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Simona Di Meo, Simona Di Meo, Lorenzo Pasotti, Ioannis Iliopoulos, Marco Pasian, et al.. Tissue-mimicking materials for breast phantoms up to 50 GHz. *Physics in Medicine and Biology*, 2019, 64 (5), pp.055006. 10.1088/1361-6560/aafec . hal-02079680

HAL Id: hal-02079680

<https://univ-rennes.hal.science/hal-02079680>

Submitted on 26 Mar 2019

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Tissue-mimicking materials for breast phantoms up to 50 GHz

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Abstract

Millimeter (mm)-wave imaging has been recently proposed as a new technique for breast cancer detection, based on the significant dielectric contrast between healthy and tumor tissues. Here we propose a procedure to fabricate, electromagnetically characterize and preserve realistic breast tissue-mimicking phantoms for testing mm-wave imaging prototypes. Low-cost, non-toxic and easy-to-produce mixtures made of sunflower oil, water and gelatin were prepared and their dielectric properties were for the first time measured in the [0.5-50] GHz frequency range using a coaxial probe kit. Different oil and gelatin percentages were tested. An alternative recipe based on a waste-oil hardener was also proposed. Finally, water and sunflower oil were investigated as preservation media. The mixtures electromagnetic properties were in good agreement with those of human breast *ex vivo* samples. By changing the ingredient concentrations or using different solidifying agents it was possible to mimic different tissue types. Besides, we show that sunflower oil represents an effective preservation medium for the developed materials. The first breast phantom mimicking a tumor mass into healthy tissues up to 50 GHz was also successfully fabricated. Results demonstrated the potential of the designed recipes to mimic breast tissues with different biological characteristics,

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6 preserving dielectric properties over time. Thus, this study represents a fundamental step towards the development of
7 heterogeneous breast phantoms able to mimic the electromagnetic behavior of healthy and tumor tissues for mm-wave imaging
8 applications.
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12 **Keywords:** breast cancer, breast phantoms, cancer screening, dielectric properties, microwave imaging, millimeter waves,
13 preservation media, mixtures
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20 21 **1. Introduction**

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24 Breast cancer is one of the main causes of cancer-related death among women worldwide (American Cancer
25 Society 2017). Early diagnosis is fundamental to increase the survival rate, and several mass screening programs
26 have been proposed to address this major healthcare problem.
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30 Nowadays, there are many diagnostic techniques for breast cancer detection. However only X-ray mammography
31 is used for screening purposes, thanks to its high image resolution and limited costs. It is especially suited for older
32 women, with a larger breast-fat content, that statistically represent a high-risk group. On the other hand,
33 mammography exposes patients to ionizing radiation, and it involves breast compression, which can cause
34 discomfort and pain. Other breast imaging techniques, mostly employed for diagnostics but not for screening
35 purposes, include ultrasound (which is especially used in younger women with denser breasts, i.e., with a lower fat
36 content), Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Positron Emission Tomography
37 (PET) (which however are more expensive and time-consuming), or new Ultrasound Computed Tomography (Duric
38 *et al* 2014) and PhotoAcoustic research systems (Piras *et al* 2010).
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50 Microwave imaging systems have been proposed as an alternative technique for breast cancer detection (Nikolova
51 2011), based on a dielectric contrast between healthy and cancerous tissues. These include both tomographic
52 systems (Grzegorzczuk *et al* 2012) able to provide quantitative maps of breast tissue dielectric properties, and radar
53 imaging systems (Fear *et al* 2013, Preece *et al* 2016, Bahramiabarghouei *et al* 2015) operating up to 10 GHz. Several
54 large-scale studies for the dielectric characterization of breast tissues have been carried out on *ex vivo* samples
55 (Lazebnik *et al* 2007a, 2007b), and promising results have been achieved. Microwave imaging systems would
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indeed allow a risk-free diagnosis for the patients, including low-cost instrumentation, thus representing an attractive complementary technique to mammography. However, current challenges still include the heterogeneity of breast tissues and penetration depth limits imposed by losses inside tissues, especially in fibroglandular ones. Furthermore, the prototypes currently available have a limited spatial resolution (Klemm *et al* 2012, Martellosio *et al* 2017) because their central operating frequencies are in the low GHz range, with relatively narrow bandwidths.

A possible solution to this last problem is to move towards millimeter (mm)-waves with wider bandwidths (Töpfer and Oberhammer 2015), which could be of particular interest for imaging of breasts with a high percentage of adipose tissues, that are indeed representative of a significant percentage of older women. In fact, for fibroglandular tissues the use of low frequencies could be somehow compensated by the high value of the dielectric permittivity ϵ of the tissue itself, in particular by the real part ϵ' (the wavelength in air is in fact roughly rescaled by the square root of ϵ'), leading to an adequate resolution even if working in the microwave range. Instead, for very fat tissues, this rescaling is comparatively modest (low values of ϵ'), thus higher frequencies are required to improve spatial resolution. Besides, in such tissues the water content is reduced and also the imaginary part of ϵ is low; thus, signal attenuations are limited and good penetration depths can be achieved in spite of the higher frequencies involved.

As a first step towards this aim, some of the authors carried out a dielectric characterization campaign of human breast tissues up to 50 GHz (Martellosio *et al* 2015, 2017, Di Meo *et al* 2017a, 2018a) to experimentally assess the persistence of a significant dielectric difference between tumor and healthy tissues at mm-wave frequencies. The same authors then proposed a feasibility analysis, based on full-wave numerical simulations, of a mm-wave imaging system based on a multi-static architecture operating at 30 GHz. It was shown that a tumor-like target embedded in fat tissues at a 4 cm depth could be successfully detected with a resolution of a few millimeters (Di Meo *et al* 2017b).

A further fundamental step towards the development and testing of a micro/mm-wave imaging prototype is the design of realistic breast tissue-mimicking phantoms. Such phantoms allow the assessment of the imaging system performance, as well as the study of algorithms for signal processing and image reconstruction, under well-controlled and reproducible conditions. Several research groups worldwide have been working on tissue-mimicking materials for breast phantoms, either investigating relatively simple oil-in-gelatin mixtures or more complex chemical compositions, possibly for 3D printing technology. As an example, a mixture of gelatin, water, grape seed oil, propylene glycol, and commercial dishwashing liquid was characterized between 1 and 4 GHz (Henin *et al*

2015). Bakar *et al.* (2011) proposed a mixture of propylene glycol, water, gelatin, grape seed oil, commercial dishwashing liquid, formalin, and glyoxal or glutaraldehyde in order to mimic low-density (i.e. fatty) tissues, and characterized the obtained mixture in the 3-11 GHz frequency range. For high-density tissues, instead, they developed a different composition consisting of agar, vegetable oil, dishwashing liquid, and corn-flour. Lazebnik *et al.* (2005) proposed mixtures composed by different percentages of kerosene and safflower oil to mimic the dielectric properties of human breast tissues up to 20 GHz. Based on this work, different percentages of p-toluic acid, n-propanol, deionized water, 200 Bloom gelatin, formaldehyde, oil, and detergent were used to emulate fat, gland, skin, and cancer tissues, and they were characterized between 1 and 6 GHz (Porter *et al* 2010). Some solutions based on 3-D printing technology have also been introduced (Lazebnik *et al* 2005, Porter *et al* 2010, Epstein *et al* 2011, Hahn and Noghianian 2012).

The preservation of phantoms is also a fundamental aspect to ensure the reproducibility of measurements over time. Strategies involving formaldehyde or formalin solutions have been proposed in the literature, and the dielectric properties of the preserved mixtures were measured up to 20 GHz (Lazebnik *et al* 2005, Madsen *et al* 2006). Vinegar was also proposed as a preservation medium for gelatin-based mixtures, but measurements were done only in the 1-6 GHz frequency range (Said and Seman 2017). In (Matrone *et al* 2017), a solution of water and benzalkonium chloride (Lysoform, Lever) was used to preserve a phantom made of agar, developed for ultrasound imaging.

The main drawbacks of existing solutions are the following: i) some commonly used ingredients are toxic (e.g., formaldehyde), thereby requiring specific laboratory equipment to be handled; ii) sophisticated and costly equipment is needed for fabrication (e.g., 3D printed phantoms); iii) characterization is carried out in a limited frequency range, iv) quantitative guidelines for the rational design of phantoms with desired electromagnetic properties still have to be defined.

In this paper, we aim to design new, low-cost, easy to produce, non-toxic, and stable-over-time mixtures for breast phantoms. Starting from the basic ingredients of ultrasound phantom recipes (Madsen *et al* 1982, 2005, 2006), the electromagnetic behavior of the produced mixtures is for the first time investigated up to 50 GHz and compared to those of *ex vivo* human breast tissues obtained after surgery. The main novel contribution of this work consists in the development of a new general methodology to produce and preserve phantoms for diagnostic applications. The electromagnetic behavior of such phantoms can be tuned by adjusting the concentration of the mixture components to accurately mimic healthy and cancerous tissues, with different adipose content.

2. Materials and methods

A realistic breast tissue-mimicking phantom for mm-wave imaging has to satisfy several requirements. First, it has to mimic the dielectric properties of real tissues in a target frequency range. Second, its electromagnetic properties have to be stable over time. Third, it is preferable that neither its production nor its preservation require expensive and/or toxic means.

The aim of this section is to introduce the design procedure of phantoms able to mimic different categories of human breast tissues (i.e. healthy and cancerous). As a reference, the dielectric permittivity ϵ of *ex vivo* breast tissue samples, measured during two experimental campaigns performed in 2014 and 2016 at the European Institute of Oncology (Milan, Italy) in (Martellosio *et al* 2015, 2017, Di Meo *et al* 2017a, 2018a), was considered.

2.1 Experimental setup

The experimental setup included both instrumentation for mixture preparation (Fig. 1a) and dielectric characterization (Fig. 1b), i.e.:

- two magnetic hot-plate stirrers (BICASA, IKA-COMBIMAG RCT);
- several glass beakers, graduated cylinders and an electronic pipettor;
- an open-ended coaxial probe (Keysight 85070E Dielectric Probe Kit), able to perform measurements in 0.5–50 GHz range;
- a Vector Network Analyzer (VNA, Keysight E8361C), used to drive the coaxial probe, as well as to retrieve, monitor, and store the dielectric permittivity of the Material Under Test (MUT);
- a high performance flexible coaxial cable (provided with the Keysight 85070E Dielectric Probe Kit), to connect the VNA to the coaxial probe;
- a mechanical positioner to keep the probe fixed during measurements;
- a mechanical mover to put the MUT in contact with the probe, which is kept fixed;
- a digital balance to control the small pressure applied on the MUT while placing the probe over it, which was necessary to avoid any air presence between the tip of the probe and the sample;
- a personal computer to store the data acquired by the VNA and to process them using Matlab (The MathWorks) or Microsoft Excel.

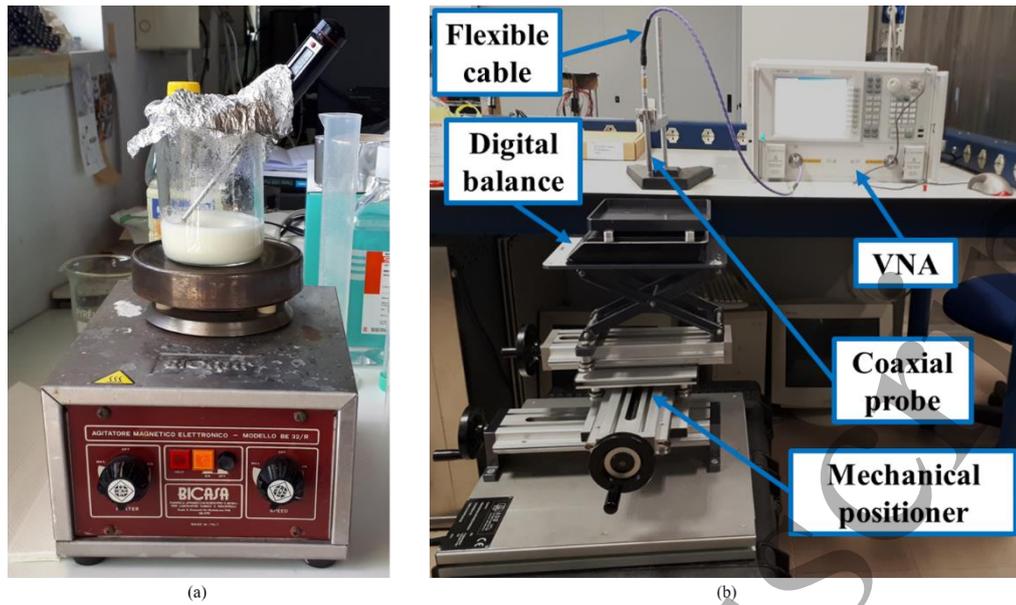


Figure 1. (a) Magnetic hot-plate stirrer during mixture preparation and (b) experimental measurement setup for dielectric characterization.

The measurement setup, preliminary discussed in (Di Meo *et al* 2018b) for the part related to the dielectric characterization, is the same as in the aforementioned experimental campaigns described in (Martellosio *et al* 2015, 2017, Di Meo *et al* 2017a, 2018a).

2.2 Mixtures preparation

Phantom materials were prepared according to the protocol described below. The composition of the fabricated mixtures is reported in Table 1. The reagents were measured using high-precision scale, graduated cylinders, or electronic pipettor.

For gelatin-based phantoms, gelatin (#G9382, Sigma Aldrich) was dissolved in deionized water (Millipore) by slowly heating the mixture up to 85°C and continuously stirring the solution on a magnetic hot-plate stirrer. The glass beaker containing the solution was tightly covered with an aluminum foil to prevent water evaporation. Heating was switched off when the solution was clear and then temperature was allowed to decrease to about 65°C. Sunflower oil (Esselunga) was heated to about 65°C and it was added to the water-gelatin mixture with dishwashing liquid (Dexcal) to form an emulsion, appearing as a uniform, dense, pale liquid. Stirring continued until temperature fell below 50°C, then the mixture was allowed to polymerize for about 3.5 h at room temperature (~25°C).

Table 1. Composition of phantom mixtures

Mixture	Tissue mimicked	Deionized water (ml)	Gelatin (g)	Sunflower oil (ml)	Dishwashing liquid (ml)
G5	-	68	3.4	0	3.8
G10	-	68	6.8	0	3.8
G20	-	68	13.6	0	3.8
G16O20	Malignant	68	13.6	17	3.8
G8O20	Malignant	68	6.8	17	3.8
G6.6O33.3	High-density	68	6.8	34	3.8
G5O50	Medium -density	68	6.8	68	3.8
G3.3O66.6	Low-density	68	6.8	136	3.8
Mixture	Tissue mimicked	Deionized water (ml)	Waste-oil hardener (g)	Sunflower oil (ml)	Polysorbate 80 (ml)
K5.7O95	Low-density	2.6	3	50	4

Mixtures with gelatin and waste-oil hardener as solidifying agent are indicated with the G and K prefix, respectively; O denotes sunflower oil. Numbers in mixture names indicate gelatin/waste-oil hardener and sunflower oil percentages, respectively.

A novel procedure is also proposed here to produce low permittivity and relatively low loss phantoms emulating fat tissues, which could not be easily mimicked by gelatin-based mixtures due to the very high oil percentage. The procedure is based on a waste-oil hardener (Kokubo & Co. Ltd., Japan). The ingredients used to produce a 5% volume concentration (v/v) water-in-oil phantom are detailed in Table 1.

Sunflower oil and deionized water were added into a beaker and rapidly stirred at room temperature until an emulsion was formed. Then, the surfactant (Polysorbate 80) was added while the emulsion was still being stirred. Once the surfactant was well diluted in the mixture, the waste-oil hardener was added. The beaker was then heated and continuously stirred (to ensure homogeneity) on a hot plate using an aluminum foil cap. When the temperature reached approximately 75°C, the waste-oil hardener became soluble in oil and its grains, previously floating in the mixture, disappeared. The mixture was removed from the hot plate, while continuously being stirred until its temperature reached 55°C. It could be then poured in the mold, where it solidified at around 40-45°C. The aforementioned procedure can be applied also to higher water concentrations: up to 15% v/v water-in-oil were tested and produced homogeneous phantoms (data not shown).

All solidified phantoms appeared as white-to-yellow materials (Fig. 2) with color and consistency dependent on the amount of solidifying agent and oil/water ratio. In all cases, the added volume of dishwashing liquid/polysorbate (reported in Table 1) was not considered when calculating the final percentages. The addition of the solidifying

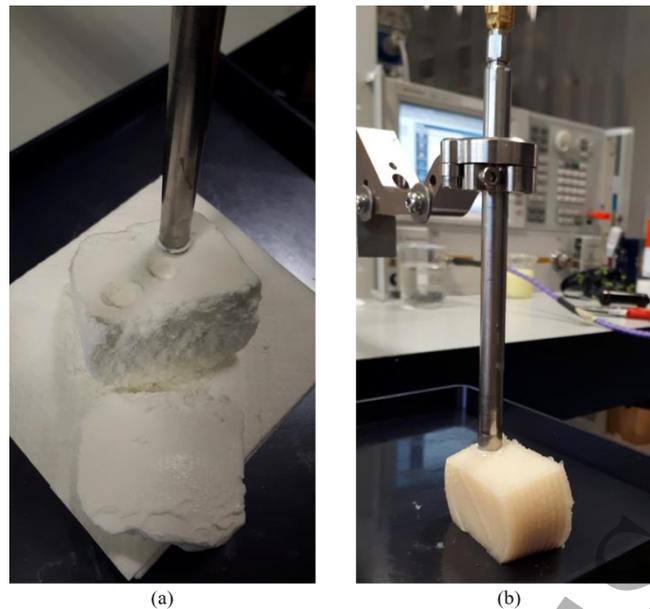


Figure 2. Example of produced (a) gelatin-based and (b) waste-oil-hardener-based mixture during dielectric measurements with the coaxial probe.

agent (gelatin or waste-oil hardener) changed the final volume by less than 5% in the worst case and, for this reason, the final mixture volume and its ingredient concentrations were not further corrected, considering the volume change negligible.

2.3 Phantom preservation protocol

One of the most important aspects for a durable tissue-mimicking mixture is the stability of its electromagnetic properties, in order to ensure a reliable testing of the imaging system prototype over time. In this paper, two simple, easy-to-manage and inexpensive materials (i.e. deionized water and sunflower oil) were tested as preservation media for the developed mixtures.

We previously showed the effectiveness of oil as preservation medium for a medium-density tissue-mimicking phantom (G5O50) (Di Meo *et al* 2018c) compared to deionized water and no-medium conditions. Following an analogous protocol, we confirmed the superior preserving capability of oil for a malignant tissue-mimicking phantom (G16O20). As in (Di Meo *et al* 2018c), the collected data are compared to the dielectric measurements performed on a phantom sample in air, i.e., with no preservation medium. Six measurements were taken over ten days, 96/144/168/192/216/240 hours after the sample preparation (*Reference*), and they are referred to as



Figure 3. The three samples of G16O20 mixture preserved (from left to right) in sunflower oil, deionized water and air.

Day4/6/7/8/9/10, respectively. Fig. 3 shows the three samples of G16O20 immersed in sunflower oil, deionized water and in air.

3. Results

In the following pages, results obtained over the 0.5-50 GHz range will be presented. In particular, the focus will be on measurements at 30 GHz, which is the central frequency we are targeting for the development of a novel mm-wave imaging system. These values will be additionally compared to those achieved at 4 GHz, in order to provide a more general overview of performance achieved in the microwave frequency range.

3.1 Dielectric characterization of the produced gelatin-based mixtures

3.1.1 Oil percentage impact on permittivity.

Human breast tissues can be divided in four categories (i.e. low/medium/high-density healthy tissues, depending on their adipose content (Di Meo *et al* 2018a), and malignant tissues), as shown in Table 2.

Fig. 4 shows the comparison among the dielectric permittivity of the produced mixtures (G8O20, G6.6O33.3, G5O50, G3.3O66.6) and the average values of dielectric permittivity of the four categories of human breast tissues. The curves of the produced mixtures were obtained as the average of three measurements in three different areas on the phantom sample, as depicted in Fig. 5 and Fig. 2a. The solidified phantom mixture was cut in two halves and three measurements at increasing depths (with a step of about 1 cm between them) were acquired with the coaxial

Table 2. Breast tissue categories

Tissue category	Adipose content	Re(ϵ)* at 30 GHz	Im(ϵ)* at 30 GHz	Re(ϵ)* at 4 GHz	Im(ϵ)* at 4 GHz
Low density	$\geq 80\%$	6.27 ± 4.46	3.27 ± 5.33	11.70 ± 12.67	2.82 ± 4.01
Medium density	20% - 80%	11.48 ± 5.48	9.57 ± 6.97	27.00 ± 16.53	7.70 ± 5.40
High density	$\leq 20\%$	16.04 ± 5.04	15.54 ± 6.74	40.71 ± 15.39	12.20 ± 5.06
Malignant	-	18.80 ± 2.83	19.28 ± 4.23	48.55 ± 8.88	14.75 ± 2.89

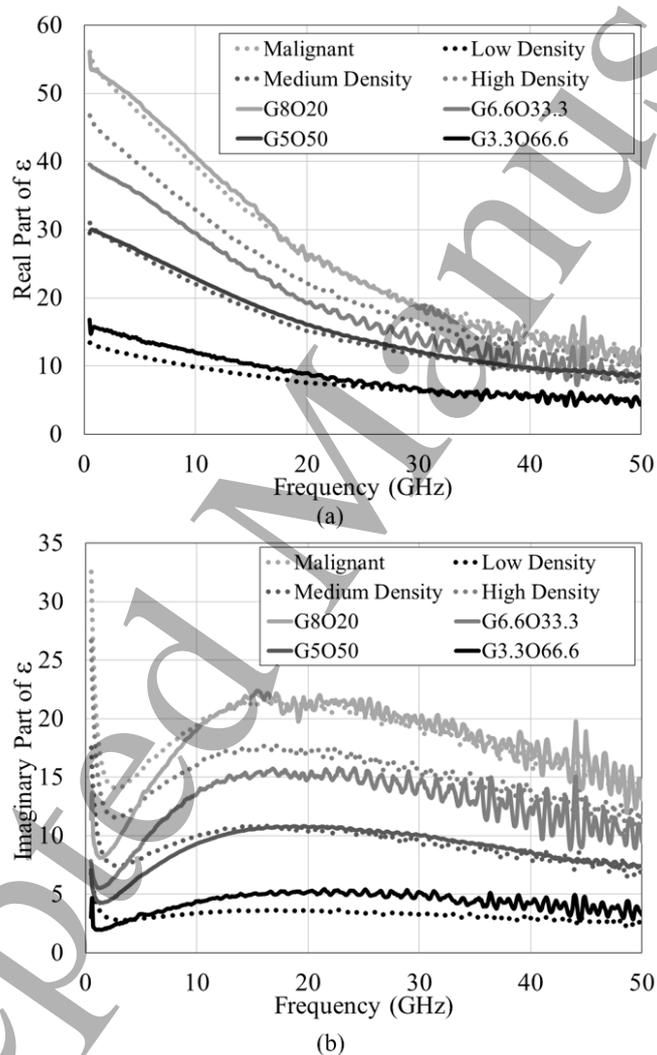
*Mean \pm standard deviation

Figure 4. Comparison between the average dielectric properties of human breast tissues, as reported in (Di Meo et al 2018a), and of the produced mixtures for the (a) real and (b) imaginary part of ϵ .

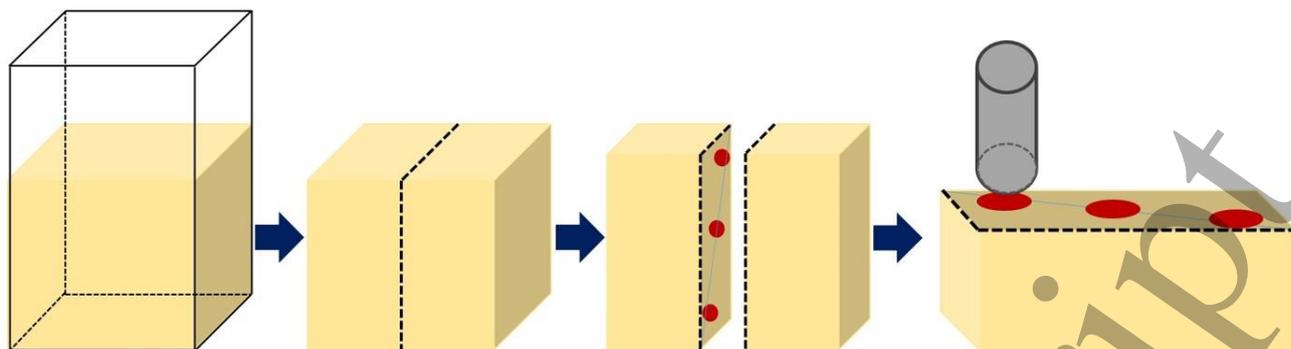


Figure 5. Schema of the measurement procedure: the solidified mixture is cut in two halves and three measurement sites (red areas), at increasing depths, are identified on the inner side of one of these two parts; the coaxial probe (grey cylinder) is then put in contact with the sample in each one of these points, and three measurements are acquired and averaged.

probe on the inner side of one of these two parts.

Differences among the three measurements were small in all the considered cases: the percent median absolute deviation (PMAD, i.e., the median of the absolute differences with the median, divided by median value) of the real and imaginary part of ϵ was lower than 3% and 2%, respectively, thanks to the homogeneity of the produced mixture. Given a mixture composition, the measured average values of ϵ at 30 GHz were also highly reproducible among independent tests in different days, in which the same mixture was fabricated. In such case, PMAD was typically lower than 3% and 5% for real and imaginary parts of ϵ , respectively. The reported variability indexes represent upper limits among the ϵ values at the frequencies of 4 and 30 GHz, which have been considered throughout the paper.

Overall, the plots in Fig. 4 show a very good agreement between measurements on *ex vivo* and phantom samples. In particular, in all the four conditions, the average ϵ at 30 GHz of the fabricated mixtures falls within the inter-subject variability range of human breast tissues measurements (reported in Table 2) (Di Meo *et al* 2018a). The same conclusion can be drawn also when working in the microwave regime, for example at 4 GHz (Table 2).

In addition, two aspects may be observed in Fig. 4. First, the ripple of the curves increases with the frequency, for both human breast tissues and the produced mixtures. This effect, while not impairing the overall trend of the measurement, is due to inaccuracies during the calibration of the coaxial probe, a common effect at such high frequencies (Martellosio *et al* 2017). The calibration of the coaxial probe is performed using three standards:

deionized water at a controlled temperature, air, and short-circuit. The measurements in air is straightforward, and the appropriateness of the measurement in water can be controlled accurately using a transparent glass for the water, in such a way that the presence of air bubbles on the probe tip can be avoided). On the other hand, for the short-circuit, this is provided using a customized metal block provided with the Keysight 85070E Dielectric Probe Kit. Especially at high frequencies, it can be difficult to guarantee the robustness of the contact between the probe tip and the metal block, and small imprecisions can hold. For this reason, the ripple is present both on phantom and *ex vivo* tissue measurement (in this last case the ripple is not visible on the curves shown in Fig. 4 thanks to averaging on more than 100 samples).

Secondly, in Fig. 4b it can be appreciated that the imaginary part increases at low frequencies. This effect can be attributed to the non-zero ionic conductivity of the dishwashing liquid (4.86 S/m, measurement performed using a HI 8733 conductivity meter [Hanna instruments]). Using different surfactant agents the conductivity can be ideally tuned to the desired value. As an example, dishwashing liquid with an higher conductivity can be used, or, vice-versa, alternative surfactant agents (i.e. Polysorbate 80, as will be shown in Section 3.3) can be used to reduce the conductivity. It is worth noting that the impact of the measured conductivity on the imaginary part of the permittivity at 4 GHz and above is in any case negligible.

In order to compare the obtained results with theoretical expectations, the Bruggeman formula (Bruggeman 1935) was used to get an estimate of the effective dielectric permittivity of the mixture, given the percentages of oil and water in it:

$$p \frac{\epsilon_{SFO} - \epsilon_{eff}}{\epsilon_{SFO} + 2\epsilon_{eff}} + (1-p) \frac{\epsilon_{H_2O} - \epsilon_{eff}}{\epsilon_{H_2O} + 2\epsilon_{eff}} = 0, \quad (1)$$

where ϵ_{H_2O} is the permittivity of water, ϵ_{SFO} is the permittivity of sunflower oil (SFO), ϵ_{eff} is the permittivity of the mixture and p represents the volumetric concentration of sunflower oil in the mixture.

Fig. 6 shows the permittivity values at 30 GHz of the produced mixtures, with different oil volume percentages, and those estimated by the Bruggeman formula. As a reference, also measurements in the microwave frequency range (i.e. at 4 GHz) have been included in the figure. A good agreement between them is shown in all cases, confirming the theoretical expectations, thereby paving the way to the rational design of breast phantoms with target dielectric properties.

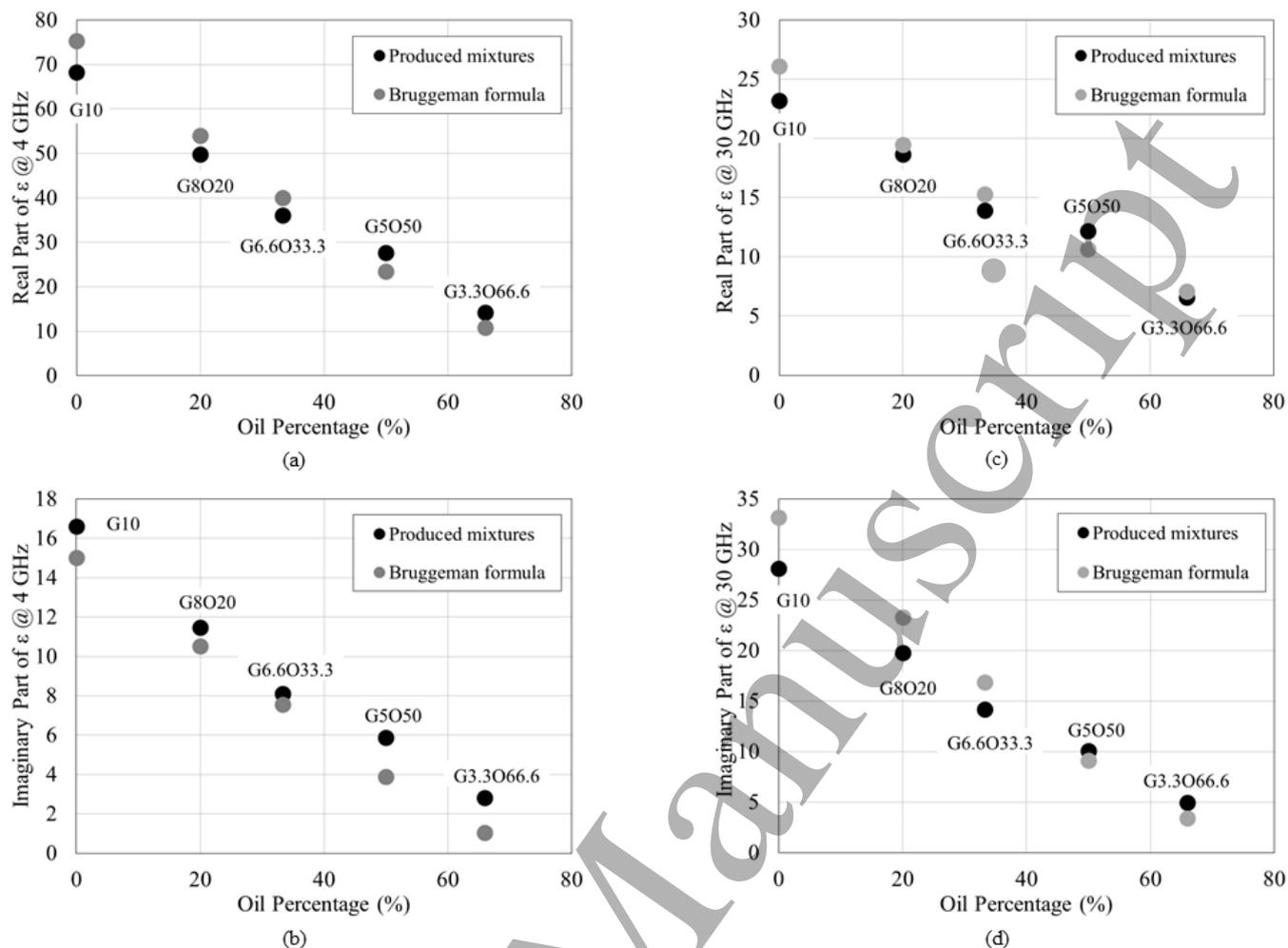


Figure 6. Comparison between the values of dielectric permittivity at (a, b) 4 GHz and (c, d) 30 GHz of the produced mixtures (G10, G8O20, G6.6O33.3, G5O50, G3.3O66.6) and the expected theoretical values obtained with the Bruggeman formula, for the (a, c) real and (b, d) imaginary part of ϵ .

3.1.2 Gelatin percentage impact on the permittivity of tumor-like mixtures

Since the clinical condition of a tissue has a direct impact on its stiffness (usually tumor tissues are stiffer than healthy ones (Sarvazyan *et al* 1995)), in order to create a realistic phantom it may be necessary to change the amount of solidifying agent. Thus, in this study we analyzed the relation between the amount of gelatin and the dielectric properties of the resulting phantom mixtures. We first prepared mixtures consisting of pure water with different gelatin percentages (cf. Table 1), in order to evaluate more clearly the impact of gelatin on ϵ . Fig. 7 shows that in general, by increasing the gelatin percentage, the dielectric properties of the produced mixtures decrease or remain almost constant. The same behavior can be observed also when fabricating phantom mixtures (i.e. with sunflower

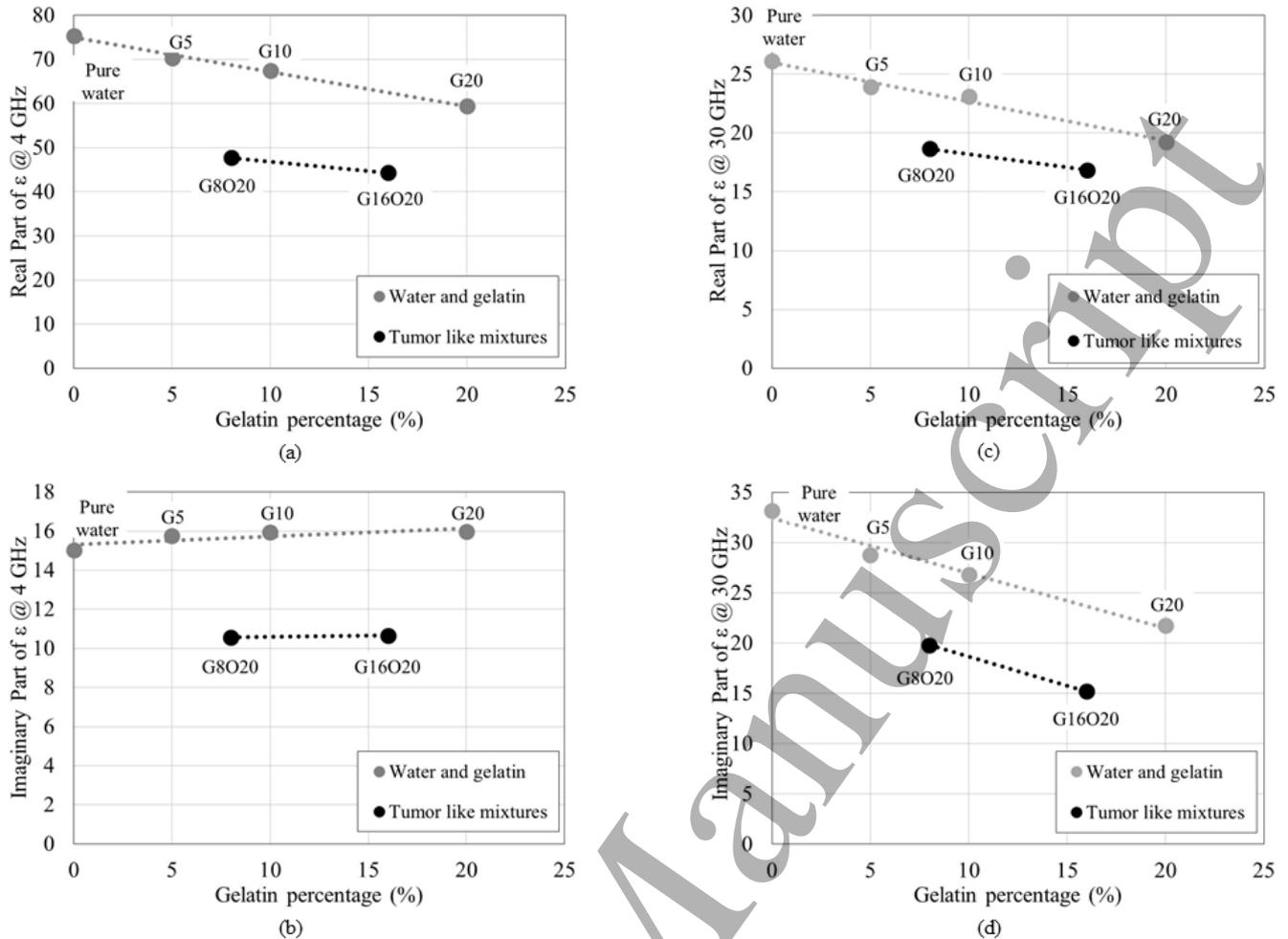


Figure 7. Comparison between the electromagnetic properties of pure water with different concentrations of gelatin and of G8O20 and G16O20, for the (a, c) real and (b, d) imaginary part of ϵ , at (a, b) 4 GHz and (c, d) 30 GHz. Dotted lines represent regression lines of the data illustrated with the same color.

oil, water, gelatin and dishwashing liquid). In Fig. 7 the permittivity of pure water with different gelatin percentages is compared to that of two mixtures mimicking malignant tissues (G8O20 and G16O20), which also shows a similar trend of ϵ when the gelatin concentration doubles.

In general, however, variations of ϵ are relatively low. For instance, Fig. 8 compares the permittivity of these two mixtures (G8O20 and G16O20) to that of human malignant tissues (mean value \pm standard deviation), showing that the dielectric properties of the phantoms are in both cases very similar to the target ones.

3.2 Mixture preservation

Fig. 9 compares the permittivity values at 30 GHz and at 4 GHz for G16O20 preserved in deionized water and

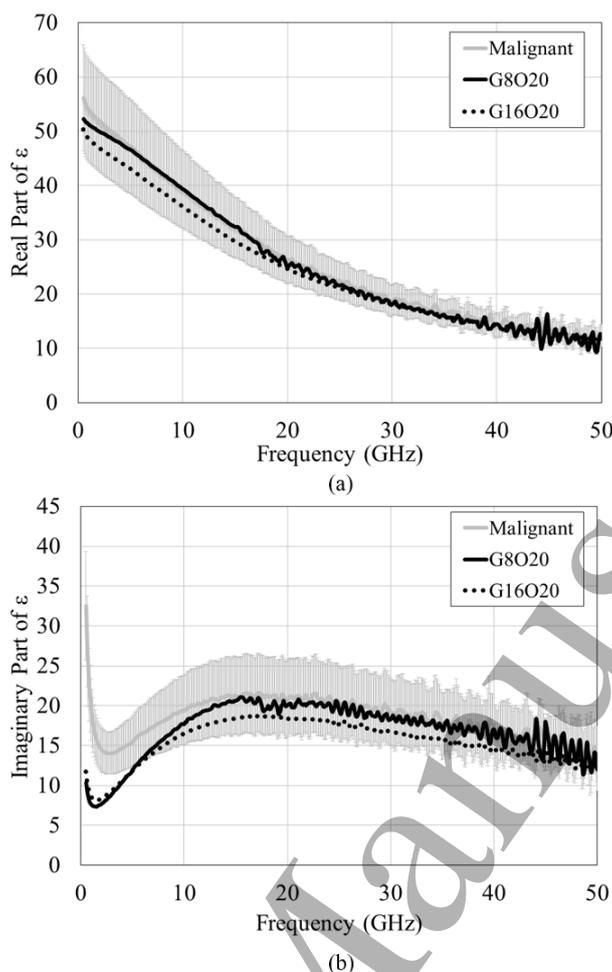


Figure 8. Comparison between G8O20, G16O20 and the average values of dielectric permittivity of human malignant tissues (mean \pm standard deviation), for the (a) real and (b) imaginary part of ϵ .

sunflower oil, or left without preservation medium. These results show that sunflower oil can be used as a preservation medium, since it allows the produced mixtures to maintain their dielectric properties almost unaltered over 10 days.

In Fig. 10, the comparison between the permittivity of G16O20 measured on the day of its preparation (*Reference*) and on the following days, when preserved in sunflower oil, is shown for the entire frequency band. When water is used as a preservation medium, instead, it is soaked by the solidified mixture, thus increasing its water content and consequently the permittivity of the mixture. On the contrary, when the phantom is preserved in air (no preservation medium), the water content reduces with time (water evaporation), resulting into a reduced permittivity. Similar results were obtained in (Di Meo et al 2018c) for G5O50 preservation, as well as for G3.3O66.6 (data not shown).

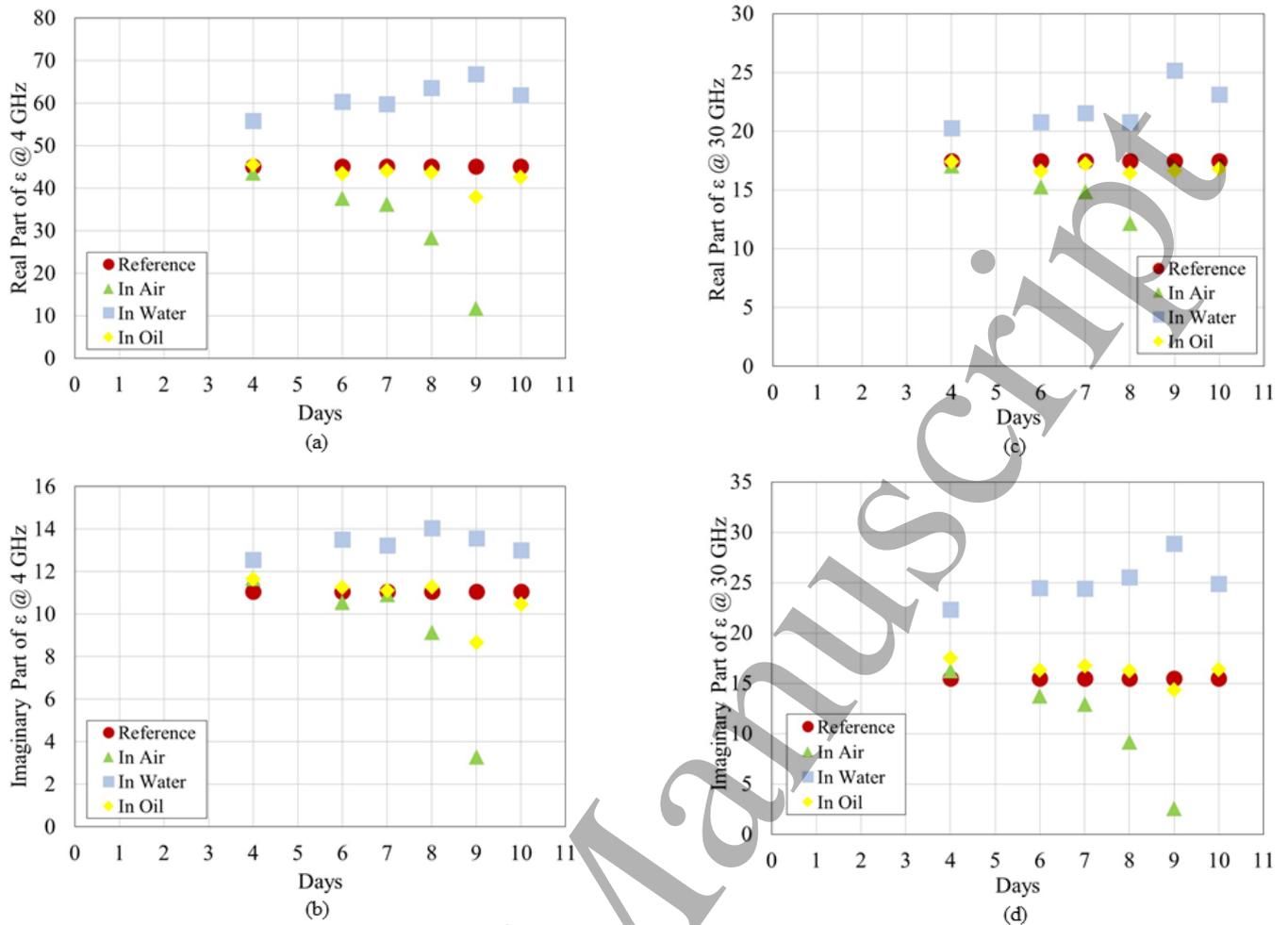


Figure 9. Comparison between the dielectric permittivity values for G16O20 preserved in deionized water, sunflower oil and air at (a, b) 4 GHz and (c, d) 30 GHz, for the (a, c) real and (b, d) imaginary part of ϵ .

3.3 Alternative mixtures with oil-hardener emulating breast tissues with a very high adipose content

Fig. 11 shows the comparison between the permittivity of human *ex vivo* tissues with low density and of the produced K5.7O95 mixture, obtained as an average between three measurements in different points on the sample.

These plots clearly demonstrate that with this novel composition it is possible to emulate tissues with a significantly low water content (adipose percentage close to 100%), therefore paving the way to the production of phantoms with increasing oil percentages. Indeed, such phantoms could be useful to emulate possible outlier fat tissue samples, considering the large variability in dielectric properties of low-density tissues. The aforementioned variability is shown in Fig. 11, where the shaded region represents the standard deviation.

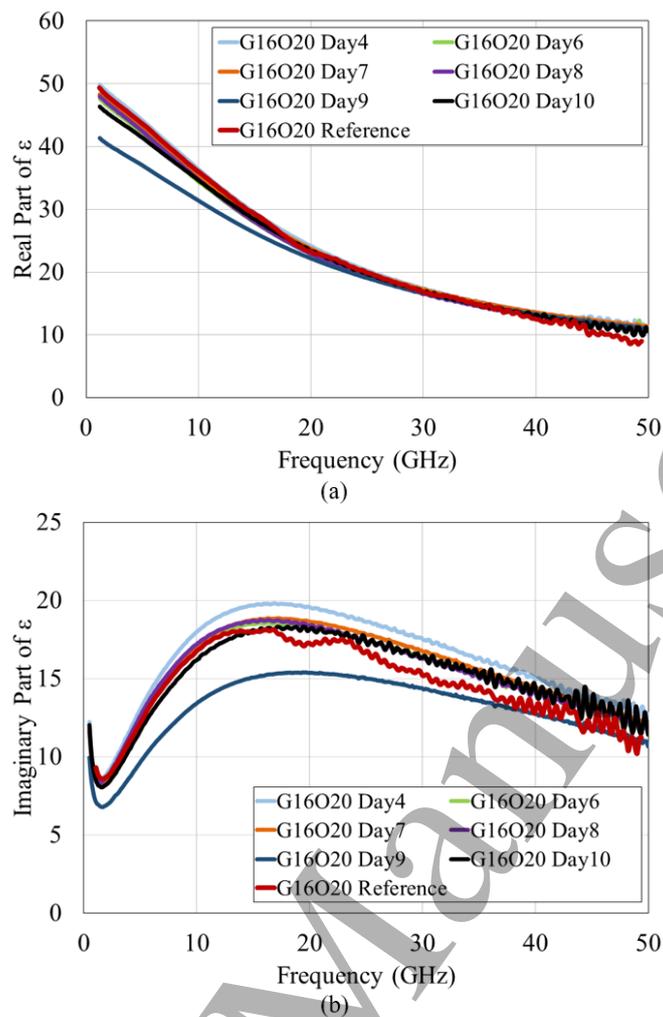


Figure 10. Comparison among the dielectric properties of G16O20 preserved in sunflower oil over 10 days, for the (a) real and (b) imaginary part of ϵ .

3.4 Breast phantom

In Fig. 12 a first example of a breast phantom, emulating a tumor mass inside a homogeneous tissue with no skin, is presented. The phantom is composed by G5O50 (medium-density tissue) with a G16O20 (tumor tissue) target embedded in it. Fig. 12a shows a lateral view of the phantom (12 cm diameter) and Fig. 12b shows its section, where the tumor-like inclusion is clearly visible.

4. Conclusion

A novel procedure to produce mixtures emulating the electromagnetic properties of human breast tissues is

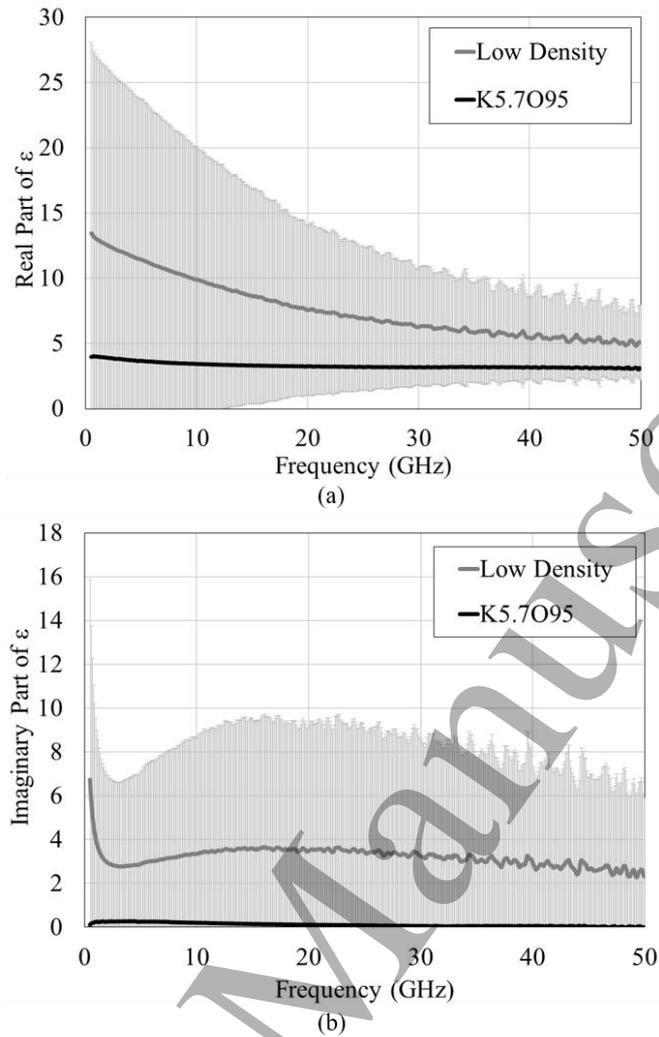


Figure 11. Comparison between the average dielectric properties of low-density breast *ex vivo* tissues (mean \pm standard deviation) and of the K5O90 mixture, for the (a) real and (b) imaginary part of ϵ .

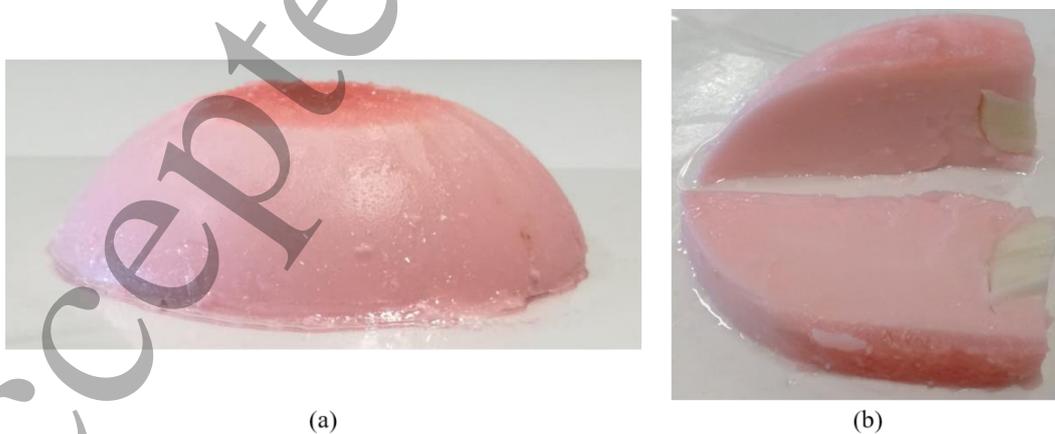


Figure 12. (a) Lateral view and (b) section of the heterogeneous breast phantom, composed by G5O50 and with a G16O20 inclusion.

presented. The proposed mixtures, consisting of sunflower oil, water and gelatin, are inspired by receipts used for ultrasound phantoms, and for the first time their permittivity is measured in the 0.5-50 GHz frequency range. The electromagnetic behavior of the mixtures was compared to the one of *ex vivo* samples directly collected from human breast tissues after surgery. Results demonstrate that, by varying the oil volume concentration, it is possible to accurately mimic different categories of breast tissues, both cancerous and healthy, as well as of different densities (i.e. adipose content). Outlier samples, with a particularly high fat percentage, can be also well emulated by using waste-oil hardener instead of gelatin and increasing the oil concentration.

The impact of the amount of solidifying agent (i.e. gelatin) on the dielectric properties of the produced mixtures was also analyzed, showing that it can be increased to mimic tissues in a more realistic way, without significantly affecting their dielectric properties. A more accurate characterization of the produced material elastic properties is foreseen as a perspective of this work.

Besides, sunflower oil is demonstrated to be an effective, low-cost and easy-to-manage means of preserving the developed phantom materials, without involving any toxic substance.

Altogether, the characterization results obtained by tuning mixture ingredients are of high significance for the rational design of breast phantoms with target dielectric properties.

Acknowledgements

This work was supported by the University of Pavia under the Blue Sky Research project MULTIWAVE.

The authors would like to thank Prof. Gabriella Cusella, Dr. Laura Benedetti, Dr. Gabriele Ceccarelli and Dr. Michela Casanova for providing reagents, materials and helpful advice.

References

- American Cancer Society 2017 Breast Cancer Facts & Figures 2017-2018, Atlanta: American Cancer Society, Inc. [Online].
<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf>
- Bahramiabarghouei H, Porter E, Santorelli A, Gosselin B, Popovic M and Rusch L A 2015 Flexible 16 antenna array for microwave breast cancer detection *IEEE Trans. Biomed. Eng.* **62** 2516–525
- Bakar A A, Abbosh A and Bialkowski M 2011 Fabrication and Characterization of a Heterogeneous Breast Phantom for Testing an Ultrawideband Microwave Imaging System *Proc. Asia-Pacific Microw. Conf. 2011*, Melbourne, Australia

- 1
2
3 Bruggeman D A G 1935 Berechnung verschiedener physikalischer Konstanten von heterogenen Substanzen. I.
4 Dielektrizitätskonstanten und Leitfähigkeiten der Mischkörper aus isotropen Substanzen *Annalen der Physik* **416** 636–64
5
6
7 Di Meo S, Espin-Lopez P F, Martellosio A, Pasian M, Bozzi M, Perregrini L, Mazzanti A, Svelto F, Summers P E, Renne G,
8 Preda L and Bellomi M 2017a Experimental Validation of the Dielectric Permittivity of Breast Cancer Tissues up to 50
9 GHz *Proc. IEEE MTT-S Intern. Microw. Workshop Series Advanced Materials and Processes*, Pavia, Italy
10
11
12 Di Meo S, Espin-Lopez P F, Martellosio A, Pasian M, Matrone G, Bozzi M, Magenes G, Mazzanti A, Perregrini L, Svelto F,
13 Summers P E, Renne G, Preda L and Bellomi M 2017b On the Feasibility of Breast Cancer Imaging Systems at Millimeter-
14 Waves Frequencies *IEEE Trans. Microw. Theory Techn.* **65** 1795-806
15
16
17
18 Di Meo S, Espin-Lopez P F, Martellosio, Pasian M, Bozzi M, Perregrini L, Mazzanti A, Svelto F, Summers P E, Renne G,
19 Preda L and Bellomi M 2018a Dielectric properties of breast tissues: experimental results up to 50 GHz *Proc. 2018 12th*
20 *Eur. Conf. Antennas Propag. (EuCAP 2018)*, London, UK
21
22
23
24 Di Meo S, Pasotti L, Pasian M and Matrone G 2018b Realization of breast tissue-mimicking phantom materials: dielectric
25 characterization in the 0.5-50 GHz frequency range *Proc. 2018 IEEE Intern. Microw. Biomed. Conf. (IMBioC)*,
26 Philadelphia, PA, USA
27
28
29
30 Di Meo S, Pasotti L, Pasian M and Matrone G 2018c On the Conservation of Materials for Breast Phantoms in the Frequency
31 Range 0.5-50 GHz *Proc. 48th European Microwave Conference 2018*, Madrid, Spain
32
33
34 Duric N, Littrup P J, Roy O, Li C, Schmidt S, Cheng X, Janer R 2014 Clinical breast imaging with ultrasound tomography: A
35 description of the SoftVue system *The Journal of the Acoustical Society of America* **135** 2155
36
37
38 Epstein N R, Golnabi A H, Meaney P M and Paulsen K D 2011 Microwave dielectric contrast imaging in a magnetic resonant
39 environment and the effect of using magnetic resonant spatial information in image reconstruction *Proc. 2011 Annu. Intern.*
40 *Conf. IEEE Eng.Med. Biol. Soc. (EMBC 2011)*, Boston, MA, USA
41
42
43
44 Fear E C, Bourqui J, Curtis C, Mew D, Docktor B and Romano C 2013 Microwave breast imaging with a monostatic radar
45 based system: a study of application to patients *IEEE Trans. Circuits Syst.* **61** 2119–28
46
47
48 Grzegorzczak T M, Meaney P M, Kaufman P A, diFlorio-Alexander R M and Paulsen K D 2012 Fast 3-D tomographic
49 microwave imaging for breast cancer detection *IEEE Trans. Med. Imag.* **31** 1584–92
50
51
52 Hahn C and Noghianian S 2012 Heterogeneous Breast Phantom Development for Microwave Imaging Using Regression Models
53 *Intern. J. Biomed. Imag.* **2012** 803607
54
55
56 Henin B, Abbosh A M and Abdulla W A 2015 Electro-Biomechanical Breast Phantom for Hybrid Breast Imaging *Proc. 2015*
57 *International Symposium on Antennas and Propagation (ISAP)*, Hobart, Tasmania, Australia
58
59
60 Klemm M, Craddock I J and Preece A W 2012 Contrast-enhanced breast cancer detection using dynamic microwave imaging

- 1
2
3 *Proc. 2012 IEEE Antennas Propagation Soc. Intern. Symp., Chicago, USA*
- 4
5 Lazebnik M, Madsen E L, Frank G R and Hagness S C 2005 Tissue-mimicking phantom materials for narrowband and
6
7 ultrawideband microwave applications *Phys. Med. Biol.* **50** 4245-58
- 8
9 Lazebnik M, McCartney L, Popovic D, Watkins C B, Lindstrom M J, Harter J, Sewall S, Magliocco A, Booske J H, Okoniewski
10
11 M and Hagness S C 2007a A large-scale study of the ultrawideband microwave dielectric properties of normal breast tissue
12
13 obtained from reduction surgeries *Phys. Med. Biol.* **52** 2637-56
- 14
15 Lazebnik M, Popovic D, McCartney L, Watkins C B, Lindstrom M J, Harter J, Sewall S, Ogilvie T, Magliocco A and Breslin
16
17 T M 2007b A large-scale study of the ultrawideband microwave dielectric properties of normal, benign and malignant breast
18
19 tissues obtained from cancer surgeries *Phys. Med. Biol.* **52** 6093-115
- 20
21 Madsen E L, Zagzebski J A and Frank G R 1982 Oil-in-Gelatine Dispersions for Use ad Ultrasonically Tissue-Mimicking
22
23 Materials *Ultrasound in Med. & Biol.* **8** 277-87
- 24
25 Madsen E L, Hobson M A, Shi H, Varghese T and Frank G R 2005 Tissue-mimicking agar/gelatin materials for use in
26
27 heterogeneous elastography phantoms *Phys. Med. Biol.* **50** 5597-618
- 28
29 Madsen E L, Hobson M A, Shi H, Varghese T and Frank G R 2006 Stability of Heterogeneous Elastography Phantoms Made
30
31 From Oil Dispersions in Aqueous Gels *Ultrasound in Med. & Biol.* **32** 261-70
- 32
33 Martellosio A, Pasian M, Bozzi M, Perregrini L, Mazzanti A, Svelto F, Summers P E, Renne G and Bellomi M 2015 0.5-50
34
35 GHz Dielectric Characterization of Breast Cancer Tissues *IET Electron. Lett.* **51** 974-5
- 36
37 Martellosio A, Pasian M, Bozzi M, Perregrini L, Mazzanti A, Svelto F, Summers P E, Renne G, Preda L and Bellomi M 2017
38
39 Dielectric properties characterization from 0.5 to 50 GHz of breast cancer tissues *IEEE Trans. Microw. Theory Techn.* **65**
40
41 998-1011
- 42
43 Matrone G, Ramalli A, Savoia A S, Quaglia F, Castellazzi G, Morbini P and Piastra M 2017 An Experimental Protocol for
44
45 Assessing the Performance of New Ultrasound Probes Based on CMUT Technology in Application to Brain Imaging *J. Vis.*
46
47 *Exp.* **127**
- 48
49 Nikolova N K 2011 Microwave imaging for breast cancer *IEEE Microwave Magazine* **12** 78-94
- 50
51 Piras D, Xia W, Steenbergen W, van Leeuwen T G and Manohar S 2010 Photoacoustic Imaging of the Breast Using the Twente
52
53 Photoacoustic Mammoscope: Present Status and Future Perspectives *IEEE J. Sel. Topics Quantum Electron.* **16** 730-9
- 54
55 Preece A W, Craddock I, Shere M, Jones L and Winton H L 2016 MARIA M4: clinical evaluation of a prototype ultrawideband
56
57 radar scanner for breast cancer detection *J. Med. Imag.* **3**
- 58
59 Porter E, Fakhoury J, Oprisor R, Coates M and Popovic M 2010 Improved tissue phantoms for experimental validation of
60
microwave breast cancer detection *Proc. 2010 4th Eur. Conf. Antennas Propag. (EuCAP 2010)*, Barcelona, Spain

1
2
3 Said M S M and Seman N 2017 Preservation of Gelatin-Based Phantom Material using Vinegar and its Life-Span Study for
4 Application in Microwave Imaging *IEEE Trans. Dielectr. and Electr. Insul.* **24** 528-34

5
6
7 Sarvazyan A, Skovoroda A R, Emelianov S, Fowlkes J B 1995 Biophysical bases of elasticity imaging *Acoustical Imaging* **21**
8 223-41

9
10 Töpfer F and Oberhammer J 2015 Millimeter-wave tissue diagnostics *IEEE Microwave Magazine* **16** 97-118
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
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28
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