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Subject | Minutes of the WG2/WG4 group Meeting Design & testing of specific coil geometries (including their proper calibration)

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

Hunguest Hotel Forrás Szeged (Hungary)
6th & 7th of March, 2017

1st day, 6th of March

Welcome to participants / Adoption of the agenda
The meeting started at 9 AM. Present are Victor Batić, Marko Bošković, Luc Dupré, Carlton Jones, Lin Fangyu, Eneko Garaio, Daniel Ortega, Marija Perović, Olivier Sandre, Simo Spassov, Etelka Tombácz and James Wells. Excused: Silvio Dutz, Neil Farrow, Vladan Kusigerski, Christophe Monnier, Liliana Maria Pires Ferreira and Fernando Plazaola.

The local organiser Etelka Tombácz and the Chair Simo Spassov opened the meeting. The agenda was adopted. Before commencing the open discussion, the milestones set in the MoU were recalled, *i.e.*

Milestone A5-2: Advancement of theoretical and technical concepts of MoU magnetic hyperthermia.

Models and techniques developed by individual partners will then be tested, discussed and evaluated. This concerns for instance:

- *the energetically efficient design of the radiofrequency coil and generator to create a magnetic field on large volumes (for in vivo experiments) with well characterised and controlled field homogeneity,*
- *real time modulation and modelling of the applied magnetic power to deposit precise thermal doses.*

W+B plan: goal current GP
Design and testing of specific coil geometries for better ferrofluid enhancement in tumours.

In reaction to this, Carl questioned what *large volume* signifies exactly. Olivier suggested to make a literature review.

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Open discussion round & presentations

The morning session started and was moderated by Olivier. He gave a review about recent advances in coil design (*cf.* ***Annex A3***)

- mainly two coil types are used for pre-clinical and clinical tests
  - Ferrite core coil
  - Solenoids
- MAGFORCE the only commercial enterprise offering MFH treatments in humans uses apparently a ferrite core coil. The treatment is limited to glioblastoma and prostate cancer. The treatment price is too high.
- It was discussed that clinical tests are not feasible within the frame of RADIOMAG and that the work in the WG's should focus on the development of coils for pre-clinical trials. Most SAR test devices work well for preclinical animal testing, at least for rodents and other small animals so far. The technical development of MFH coils should focus rather on humans.
- Commercial MFH setups have problems with field control.
  - Only for some, fields are controlled by shifting the operating frequency little out of the resonance frequency.
- In Bordeaux, the integral of $T(t)$ above a certain threshold (which?) is considered as thermal dose.
- For the setup at UPV / EHU the SAR is determined via AC hysteresis loops. Calorimetric, *i.e.* $T(t)$ measurements are not required. The results are fairly identical with those of calorimetric methods.
- Sources of error when doing *in vitro* MFH tests on cell cultures.
  - As the buffer solution contains free ions, eddy currents can be induced to some extent.
  - It was suggested to make always a control MFH test on the buffer solution only, *i.e.* no MNPs inside, to check if temperature rises due to eddy currents or not.
- Next, new advances in coil design were presented.
  - Two turn Helmholtz coil
  - Daniel presented a paper by Bauer et al. 2016, testing the combination of MPI and MFH on Zn-doped iron oxide FFs. This was done by placing an AMF coil between two oppositely poled permanent magnets. The resulting gradient field was able confine the temperature increase to the centre of the sample holder albeit FF was present also in the outer regions.
  - As instantaneous temperature monitoring is indispensable during clinical MFH application, temperature monitoring employing MPI should be further investigated taking into account the higher harmonics of the signal.
- Concerning MFH setup calibration, the non-commercial FEMM software (www.femm.info) is considered as valuable tool for modelling magnetic field distributions inside SAR test devices.
- Proper field mapping may be done also with a Rogowski coil.

Next, Carl presented advances in instrumentation developed by Nanotherics and communicated their experience in calorimetric SAR measurements (*cf.* ***Annex A4***).

- The sensitiveness of T-type thermocouples to heating is negligible during the initial phase of the SAR measurement, *i.e.* for $t = 0 – 15$ *s*. Still, noise is generated in the $T(t)$-curve. The use of fiber optic thermos-sensors or infrared thermography is suggested instead.
- At higher frequencies (above which exactly???). the temperature difference increases. This effect was observed in a 6 *mT* (4.77 *kA/m*) field.
- When working at higher frequencies pulsing the field was suggested to avoid this instrumentation related temperature increases. Illustrative data is available at NanoTherics website.
- Nanotherics provides new a live cell applicator for MFH, allowing to study MFH efficiency *in-vitro*.
  - The AMF is generated by a pancake coil.
  - A thermocouple can be fixed directly in the Petri dish but one risks to damage the cell ultrastructure
  - Alternatively temperature can be monitored, by gluing the fibre optics sensor underneath the Petri dish. In this case, however, a delayed temperature increase in the order of some minutes must be considered, as the cells heat fast than the fibre optic sensor reacts.

- Nanotherics offers now a digital version of the magneTherm . All parameters are fully software controlled.
- It was mentioned that field-induced magnetic drug release could be a topic for a next COST.

Next, Eneko presented on non-calorimetric SAR determination using dynamic hysteresis loops (*cf.* ***Annex A5***).

The field calibration of coils was discussed for clinical MFH application. As tumours have rather fractal geometries instead of simple shapes, it is important that all parts of the tumour are exposed to the same field intensity. A precise knowledge of the homogenous field distribution inside the AMF coil seems of fundamental importance in order to exclude temperature differences due to magnetic field variations. After administration, most FF accumulates in the liver. An exact knowledge of the field distribution and field free regions (for specific coil types) is of crucial importance for avoiding collateral damage of healthy tissue.

- Field mapping may be done for a particular tumour type, but such mapping cannot be considered as field calibration.
- Another option would be simulations using the FEMM.
- However, for practical MFH application in the clinic only instantaneous temperature mapping of the tumour region is of interest for the surgeon.
- Test on tumour phantoms should be carried out.
- A problem could be the occurrence of indirect electric fields.
- The idea came up for a joint meeting with the International Society for Electroporation-Based Technologies and Treatments discussing:
    - nanoscale heat transfer,
    - electromagnetic effects on cells, cold MFH,
    - safety issues related to eddy currents, and
    - stimulation of membrane potential by EM field.
- The field distribution of pancake coils was discussed. Their use for MFH application seems advantageous for very local tumour treatments. There is no need to place the entire body in an AMF coil. However, due to its flat geometry, the field has a rather moderate penetration depth limiting its use to near skin surface tumours.

Olivier summarises the session and highlights again the most important points:

- Temperature measurements should be
    - contactless and
    - made outside the body.
- Coil field mapping prior MFH application remains an important issue.
- There must be a save field region particularly for the liver (unless the tumour is not situated there).
- It is also important to have knowledge about the temperature changes induced by the coil itself.
- Pulsed fields are an option to reduce or avoid coil related heating, when operating at high frequencies.

Lunch

During the afternoon session Luc presented on upscaling laboratory MFH devices for clinical applications, showing theoretical considerations and MFH experiments (*cf.* ***Annex A6***). It was discussed that simple upscaling of whole body cylindrical MFH coils is unrealistic due to the enormous power consumption. Pancake type coils were proposed as solution. An *in vitro* experiment was presented using this type of coils on a beef bone prepared with PMMA bone cement containing MNPs. The MNPs were placed at

approximately 10 *cm* axial and 0 *cm* radial distance from the coil centre and 5.7 °C above body temperature were reached after about 4 *min* AMF application (1.75 *kA/m*, 160 *kHz*). Albeit the rather inhomogeneous field distribution of the pancake coil it demonstrates its potential for clinical MFH application for specific tumours.

Closing first day, around 6 PM, visit of the old town and dinner together.

2nd day, 7th of March

Open discussion round & presentations

Commencing at 9 AM, the 2nd day began with a discussion on the SAR. It was suggested to include also AC-SAR determinations in the SAR ring test for comparison. The AC-SAR is calculated from dynamic hysteresis loops and does not involve any calorimetric measurements. Eneko had demonstrated in his PhD thesis that AC-SARs are more accurate and reproducible than the calorimetric SARs. AC and calorimetric SAR are fairly in agreement, particularly at higher power densities.

Next, Daniel presented *in silico* simulations he carried out within the frame of the NoCanTher project (*cf.* ***Annex A7***). Deep seeded tumours such as pancreatic cancer have a very high mortality rate, and there is no successful treatment. MFH could be a solution. Model results done with SIM4life were presented. Daniel underlined that modelling is an important task for MFH treatment planning, as it offers the possibility of testing multiple coil configurations and evaluates *a priori* both specific and non-specific effects on the patient. Sim4life is a simulation platform allowing for studying the interaction of animal and human models with electromagnetic fields through the use of realistic computable phantoms.

The paper from Yamada et al., JJSAEM, 2015, was discussed. The authors combined two pancake coils, each having a back yoke. The latter increased considerably the magnetic field intensity between both pancake coils, *i.e.* the position where the patient is placed.

The meeting ended with the presentation James who showed experimental results of the SAR ring test (*cf.* ***Annex A8***). At the PTB (Germany), Uwe Steinhoff carried out calorimetric SAR determinations using millimetre sized metallic spheres in order to develop a relative calibration procedure for the SAR. Initial tests done by Silvio Dutz (TU Ilmenau, Germany) failed, because the spheres were not regularly arranged in vial but accumulated at the bottom. Uwe tried to fix them inside a PCV matrix and indeed a temperature increase was observed when applying an AMF. Unfortunately, the experiments were not reproducible. Uwe and James work further on this topic. It was discussed to use instead of metallic spheres, water of a given conductivity.

Closing at noon and lunch together.

In the afternoon, small post-meeting between Daniel and Simo discussing the Actions progress and the contingency plan.

Abbreviations

AC	Alternating current
AMF	Alternating magnetic field
EM	Electromagnetic
FF	Ferrofluid
FEM	Finite element method
MFH	Magnetic fluid hyperthermia
MNP	Magnetic nanoparticle
MPI	Magnetic particle imaging
MRI	Magnetic resonance imaging
NP	Nanoparticle
PMMA	Polymethylmethacrylate
PTB	Physikalisch Technische Bundesanstalt (German metrology institute)
SAR	Specific absorption rate
UPV / EHU	University of the Bask Country

List of Annexes

Annex A1: Meeting agenda
Annex A2: Signed COST Attendance list
Annex A3: Presentation Olivier Sandre
Annex A4: Presentation Carlton Jones
Annex A5: Presentation Eneko Garayo
Annex A6: Presentation Luc Dupré
Annex A7: Presentation Daniel Ortega
Annex A8: Presentation James Wells