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Subject | Minutes of the WG2 subgroup meeting, COST Action TD1402 "Data analysis strategy for the SAR ring test"

IMDEA Nanoscience, Madrid (Spain)
9-10th of March 2016

1. Welcome to participants

The meeting started at 9:00 AM. Present are: Silvio Dutz, Eva Natividad, Daniel Ortega, Uwe Steinhoff, Simo Spassov and James Wells.

2. Adoption of the agenda

The agenda was adopted.

3. Meeting content

1st Day – *Morning*
The participants were welcomed by Daniel Ortega (local organiser) at the IMDEA Nanoscience; short ice-breaker coffee break; the meeting started at 9 AM. Daniel gave a presentation on the methodology SAR result evaluation, including the pre-experiment questionnaire and the statistics of the used equipments / parameters for obtaining the $T(t)$ curve. He proposed to use a Youden-plot for analysing systematic and random errors when comparing the results of different laboratories. During the subsequent discussion following was stated:

- Only 11 laboratories have submitted their results so far, an e-mail should be sent around to encourage the submission of missing results
- As there was no consensus during previous RADIOMAG meetings which *f-H* combinations should be used for the SAR ring-test, the used *f* and *H* values cover a wide spectrum
- Apparently some measurers misunderstood the difference between adiabatic and non-adiabatic $T(t)$ measurement equipment
- Problems occurred as not all measurers determined precisely the volume used for the $T(t)$-curve measurements

- The Youden-plot established with the results so far, shows considerable differences in the SAR values, up to xxx%. These differences are partly related to the different frequency and field values chosen when measuring the *T*(*t*)curve
- It was proposed to draw the error ellipses in the Youden-plot for each *T*(*t*) setup; however there is also a systematic error for each one, and according to the experience of Eva, the systematic error > random error. In her laboratory a metal cylinder is used for determining the systematic error of the *T*(*t*) setup
- in future:
    - establish field and frequency ranges, to better compare the different SAR,
    - send around also blank sample containing distilled water only
    - explain better what is meant with adiabatic and non-adiabatic measurement equipment
    - supply empty vials also

Lunch between 1:30 PM and 2:30 PM offered by the local organiser

1st Day – *Afternoon*

Preamble: In preparation of the SAR ring-test, Daniel developed a SOP (Excel-spreadsheet) including measuring instructions, calculations result input fields. The measures had to:

- measure FF sample №1 from laboratory L3S8 and №2 from laboratory Y2C6 three times each
- calculate the SAR value according to their usual practice
- provide information on the used measurement setup and the method for SAR calculation

The results of the different laboratories obtained so far were screened for errors / specifics. For better visibility, Daniel replotted the results in each result file and made a summarising table. The screening gave following:

- AW15: all three measurements okay
- EM99: individual *T*(*t*) curves for FF 1 vary by less than 5 %, results considered okay
- DG51: okay
- FC76: okay
- FF55: okay
- FR48: required measurement protocol was not followed. The first 900 *s* monitoring the temperature equilibration of the setup are not given
- ND33: too high maximal temperature, probably due to the use of a ferrite coil
- QC55: okay
- RN49: okay
- SL05: not okay, different maximal temperatures for the 3 individual measurement of the same FF
- TN56: okay

Measures AW15 / ND33 as well as FC76 / QC95 used similar field intensities and frequencies. The measurer couple FC76 / QC95 was compared in detail. Nevertheless the temperature vs. time data were not identical, and the SARs for FF №1 and №2 differ by a factor 1.6 and 1.4, respectively.

General observation:

- not all measurers abode the measurement protocol
- some measurers have time resolutions < 1 *s*. Resolutions < 1 *s* may be irrelevant for volumes in mL range. *Pers. comm. from Paul Southern*: a time resolution <1s is pretty pointless since thermocouples/probes likely have a response time ~1s and given the volume of measured material is in mL range I wouldn't expect uniform heating throughout and some delay in "equilibrium" will be again of the order of seconds not milliseconds.
- often all three curves from each FF sample were not measured until the end

Following error sources of the SAR determination were elicited and discussed:

- the AF coil produces heat itself when switched on and this heat can be taken up by the FF
- sample volume
- position / kind of the thermometry sensor
- sample holder geometry
- thermal insulation
- the method of SAR calculation

The first meeting day finished around 6 PM.

2nd Day – *Morning*

The meeting participants were welcome by Francisco Terán at 10 AM who conducted guided tour through the IMDEA Nanoscience giving an insight to recent and ongoing research activities. The meeting started with a brainstorming by Uwe demonstrating the complexity of $T(t)$ measurements. His points were:

- For future ring-tests one would have to define three individual sub-procedures:
  - measurement preparation procedure
  - measurement procedure
  - data analysis procedure
- The heat Q generated by MNPs does not only depend on their intrinsic properties, but also on instrumental ones. The measured $T(t)$ curve is thus a convolution of instrumental and intrinsic properties.
- In order to extract the instrumental influences it is proposed to re-conduct the ring-test at smaller scale, *i.e.* only involving 3 laboratories (Eva, Silvio, Uwe) by using a calibration set with different concentrations of particles. Such set should have following properties:
  - contain particles with exactly the same spherical shape and diameter
  - the specific heat capacity of the particles should be known
  - the concentration should be exactly determinable, possibly without using usual methods for concentration measurements (titration, ICP-MS)

  The proportion of different concentrations in relation to the proportion of SAR values for pre-defined well-known particle concentrations should filter out the instrumental properties.

- Following options for a possible test calibration set were discussed:
  - Dynabeads in polymer matrix: not good, because polymer agglomerations may occur
  - MRI phantoms made of silica polymers
  - metallic spherules well-defined diameters in µm range: easy to produce different concentration just by counting. It was opted to go on with metallic spherules

  It is concluded that a set with different concentration countable spherules (micrometre-sized) is the best for making a calibration set. Such set could be easily prepared by placing a ring containing metallic spherules in a vial (glued?). Several vials containing a different number of spherules can be prepared, and the measurer would only have to add a defined volume of distilled water.

Lunch between 1 PM and 2 PM offered by the local organiser.

2nd Day – *Afternoon*

Next, ameliorations of the operational procedure for a second run of SAR-ring test were discussed. Following points were decided:

- measure $T(t)$ using a constant volume (micropipette). No decision on volume yet.
- provide an empty measurement vial
- send a blank sample containing water with low electrical conductivity
- based on the first round group the f and H into classes
- explain better adiabatic vs. non-adiabatic MFH testing device in the preliminary instructions
- the second run will be done again on FF samples №1 and №2
- the time interval Δ_{t1-t0} can be shorten from 900 s to 200 s
- the position of the temperature probe is very important, the thermocouple should be always at the same position during the all measurements. Besides, the thermocouple should not touch the sample container by any means and should stay as much centred as possible.

Another point discussed concerned the real field values of the magnetic field. The field values set during the $T(t)$ measurements refer to the calibration table provided by the MFH testing device producers in case of commercial devices. It was proposed that one participant (Silvio) visits all measurers in order to measure the field in the AF coils.

Due to the large variability of instrumental and measurement influences it was decided that the data presentation of the first round should be kept as simple as possible. Uwe proposed a bubble plot of "pseudo-SAR" (and ILP) values. In a f vs H plot, the SAR of a sample is presented by a circle, the diameter represents the SAR value while f and H determine the position within the plot. Simo and Daniel will recalculate the SAR (ILP) using the same method for all measurers, *i.e.* the one proposed by Wildeboer, Southern & Pankhurst published in J. Phys. D: Appl. Phys. 47 (2014) 495003.

Finally, a post-experiment survey was prepared by Daniel and discussed between the meeting participants and a schedule for next activities was set up.

The meeting was closed around 5:30 PM.

ToDo- list

Action	Deadline	Responsible
Re-call to missing measurers that the deadline for result submission is 16. III. 2016	10. III. 02016	Simo (done)
Sending out the post experiment survey to measurers	16. III. 2016	Daniel (done)
Discuss SAR recalculation on phone	21. III. 2016	Daniel, Simo (done)
Feedback from measurers post experiment survey & Re-feedback to measurers during the meeting in Athens	24. III. 2016 / 08. IV. 2016	Daniel, measurers, Simo (done)
Ameliorating the SOP for the 2nd round and sending it to the measurers	24. III. 2016	Daniel
Ameliorating the standard operation procedure for the 2nd round	24. III. 2016	Daniel
Recalculate the SAR/ILPs of the 1st round and make bubble plots	03. IV. 2016	Daniel, Simo (done)
Sending out SOP for 2nd round & recalling that the deadline for result submission is 24. IV.2016	04. IV. 2016	Daniel
Presentation of results from 1st round during RADIOMAG workshop in Athens	07. IV. 2016	Simo (done)
Delivering empty vials, blank samples and remaining samples to measurers during the Athens meeting	07. IV. 2016	Simo (done)
Looking for possible metallic spherules for calibration set	asap	Uwe (done)
Acquisition of appropriate metal spheres, Making calibration set & conducting tests	asap	Eva, Silvio, Uwe (in progress)
Check for procedures to measure temperature exactly. Get in touch with the NPL's thermometry group	asap	James (in progress)

Abbreviations

AF – alternating magnetic field
f – frequency of the alternating magnetic field
FF – ferrofluid
H – root mean square value of the field intensity of the alternating magnetic field
ILP – intrinsic loss parameter
MFH – magnetic fluid hyperthermia
MNP – magnetic nanoparticle
SAR specific absorption rate
SOP – standard operation procedure

List of Annexes

Annex 1: Meeting agenda
Annex 2: Signed COST Attendance list
Annex 3: presentation from Daniel (pre-experiment survey, Youden plots)