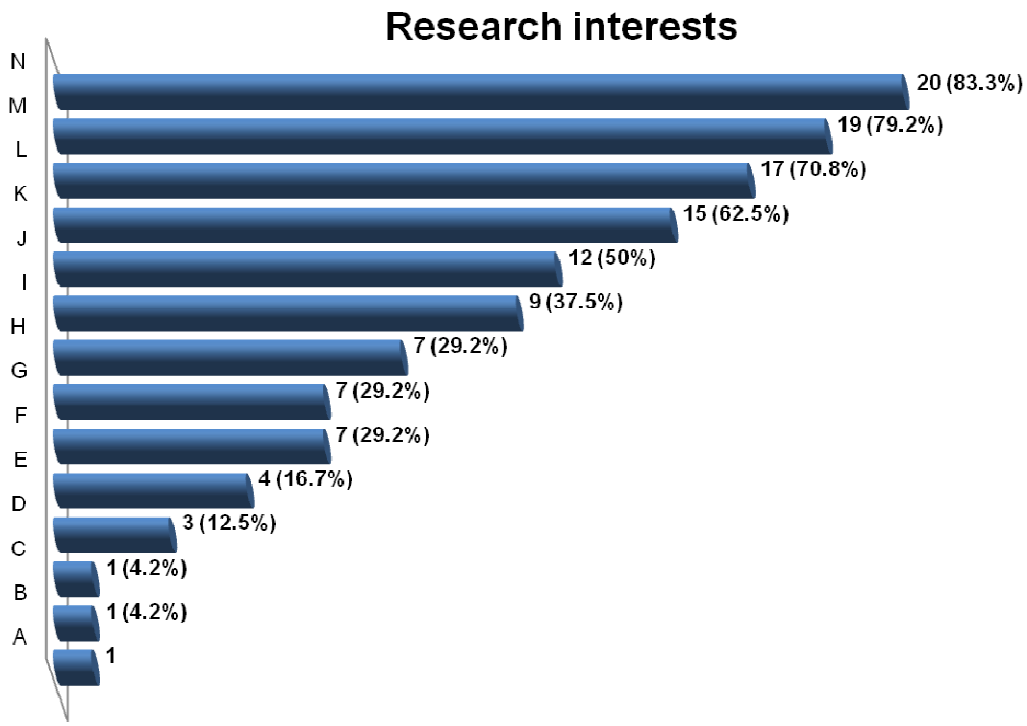
9. Research interests

One of the main values of COST actions is to bring together researchers with either common or complementary research interests under the umbrella of a given topic, magnetic hyperthermia and radiotherapy in our case. The survey conducted in WG2 (Annex I, page 14) includes a dedicated section to explore the popularity of some relevant research topics among WG2 members. The results of the survey reveal, at the same time, the stronger areas of our working group as well as some noticeable lacks that need to be addressed with relative urgency.

On the positive side, the WG core expertise is heavily inclined towards the characterisation of static/dynamic magnetic properties of nanoparticles (83.3%) and their structural determination (79.2%). Of particular note is the interest for studying interparticle interaction phenomena in magnetic nanoparticles, a topic of special relevance for magnetic hyperthermia given its influence on the absorption of electromagnetic energy by magnetic colloids.

On the negative side, there is a remarkable lack of expertise in (either theoretical or experimental) radiation physics in WG2, regardless of whether magnetic nanoparticles are used as vehicle for delivering both heat and radiation to tumours or are used for magnetic hyperthermia concomitant with radiotherapy[4]. If, as originally proposed for the action, the nanoparticle-mediated radiotherapy route is to be explored, then WG2 has to incorporate radiation physicists before the 12/11/2017, as no more participants can be enrolled within the last year of the action.

[4] *It has to be noted that there is some expertise in radiology in WG3.*



A Physical models: biophysics/radiation physics
B In vitro testing of radiosensitisation
C In vivo testing of radiosensitisation
D Other
E In vivo testing of magnetic hyperthermia
F Spatial detection of nanoparticles
G Temperature distribution Physical models: power losses
H Physical models: power losses
I In vitro testing of magnetic hyperthermia
J Standardisation of testing
K Characterisation of power losses (SAR, ILP)
L Interparticle interactions
M Structural characterisation of nanoparticles
N Characterisation of other static and dynamic properties of nanoparticles (relaxometry, DC magnetometry, etc.)

Fig. 4 Popularity of some research topics among members of WG2. The topics are listed below the graph. At the right of each bar, the number and the percentage of interested members are shown.

10. Contribution to objectives. Synergies

Besides the Action's general objectives stated in the Memorandum of Understanding (MoU) available at COST website (http://www.cost.eu/COST_Actions/tdp/TD1402), there are more specific objectives relevant to WG2 (Table 1), as previously mentioned. These are central to the overall timeline/roadmap/working strategy of RADIOMAG. The degree of accomplishment for each objective is periodically revised and reported by the WG2 to the action's core group and Management Committee in every meeting.

WG2 members have been asked about the objective/s they can contribute to in view of their expertise and future research directions. In general terms, the data gathered confirms the main conclusions extracted from the results presented in the previous section about the research interests survey. Objectives 1 (modelling & characterisation) and 2 (standardisation) are equally represented in the distribution of responses (Fig. 5). Objective 3 (in vivo MH), and especially objective 4 (radiation & combination therapy), do not have the expected representation yet. Even though there are radiology experts in WG3, the collaboration between the two groups has not gained traction due to the inherent lack of researchers with a core expertise in radiation physics. For example, ways of improving nanoparticle radiolabelling or the radioenhancer effect of some nanoparticle systems were much sought after in the original RADIOMAG proposal, but currently absent from any. As a consequence, the future recruitment efforts should be clearly directed towards gaining this missing expertise; if deemed necessary to keep the progress of the project at adequate pace.

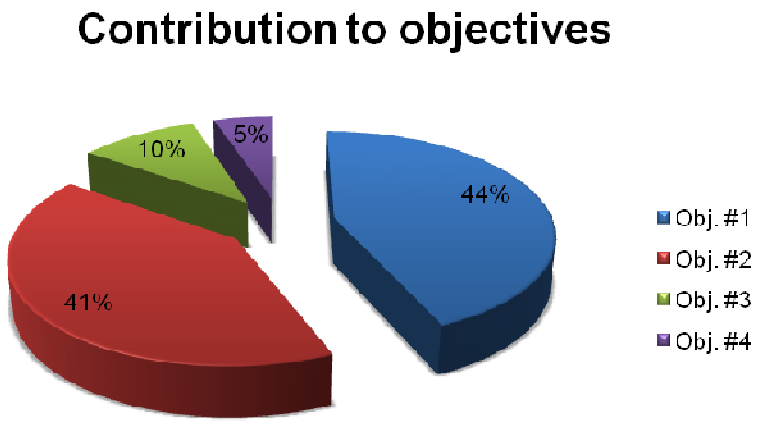


Fig. 5 Percentages of the contribution from WG2 to each of the objectives set in the working strategy.

Arranged in a different way, the data gathered from this survey may also be employed to facilitate the interaction between members. **Table 3** shows the direct correlation between the preferred objectives chosen by WG2 members, with indication of the matched objectives. Considering just the researchers that took the survey, there are **325** possible unique correlations[5], out of which **226** becomes effective (that means about **70%** of research interest matching between members). On the one hand, this correlogram can be taken as a map of potential research collaborations with different intensities, since participants coincide in more than one objective in some cases (red cells in **Table 3**). On the other hand, it can be taken the other way around by considering the lack of correlation (grey cells in **Table 3**) as a stimulus to build collaborations on the basis of complementary skills. All this information, along with the available instrumentation detailed in Table 2 is useful to identify potential partners in a project proposal, or a specific research collaboration.

[5] *Calculated as N*(N-1)/2, where N is the number of researchers.*

	V. Kusigerski	F. J. Terán	Q. Pankhurst	O. Kazakova	S. Spassov	J. Dobson	J. M. de la Fuente	K. Knudsen	M. F. Hansen/C. Frandsen	A. Millán	C. Sangregorio	U. Steinhoff	E. Natividad	L. Dupré	J. Carrey	F. Plazaola	L. P. Ferreira	A. Bakandritsos	C. Johansson	S. Dutz	G. F. Goya	O. Iglesias	B. Kalska-Szostko	C. Wilhelm	A. Lascialfari	J. Mariano
Vladan Kusigerski				2					2		2	2	2		2	2	2	2	2	2	2		2	2	2	
Francisco J. Terán			1	1	1	1		1		1	1	1			1	1			1	1	1	1			1	1
Quentin Pankhurst		1		1	1	1		1		1	1	1			1	1			1	1	1	1			1	1
Olga Kazakova	2	1	1		1	1		1	2	1	1,2	1,2	2		1,2	1,2	2	2	1,2	1,2	1,2	1	2	2	1,2	1
Simo Spassov		1	1	1		1		1		1	1	1			1	1			1	1	1	1			1	1
Jon Dobson		1	1	1	1			1		1	1	1			1	1			1	1	1	1			1	1
Jesús M de la Fuente														3							3			3		
Kenneth Knudsen		1	1	1	1	1				1	1	1			1	1			1	1	1	1			1	1
Mikkel F. Hansen/Cathrine Frandsen	2			2							2	2	2		2	2	2	2	2	2	2		2	2	2	
Angel Millán		1	1	1	1	1		1			1	1			1	1			1	1	1	1			1	1
Claudio Sangregorio	2	1	1	1,2	1	1		1	2	1		1,2	2		1,2	1,2	2	2	1,2	1,2	1,2	1	2	2	1,2	1
Uwe Steinhoff	2	1	1	1,2	1	1		1	2	1	1,2		2		1,2	1,2	2	2	1,2	1,2	1,2	1	2	2	1,2	1
Eva Natividad	2			2					2		2	2			2	2	2	2	2	2	2		2	2	2	
Luc Dupré							3														3			3		
Julian Carrey	2	1	1	1,2	1	1		1	2	1	1,2	1,2	2			1,2	2	2	1,2	1,2	1,2	1	2	2	1,2	1
Fernando Plazaola	2	1	1	1,2	1	1		1	2	1	1,2	1,2	2		1,2		2	2	1,2	1,2	1,2	1	2	2	1,2	1
Liliana P. Ferreira	2			2					2		2	2	2		2	2		2	2	2	2		2	2		
Aristides Bakandritsos	2			2					2		2	2	2		2	2	2		2	2	2		2	2		
Christer Johansson	2	1	1	1,2	1	1		1	2	1	1,2	1,2	2		1,2	1,2	2	2		1,2	1,2	1	2	2	1,2	1
Silvio Dutz	2	1	1	1,2	1	1		1	2	1	1,2	1,2	2		1,2	1,2	2	2	1,2		1,2	1	2	2	1,2	1
Gerardo F. Goya	2	1	1	1,2	1	1	3	1	2	1	1,2	1,2	2	3	1,2	1,2	2	2	1,2	1,2		1	2	2,3,4	1,2	1
Oscar Iglesias		1	1	1	1	1		1		1	1	1			1	1			1	1	1				1	1
Beata Kalska-Szostko	2			2					2		2	2	2		2	2	2	2	2	2	2			2	2	
Claire Wilhelm	2			2			3		2		2	2	2	3	2	2	2	2	2	2	2,3,4		2		2	
Alessandro Lascialfari	2	1	1	1,2	1	1		1	2	1	1,2	1,2	2		1,2	1,2			1,2	1,2	1,2	1	2	2		1
José Mariano		1	1	1	1	1		1		1	1	1			1	1			1	1	1	1			1	

Table 3 Synergies between groups in terms of the contribution towards WG2 objectives. Light grey cells: no direct correlation between the pairs; dark grey cells: correlation of each participant with herself/himself; blue cells: one common objective; red cells: two common objectives; dark blue cells: three common objectives. Objective numbers are indicated.

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COST Office
Avenue Louise 149
1050 Brussels, Belgium
t: +32 (0)2 533 3800
f: +32 (0)2 533 3890
office@cost.eu

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Abbreviations

A4F - asymmetric flow field-flow fractionation
AC - alternating current
AFM - atomic force microscopy
AMF - alternating magnetic field
BET - Brunauer-Emmett-Teller (related to specific surface measurement)
DC - direct current
DLS - dynamic light scattering
FE - field emission
FORC - first order reversal curve
IR - infrared
MFH - magnetic fluid hyperthermia
MFM - magnetic force microscopy
MH - magnetic hyperthermia
MPI - magnetic particle imaging
MR - magnetic resonance
NMR - nuclear magnetic resonance
SANS - small-angle neutron scattering
SAR - specific absorption rate
SEM - scanning electron microscopy
SQUID - superconducting quantum interference device
TEM - transmission electron microscopy
TGA - thermogravimetric analysis
VSM - vibrating sample magnetometry
XRD - x-ray diffraction
MUSR - Muon spin resonance

Acknowledgements

Suggestions and corrections from Prof. Ann Hirt, Dr. Silvio Dutz and Dr. Simo Spassov are here acknowledged.

List of Annexes

Annex 1: form used for gathering the information from the research groups included in WG2.
Annex 2: list of WG2 members.

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ANNEX I - FORM USED FOR GATHERING THE INFORMATION FROM THE RESEARCH GROUPS INCLUDED IN WG2

WG2 - core expertise and strategy

*Required

1. **Country** *

_____

2. **Name of the representative researcher of the group/unit** *

_____

3. **Type of research** *
Mark only one oval.

- ◯ Theoretical
- ◯ Experimental
- ◯ Theoretical/experimental

4. **Contribution to objectives** *
In view of the core expertise of the group/unit, select those objectives towards which the group/unit can contribute best
Tick all that apply.

- ☐ Objective 1 (Modelisation of hysteresis loops (hysteretic losses). Experiment design to validate proposed models. Modelisation of spatial heat distribution at the nanoscale. Experiment design for measuring heat dissipation at the nanoscale (improvement). DC & AC magnetometry measurements. Comparison with theoretical models)
- ☐ Objective 2 (Survey/revision of the existing energy absorption parameters: amendments and/or proposition of new ones, including safety/tolerance levels. Data analysis and interpretation from calorimetry measurements. DC & AC magnetometry measurements. Comparison with theoretical models)
- ☐ Objective 3 (Simulation of temperature distribution in cells and tissues (bio-heat equation). Experiment design (field application & thermometry) for clinical MH sessions in humans. Data processing and interpretation)
- ☐ Objective 4 (Simulation of the penetration depth of radiation in cells and tissues from either independent radioactive sources or combined with magnetic nanoparticles. Experiment design for conducting combined ERT & MH treatments in humans. Suitability of simultaneous sessions)

5. **Available techniques/instrumentation** *

Briefly list the available techniques and/or instrumentation relevant to the action's theme, i.e. magnetic hyperthermia and indirect radiation therapy. For example, numerical simulations of hysteresis, AC susceptometry, DC magnetometry, dynamic light scattering, neutron techniques, etc

_____

_____

_____

_____

_____

6. **Expertise and/or research interests** *

Tick all the options that apply to the your group/unit. Please suggest any other not listed here.

Tick all that apply.

- [ ] Physical models: power losses
- [ ] Physical models: biophysics/radiation physics
- [ ] Characterisation of power losses (SAR, ILP)
- [ ] Characterisation of other static and dynamic properties of nanoparticles (relaxometry, DC magnetometry, etc)
- [ ] Structural characterisation of nanoparticles
- [ ] In vitro testing of magnetic hyperthermia
- [ ] In vivo testing of magnetic hyperthermia
- [ ] Interparticle interactions
- [ ] Spatial detection of nanoparticles
- [ ] Temperature distribution
- [ ] Standardisation of testing
- [ ] In vitro testing of radiosensitisation
- [ ] In vivo testing of radiosensitisation
- [ ] Other: _____

ANNEX II - LIST OF WG2 MEMBERS

Only those members holding a primary affiliation to WG2 have been included in this list.

Surname	Name	Institution	Country
Egli	Ramon	Central Institute for Meteorology and Geodynamics	Austria
Crevecoeur	Guillaume	Ghent University	Belgium
Dupré	Luc	Ghent University	Belgium
Spassov	Simo	Centre de Physique du Globe de l'Institut Royal Météorologique de Belgique	Belgium
Frandsen	Cathrine	Danmarks Tekniske Universitet	Denmark
Beleggia	Marco	Danmarks Tekniske Universitet	Denmark
Hansen	Mikkel	Danmarks Tekniske Universitet	Denmark
Gazeau	Florence	Université Paris Diderot	France
Wilhelm	Claire	Université Paris Diderot	France
Dutz	Silvio	Institute of Biomedical Engineering and Informatics, Technische Universität Ilmenau	Germany
Steinhoff	Uwe	Physikalisch-Technische Bundesanstalt	Germany
Szalai	István	University of Pannonia	Hungary
Innocenti	Claudia	Institute of Molecular Science and Technologies, CNR	Italy
Sangregorio	Claudio	Institute of Molecular Science and Technologies, CNR	Italy
Helgesen	Geir	Institute for Energy Technology	Norway
Knudsen	Kenneth	Institute for Energy Technology	Norway
Ferreira Pires	Liliana Maria	Faculty of Sciences, Lisbon University	Portugal
Mariano	José	University of the Algarve	Portugal
Cruz	Margarida	University of Lisboa	Portugal
Kusigerski	Vladan	The Vinca Institute of Nuclear Sciences	Republic of Serbia
Perovic	Marija	The Vinca Institute of Nuclear Sciences	Republic of Serbia
Timko	Milan	Slovak Academy of Sciences	Slovakia
Natividad	Eva	Aragón Materials Science Institute	Spain
Ortega	Daniel	IMDEA Nanoscience	Spain
Fuente de la	Jesús Martínez	Aragón Materials Science Institute	Spain
Garitaonandia, Sáiz	José Javier	University of the Basque Country	Spain
Iglesias	Oscar	University of Barcelona	Spain
Johansson	Christer	Chalmers University of Technology & ACREO	Sweden
Kuster	Niels	IT'IS Foundation	Switzerland
Hirt	Ann	ETH Zurich	Switzerland
Kazakova	Olga	National Physical Laboratory	United Kingdom
Pankhurst	Quentin	University College London	United Kingdom
Southern	Paul	Resonant Circuits Ltd.	United Kingdom
Dobson	Jon	University of Florida	United States