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Home Institution:	CNR - IREA, Napoli-ITALY
Host Institution:	TU-Ilmenau, GERMANY

Abstract

The adoption of Magnetic NanoParticles (MNPs) as contrast agents for microwave imaging of breast cancer is an emerging and effective diagnostic technique that has been pioneered by the researchers of CNR-IREA and "Federico II" University of Naples. Recently, the researchers at TU-Ilmenau have also studied the development of this technique for Ultra-Wide Band (UWB) radar systems, as a means for breast cancer detection. As such, the two groups are currently engaged in a mutual cooperation aimed at bringing this novel technique closer to the stage of pre-clinical trials, which will provide the first assessment of its performance. With respect to this framework, this STSM has been mainly aimed at appraising the optimal working conditions of the UWB technique, by determining the intensity of the magnetic field (MF) adopted to drive the MNPs response at microwaves in such a way to maximize the signal useful for detection/diagnosis. Besides this specific goal the overall activities have set the ground for fruitful synergic cooperation between the two institutions on this topic, which is expected to bring results that will be relevant for the whole MiMed network.

1 Purpose of the STSM

Magnetic NanoParticles (MNPs) enhanced microwave imaging is an innovative diagnostic technique for breast cancer that has been proposed by the researchers of CNR-IREA and "Federico II" University of Naples [1].

Such a technique takes advantage of two circumstances:

- the first one is that it is possible to deliver MNPs within the tumor in a selective way, therein inducing a local variation of the magnetic permeability. Being the surrounding tissue non-magnetic, this allows to achieve a highly specific contrast enhancement.
- the second circumstance is that the response of MNPs at microwaves can be driven by applying an external MF, thus changing the magnetic induced contrast

> accordingly. As long as proper field intensities are exploited, this allows even to switch "on" and "off" the signal due to the contrast agent and therefore enables a differential measurement technique that can directly provide the signal useful for diagnostic purposes. The low amount of MNPs that can be targeted with currently delivery methods makes this arrangement necessary to separate the useful signal from the "background" one[1].

The researchers at TU-Ilmenau have an assessed experience in UWB radar systems and techniques. In particular, they have developed a M-Sequence UWB technology capable of detecting very small signals immersed into noise. By relying on this technology, they have recently approached the exploitation of MF modulated MNPs as a means for contrast enhanced breast cancer detection via UWB radar.

Basing on the full MNPs characterization performed at CNR-IREA (which can be considered as the first part of this work), using an innovative t measurement technique [1], the purpose of this STSM has been to assess the optimal working conditions for MNPs enhanced breast cancer detection, using the M-Sequence UWB technology developed at TU-Ilmenau.

The assessment has been carried out by experimental trials (in phantom) using different MNPs concentrations, volumes and different magnetic field intensities, in order to establish the lowest concentration of magnetite and the lowest volume for the signal to be detected. Moreover, thanks to the extremely adaptability of the UWB system, a broad-band spectroscopic characterization of MNPs using the TU-Ilmenau UWB system and the coaxial cell developed at University of Naples "Federico II" and CNR-IREA has been performed for the first time.

2 Description of the work carried out during the STSM

Since MNPs enhanced breast cancer detection involves many parameters and aspects, each of the following paragraphs is focused on a particular aspect of the work carried out during this STSM.

2.1 Preliminary work: Broadband Spectroscopy of diluted MNPs

To determine the optimal working conditions, it is necessary to maximize the signal backscattered by the MNPs when exposed to the polarizing magnetic field. As a matter of fact, thanks to the MNPs properties, it is possible to shift, in frequency, the magnetic response of MNPs by applying an external MF.

To this end, the preliminary stage of the STMS, carried out at CNR-IREA right before moving to Ilmenau, has been devoted to the broadband spectroscopy of MNPs diluted in distilled water (due to its biocompatibility), by exposing them to different MF intensities $(0 - 40 - 80 - 100 - 120 - 160kA/m)$.

It is important to stress that these measurements were made possible by the adoption of an innovative technique developed at the "Federico II" University of Naples, the so-called $ON - OFF$ technique [1]. Indeed, this technique allows the physical separation

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[1] On the other hand, being the MNP concentration at target low, the separation achieve via the differential measure is almost exact

of the weak magnetic response (due to the low concentration that can be targeted on the tumor) from the strong electric response of the scenario (the solvent: water or PBS).

2.2 Phantom DSP

In Ilmenau, the first week has been aimed at getting an insight in the facilities and the techniques developed by the Host Institution. After this introductory stage, the characteristics of the Tissue Mimicking Phantoms (TM Phantom) [4] used for the experimental campaigns, together with the procedures adopted to create it have been studied.

The adopted TM phantom is a mixture of water, kerosene and oil [5], whose proprieties rely on the oil content. Hence, TM Phantoms mimicking healthy tissues,with 40% oil content, have been built. This approximately corresponds to group II of adipose-defined tissue (31%-84% adipose tissue) according to [5].

Overall, as already said, by only varying the oil content, the dielectric properties of the obtained TM Phantom can fit all the tissues within the breast. For sake of completeness, a dielectric spectroscopy of three different oil-content-TM phantoms has been performed (25-40-55% of oil). The achieved results are in agreement with [5]. Such a dielectric spectroscopy has been performed using an M-Sequence UWB radar developed at TU-Ilmenau, properly adapted to work as a VNA, together with an Agilent probe.

2.3 Measurement SetUp & First Experimental Campaigns

To test the MNP enhanced UWB breast cancer detection technique developed at TU-Ilmenau, a measurement scenario, similar to the one in [2], has been set up.

M-Sequence sensor technology has been used together with very small active broadband dipole antennae in direct contact with the TM Phantom. The equivalent sampling frequency of the used device is $10.09GHz$, with an instantaneous bandwidth from $100MHz$ up to almost $5GHz$.

The antennae are fabricated on Rogers® 4003 substrate (0.5mm) using PCB technology. The dimension of the bow-ties are 8 mm x 4 mm with a differential fed, realized by a differential amplifier circuit. Using a programmable power supply plugged to the electromagnet, it was possible to achieve different magnetic field values, determined by measuring the absolute magnetic flux density using a Gauss Meter (Model 7030 Gauss/Tesla Meter, F.W. Bell, Milwauki, USA).

By applying this external MF applied, it has been possible to modulate MNPs response enhancing the contrast, obtaining different signals depending on the MF strength.

The experimental campaign is different from the one in [2], since in the present study a TM phantom of 10cm has been adopted. As in [2], the antennae have been placed on both sides of the phantom, so to detect both the reflected and the transmitted signals. Notably, thanks to the larger dimension of the phantom, the antennae are located at a larger distance from the magnet poles, so that it has been possible to avoid (almost completely) the interaction between the MF and the (active) antennas. Figure 1 shows the adopted measurement setup.

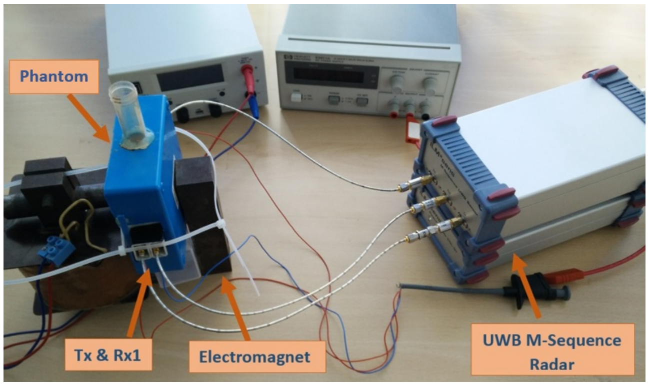

Figure 1: *Picture of the experimental measurement setup for MNPs contrast investigations.*

Two measurement campaigns have been carried out: the first one varying the MNP concentration inside the dilution hosted in a test glass mimicking the tumor (ø=1.5cm), and then varying the volume where the same amount of MNPs was diluted.
The results are described below.

2.3.1 Analysis when changing the concentration

This experimental campaign has been carried out keeping the volume mimicking the tumor mass constant ($2ml$ of distilled water) and varying the magnetite mass diluted in it ($5, 10, 15, 20, 30, 40, 50mg$). Each concentration has been measured applying $20 - 40 - 60kA/m$.

As expected, the signal scattered by the MNPs is proportional to the iron mass, and a linear trend can be clearly seen from both the transmission and the reflection signals.
The remarkable result of this analysis is the possibility of detecting the signal scattered by a MNP concentration of just $2.5mg/ml$ in a $10cm$ Phantom, with a low possibility of false detection. This is possible when an external MF of, at least, $40kA/m$ is applied.
For what concerns these first trials, due to the impossibility of reaching higher MF strengths, it is possible to state that, for this existing system, the optimal working conditions, that is those for which the MNPs response is maximized, are achieved when applying the largest MF allowed by the available magnet (i.e., about $60kA/m$).
A first check on the obtained results has been made performing the same measurements, when varying the MF intensity but without diluting any iron mass in the test glass mimicking the tumor, where, for sake of comparison, $2ml$ of distilled water were placed. As predictable, due to the non-magnetic behavior of the TM Phantom, of the distilled water in the test glass and the plastic test glass itself, no signal variation can be detected by applying an external MF (whatever the intensity).

2.3.2 Analysis when changing the volume

To asses which is the smallest volume detectable by MNP enhanced UWB radar system, a dual experiment with respect to the one described above has been performed. In this case, the iron mass diluted in the distilled water host in the "tumor" was kept constant (40mg of magnetite), while the tumor volume was varied ($0.5, 1, 1.5$ and $2ml$).

According to the previous result, the adopted PMF intensity has been the "optimal" one, that is, 60kA/m.

By using the same notation as in [3], let $\triangle v(t)$ be the differential measured voltage at the receiver antenna. Then, the signal detected is given by:

$$\triangle v(t) = Cm_{Fe}\frac{\partial \mu_{Fe}}{\partial H} \mid \times x(t-\tau)\triangle H, \tag{1}$$

where C is a constant proportional to the geometry, m_{Fe} is the iron mass, $\triangle H$ is the change of the MF and $x(t-\tau)$ is the time shape of the received signal, which is not influenced by the MF. The reader is refereed to [3] for detailed parameters description.

According to (1), the magnitude of the detected signal is proportional to the total mass of the magnetite, but it does not depend on the volume within the particles are diluted. This has been indeed observed in both the transmission and the reflection configuration, but only over the volume range $1-2ml$. When the same amount of iron mass ($40mg$) is diluted in a volume of $0.5ml$, the scattered signal is lower, as compared to the case when the tumor mass is above $1ml$.

The result of this analysis is that, by applying a MF of 60kA/m, it is possible to detect, with a really low possibility of false detection, the signal associated with a volume of 0.5ml.

2.4 Optimal MF modulation

In order to succeed in assessing the optimal working condition in terms of MF intensities to optimize the detected signal, the bandwidth of the a TM Phantom has been measured, by simply transforming via Fourier the transmission signal, measured in time domain. This result gives the possibility to determine the bandwidth of the system, defined as $-10dB$ Band (see figure 2). Given the bandwidth, the broadband spectroscopy carried out in the preliminary stage allows to find out which are the two MF intensities that maximize the differential signal (and hence the contrast enhancement due to the MNPs) between the ON and OFF stages of the measurement process.

2.5 Blind Detection Procedure by mean of ACF

In the described measurements, the detected signal has been estimated by direct inspection of the radargram (after an appropriate background subtraction procedure) at the suitable propagation time.

This implies to identify, in the radargram, the propagation time where MNPs response occurs. It follow that, since the test glass, holding the MNPs diluted, has a diameter of $1.5cm$, the propagation time at which the scattered signal has to be expected is not

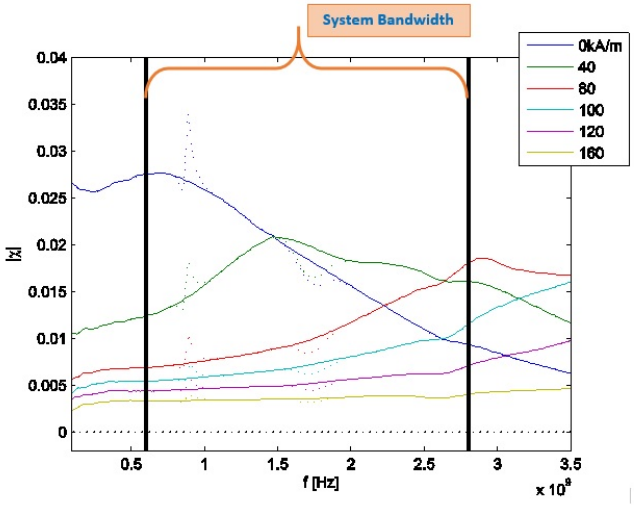

Figure 2: $|\chi|$ *when different PMF are applied together with the system bandwidth.*

a single propagation time sample, but it covers more than 10 samples in the propagation time direction, (this comes from the limited bandwidth of the antennas and the propagation medium). Moreover, due to the background subtraction procedures and to the drift, the peak of the contrast signal can slightly differ, in the propagation time direction, from sample to sample (taking into account that samples are equally spaced in time with a $t_0 = 9.910810^{-11}s$).

To the aim of optimizing the detection procedure, a new blind procedure has been implemented. Such a procedure is based on the detection function:

$$\begin{aligned}\Xi(\phi,\psi) &= \frac{1}{\triangle t \triangle T}\int_{\triangle t}\int_{\triangle T} \triangle v_n(t,T) y_0(t-\phi) h_0(t-\psi)\, dt dT \\ &= \frac{1}{\triangle t}\int_{\triangle T} \zeta(t,\psi) y_0(t-\phi) h_0(t-\psi)\, dt,\end{aligned} \tag{2}$$

where

$$\zeta(t,\psi) = \frac{1}{\triangle T}\int_{\triangle T} \triangle v_n(t,T) h_0(t-\psi)\, dT \tag{3}$$

and $\triangle v_n(t,T)$ is the actual signal measured, affected by noise[2]. $y_0(t-\phi)$ and $h_0(t-\psi)$ are two a priori known functions: h_0 is the modulation of the magnet ($\triangle H(T) = kh_0(t)$) and y_0 has to be identified as $y_0(t) = \xi(t,\psi)$ itself, determining the autocorrelation function in the propagation time direction. The reader is refereed to [3] for more details.

As predictable, the trend of the detected signal obtained by varying the iron mass switches from linear to quadratic, since the autocorrelation function has been estimated.

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[2] Noise can be considered as white, sampling jitter can be neglected in m-sequence receivers

However, this can be seen only for the transmission measurements. Hence, the main drawback of this detection procedure is the impossibility of applying it to reflection measurements.

Since the geometry wherein the antennas are placed for the reflection measurements, the antenna cross-talk is large as compared to the signal to be detected. In principle, this problem could be overcome by the background subtraction procedure. However, due to the temperature drift (consisting in shift and gain drift) occurring during the time required for the measurement procedure, the background removal is only partially effective, thus impairing, at least for these preliminary experiments, the possibility of applying the blind detection procedure to reflection measurements.

2.6 Broadband MNPs diluted Spectroscopy by means of M-Sequence UWB Tech

The last step of this STSM has been to perform, for the first time, a broadband spectroscopy (as in par. 2.1), by means of the coaxial cell (developed at the "Federico II" University and CNR-IREA) jointly used with the M-Sequence UWB Technology mimicking a VNA (developed at TU-Ilmenau).

For the sake of comparison, the same sample as the one in par. 2.1 has been used. This broadband spectroscopy measurement campaign has been carried out using the same ON-OFF approach [1], and by applying different MF intensities (0, 40, $80 kA/m$).

It is worth to remark that, apart from the adopted device, several differences arise with respect to the spectroscopic characterization carried out during the preliminary stage done in Naples. First, due to the limited strength of the electromagnet available at TU-Ilmenau, the MNPs OFF data were collected with a lower MF intensity value (actually one third) as compared to the intensity used in Naples. Second, due to the geometry of the magnet, the MF distribution in the air gap between the poles where the coaxial cell is placed highly inhomogeneous, whereas the CNR-IREA magnet ensures a quite uniform field along the cell.

This notwithstanding, the results achieved by these first trials are fully consistent, in terms of signal strength, with those achieved in Naples (see par. 2.1). On the other hand, the band wherein those results are reliable is very narrow since the MF exploited for *"switching off"* MNPs response is not strong enough. Moreover, probably due to the inhomogeneity of the field, the shift achieved by applying an external MF is quite different from the results in par. 2.1, and this will be matter of further investigations.

3 Description of the main results obtained

In this STSM, it has been possible to move some meaningful steps towards the development of MNPs enhanced breast cancer detection via M-sequence UWB radar.

Despite the weakness of the signal associated with the MNPs, due to the very low concentration that can be biologically targeted on the tumor, the experimental campaigns carried out during the STSM indicate the possibility to detect a MNPs permeability change induced by a MF. Two different degrees of freedom have been investigated: the behavior of iron mass targeted on the tumor and the volume of the tumor itself.

From the first, as predictable a linear trend with respect to the iron mass can be clearly recognized. The latter have laid the groundwork for further investigation.

By and large, for this existing system, with a given bandwidth (see black vertical lines in figure 2), by mean of an ONOFF modulation, the optimal choice of the two MF intensities, in order to maximize the contrast signal are 0 and $60kA/m$. This will be matter of further joint investigation (see next paragraph).

In the end, the groundwork for a blind detection procedure was laid.

4 Future collaboration with the host institution

As a result of this synergic and fruitful cooperative work fostered by the STSM, hopefully, it would be of great interest to give an answer to some open questions raised during these months.

First, the UWB system used to perform the two campaigns (concentration and volume dependence) will be used together with the electromagnet availble at CNR- IREA, to test the effect of using larger MF intensities. This is expected to allow reaching a better ON-OFF sepration, thus further improving the "optimality" of the working conditions.

Moreover, due to the impossibility to dilute the same amount of iron mass in a volume smaller than $0.5ml$, it was not possible to go deeper in the volume dependence measurement campaign. Hence this point will be matter of further joint investigations as well.

Finally, it will be of great interest to further develop the blind detection procedure, extending it to reflection measurements as well.

5 Confirmation of the host of the successful execution of the STSM

We confirm that GENNARO BELLIZZI from CNR-IREA worked in our laboratories at TU Ilmeanu from April 20^{th} to July 16^{th}, 2015.

He has shown large engagement in his work and he was well connected to the members of the lab. He also demonstrated great skill in the handling of a new sensor technology.

The visit has been successful and the results, which we will foster further cooperation between the two involved institutions and provide the basis for joint publications, are described in this report, which I confirm.

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