

Cole-Cole model for the Dielectric Characterization of Healthy Skin and Basal Cell Carcinoma at THz Frequencies

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Abstract—THz radiation effectively probes biological tissue water content due to its high sensibility to polar molecules. Skin and basal cell carcinoma (BCC), both rich in water, have been extensively studied in the THz range. Typically, the Double Debye model is used to study their dielectric permittivity. This work focuses on the viability of the multipole Cole-Cole model as an alternative dielectric model. To determine the best fit parameters, we used a genetic algorithm-based approach, solving a least squares problem. Compared with the Double Debye model, a maximum reduction of the RMSE value up to more than 50% and maximum relative percentage errors of 2.8% have been measured for both second and third order Cole-Cole models. Since the errors of the second and third order Cole-Cole models are similar, a two-poles model is enough to describe the behaviour both tissues from 0.2 THz to 2 THz.

Index Terms—basal cell carcinoma, Cole-Cole model, Double Debye model, dielectric, terahertz.

Impact Statement- The authors employed a third and second order Cole-Cole model to describe with minimal errors the permittivity of healthy skin and basal cell carcinoma in the THz range.

I. INTRODUCTION

TERAHERTZ (THz) technology is gaining large attention from the scientific community for its potential in healthcare applications. The THz band is usually defined as the region of the electromagnetic spectrum with frequencies ranging from 0.1 to 10 THz, between the microwave and infrared regions [1]. From a biomedical point of view THz radiation exhibits interesting properties, namely its non-invasive and non-ionizing nature allows a safe interaction with the human body [2].

The research leading to these results has received funding from the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PE 00000019 "HEALITALIA" to Enrico Mattana, Matteo Bruno Lodi and Alessandro Fanti CUP F53C22000750006 University of Cagliari. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

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Among a large number of biomedical applications of interest such as sensing, spectroscopy and imaging, significant attention is directed to cancer detection and diagnosis [3]. THz waves are incredibly sensitive to polar molecules, in particular to water, thus strongly limiting the penetration depth in living tissues [4]. It is also possible to detect small and simple biomolecules by exploiting their unique spectral fingerprints, allowing for early detection of cancer biomarkers. The research has focused mainly on the skin tissue and its pathologies, since the THz radiation is able to penetrate through its outer layers without excessive losses and as a result can provide precious information of both water content and tissue structure [5], [6].

Non-melanoma skin cancers (NMSC) are the most widespread malignancy and their incidence is sharply rising globally. Basal cell carcinoma (BCC) is the most common form of NMSC and represents an important economic burden on healthcare services. Both mortality rate and metastatic risk are extremely low, so BCC is usually easily curable [7]. Usually a large number of therapeutic options are available, which includes curettage and electrodesiccation, tangential shave removal, surgical excision and Mohs micrographic surgery (MMS) [8]. Skin tumors usually exhibit a larger concentration of water molecules with respect to healthy tissues [9], indeed this is the major contrast mechanism in the THz range. For this reason both terahertz pulsed spectroscopy (TPS) and terahertz pulsed imaging (TPI) are able to provide insightful information on the histologic subtype of BCC, its size and margins, thereby supporting lesion removal and allowing for early detection [10]–[14].

Several research efforts in this field, and so this work, have been directed to the modeling of the frequency-dependent complex dielectric permittivity of both skin and BCC within the frequency range of 0.2 THz to 2 THz. The skin contains a large amount of water that heavily influences its dielectric response in the THz range [15]–[18], because of this the prevalent model to approximate the permittivity is the Double Debye (DD), as it accurately represents the complex behavior exhibited by liquid water at these high frequencies [19], [20]. In [19] authors claim that the DD model is able to accurately represent water permittivity up to 1 THz while, for higher frequencies, two Lorentzian resonance terms were incorporated to refine the model. In [16] the DD was employed to simulate THz pulses interaction with both healthy skin and BCC from 0.2 to 2 THz,

with the goal to understand the interaction between THz pulses and the skin. The DD model failed to accurately replicate the behavior of tissues below 0.6 THz, exhibiting maximum errors of approximately 17% of the permittivity.

In [21] a global optimization approach based on the branch and bounding method was developed to improve the accuracy of the DD model, demonstrating that it is able to model both healthy skin and BCC across the full [0.2,2] THz range. Moreover, in [22], it has been demonstrated that the improved fitting algorithm allows to use the static permittivity at low frequencies of the DD model to discriminate between cancerous and healthy skin tissue. Despite this, using the parameters extracted thanks to the least squares approach of [21], there are still errors as high as 4%-4.5% especially near the extremes of the interval of interest.

BCC is not the only skin tumour investigated and characterized at THz frequencies. In [23], [24] THz TPS has been successfully employed to study the dielectric properties of in vivo healthy skin, non-dysplastic and dysplastic skin nevi. THz dielectric dispersion allows to differentiate between non dysplastic and dysplastic skin nevi, with the latter known as a precursor to melanoma. In [25], a THz TDS system was utilized to study a mouse skin sample containing melanoma. The tumor was correctly identified since it has a higher absorption coefficient and refractive index than normal tissue. Finally, the dielectric permittivity of artificial healthy skin and melanoma was examined across the 0.4 THz to 1.6 THz range in [26]. The particle swarm optimization (PSO) algorithm was utilized to extract the best fit parameters. The study demonstrated that these parameters were influenced not only by the water content in both tissues but also by cell type and density. Moreover, they can be used to effectively differentiate between healthy and tumoral tissue.

In recent studies [27], a DD model extracted with a combinatorial optimization algorithm has been employed to investigate the impact of anticancer drugs on the dielectric permittivity of a 3-D organotypic model of BCC in a narrower frequency range, from 0.4 THz to 1.6 THz. Since THz science and technology is looking forward to tissue phantoms, for device prototyping and testing, that can mimick both healthy and pathologic skin tissues, a deeper understanding of their THz dielectric response is needed. From the above discussion, it must be critically recognized that there is still room for improvement when it comes to dielectric models employed to interpret and approximate the permittivity of both healthy skin and BCC. Dielectric models able to describe with minimal errors the tissues' permittivity are essential, also to obtain reliable results in numerical simulations, reduce their computational workload and providing deeper insights on the tissues relaxation mechanisms, as well as physio-pathological state. Therefore, as alternative to DD models, multipoles Cole-Cole models can be considered as valid physical frameworks for the THz dielectric spectra of healthy and pathologic skin tissues.

Since the integration of THz technologies in healthcare is an ongoing challenge, to facilitate this process it is of crucial importance the development of models capable of analytically describing the dielectric properties of skin cancer cells at

THz. This work will deal with demonstrating the feasibility of employing the second and third order Cole-Cole model to accurately approximate the permittivity of both skin and BCC and then we will critically compare the results with the DD models available in the literature.

II. MATERIALS AND METHODS

In this section a brief description of the Cole-Cole dielectric model, the formulation of the non linear least-squares problem and the settings of the employed genetic algorithm are presented.

A. The Cole-Cole Model

Based on the first order Cole-Cole model, the complex relative permittivity $\epsilon_r^{CC}(\omega)$ can be expressed as [28]

$$\epsilon_r^{CC}(\omega) = \epsilon_\infty + \frac{\epsilon_s - \epsilon_\infty}{1 + (j\omega\tau)^n}, \quad (1)$$

where ϵ_s and ϵ_∞ are respectively the static and the high frequency limit of permittivity, and τ is the generalized relaxation time constant. The shape of the spectral profile depends on the distribution parameter n , for $n = 1$ the equation simplifies to a Debye model, while smaller n corresponds to a broader dispersion curve and distribution of relaxation times [29]. The generalization to the N th order is defined as [30]

$$\epsilon_r^{CC}(\omega) = \epsilon_\infty + \sum_{i=1}^N \frac{\Delta\epsilon_i}{1 + (j\omega\tau_i)^{n_i}}, \quad (2)$$

where N corresponds to the number of poles and $\Delta\epsilon_i$ is the difference between the i th static permittivity and ϵ_∞ and represents the magnitude of the i th dispersion. Relaxation is a reactive process involving translational and rotational diffusion, hydrogen bond rearrangement, and structural changes. These processes are time-scale dependent and have specific activation energies, leading to significant temperature dependence [31], [32]. Liquid water organizes in a hydrogen-bond network of tetrahedral cages. When excited by THz radiation, this structure is disrupted and four hydrogen bonds must break in order for the molecules to reorient, this is a slow process described by the time constant τ_1 . Subsequently, the single water molecules reorient and move to a new tetrahedral site, this is a fast process described by τ_2 . This is the reason why the Double Debye model ($N = 2$, $n_1 = n_2 = 1$) is used to describe the permittivity of liquid water, as it can effectively model these two relaxation processes. The skin, however, is a complex biological and chemical environment and its dielectric properties do not exclusively depend on water content [26]. Therefore, given that in the tumor microenvironment several macromolecules and proteins are synthesized and concentrates, the water dynamics and THz-response is altered, leading to a continuum of relaxation processes and times. Therefore, Cole-Cole models, with their non-resonant and broad response, are suitable for framing and understanding these dielectric features. Furthermore, as N increases, the multipole Cole-Cole becomes capable of describing complex relaxation laws manifested by biological tissues [29]. This is because the superposition of the Cole-Cole dispersion curves in the frequency domain

can account for dipole-dipole interactions and distribution of relaxation times, which may vary in terms of broadness.

B. Problem Modeling

From [16] and [17], we extracted the data of the real part of the refractive index $n(\omega)$ and the absorption coefficient $\alpha(\omega)$ of both healthy skin and BCC in the frequency range [0.2,2] THz, with a total of $N_{s1} = 29$ samples for the first dataset and $N_{s2} = 57$. The complex relative permittivity can be easily obtained since [16]

$$\epsilon_r(\omega) = \epsilon' - j\epsilon'' = \left(n(\omega) - j\frac{c\alpha(\omega)}{2\omega} \right)^2, \quad (3)$$

where c is the speed of light in vacuum, ϵ' and ϵ'' are respectively the real and imaginary part of the complex dielectric permittivity.

To estimate the parameters of the second and third order Cole-Cole model a nonlinear least squares problem has been resolved. For every discrete circular frequency ω_k , we defined the k th residual r_k as the squared module of the difference between the actual value of the complex permittivity, $\epsilon_r(\omega)$, and the value predicted by the second and third order Cole-Cole models, denoted as $\epsilon_r^{CC}(\omega)$

$$r_k = |\epsilon_r(\omega_k) - \epsilon_r^{CC}(\omega_k)|^2. \quad (4)$$

The objective function to minimize is the total square error function, defined as

$$\min_{\mathbf{x}} \frac{1}{N_s} \left(\sum_{k=1}^{N_s} r_k \right), \quad (5)$$

where N_s is the number of samples and \mathbf{x} is the vector containing the $3N + 1$ unknown parameters of the N th order Cole-Cole model (see (2)). The search for the optimal Cole-Cole parameters is subject to the following boundaries

$$\epsilon_\infty > 0, \quad (6)$$

$$\tau_i > 10\tau_{i+1} \quad i = 1, \dots, N-1, \quad (7)$$

$$\Delta\epsilon_j > 0, \quad 0 \leq n_j \leq 1, \quad j = 1, \dots, N. \quad (8)$$

To analytically estimate the fit goodness the percentage relative errors and the root-mean-square error (RMSE), i.e., the square root of the minimized total error function, were considered.

C. Algorithm

The minimization of (5) was performed employing the genetic algorithm (GA) of Matlab v2021b (The MathWorks Inc., MA USA) global optimization toolbox. In this study, a stochastic uniform selection method was considered with a starting population size of 250 individuals and a crossover probability of 0.8. This selection method ensures that parents are selected with a probability linked to their scaled fitness value, which is inversely proportional to the value of the total square error function (5). The optimization problem has bounds and a linear inequality (see Eqs.(6)-(8)), the crossover function creates children as the weighted average of the parents in order

to avoid poorly distributed populations. Moreover, since the bounds and inequality are strictly linked to the physics of the problem, an adaptive mutation function ensuring that directions and step lengths are compatible with these constraints has been employed. The GA solver iteratively refines the selection vector \mathbf{x} through operations of crossover and mutation until it meets a termination criteria, which is either a maximum number of iterates equals to 20000 or an average relative change in the best fitness function value less than 10^{-7} . The optimization problem was solved 15 times, and in the next section the models that best fit the experimental data will be presented.

III. RESULTS

The second and third order Cole-Cole parameters for both healthy skin (HS) and BCC are listed in Table. I and Table. II, respectively. For both models and both dataset of dielectric data, it can be noticed from Table. 1 and Table. 2 that, since $n_1 \approx 1$, the first pole of the models behaves like a quasi-Debye term and its center is within the range [1.59,25] GHz. The second dispersion curve is much broader with $n_2 < 1$ and is centered inside the frequency band of interest [0.2,2] THz. Finally, for the third order Cole-Cole model the last poles are centered at frequencies higher than 3.5 THz.

TABLE I. Third order Cole-Cole parameters

	$[\epsilon_\infty, \Delta\epsilon_1, \Delta\epsilon_2, \Delta\epsilon_3]$	$[\tau_1, \tau_2, \tau_3]$ (ps)	$[n_1, n_2, n_3]$
HS [16]	[1.33, 231.36, 2.41, 2.87]	[63.40, 0.70, 0.025]	[1, 0.86, 0.72]
BCC [16]	[0.52, 243.89, 3.5, 3.05]	[53.65, 0.61, 0.012]	[1, 0.76, 0.86]
HS [17]	[2.34, 208.14, 2.41, 1.71]	[6.33, 0.64, 0.044]	[1, 0.84, 0.85]
BCC [17]	[0.50, 65.53, 3.79, 2.42]	[11.16, 0.32, 0.009]	[1, 0.66, 1.00]

TABLE II. Second order Cole-Cole parameters

	$[\epsilon_\infty, \Delta\epsilon_1, \Delta\epsilon_2]$	$[\tau_1, \tau_2]$	$[n_1, n_2]$
HS [16]	[0.69, 280.57, 6.54]	[100.1, 0.15]	[0.92, 0.36]
BCC [16]	[0.9, 300.51, 6.84]	[82.47, 0.23]	[0.93, 0.37]
HS [17]	[1.54, 205.89, 5.52]	[67.32, 0.23]	[0.94, 0.41]
BCC [17]	[1.14, 114.84, 5.69]	[22.78, 0.12]	[0.94, 0.44]

Fig. 1 shows the real (ϵ') and imaginary (ϵ'') part of the dielectric permittivity of healthy skin extracted from [16] and [17] and the relative percentage error for the fittings with different models. The dielectric data from the two different datasets [16], [17] are very similar. From Fig. 1c The DD model proposed in [16], available only for the first dataset, is able to approximate the permittivity of healthy skin with errors with respect to the module lower than 1% for frequencies higher than 0.85 THz, while unable to do the same for lower ones, reaching errors as high as 15% around 0.2 THz. The DD model proposed in [21] exhibits better tracking capabilities, trading off the accuracy in the higher end of the frequency range for errors on the module of permittivity $\leq 2\%$ in a broader band, approximately [0.5,1.65] THz for both datasets. The second and third order Cole-Cole models have comparable errors and follow similar trends. The highest error registered for the third order Cole-Cole model on the real part of $\epsilon_r(\omega)$

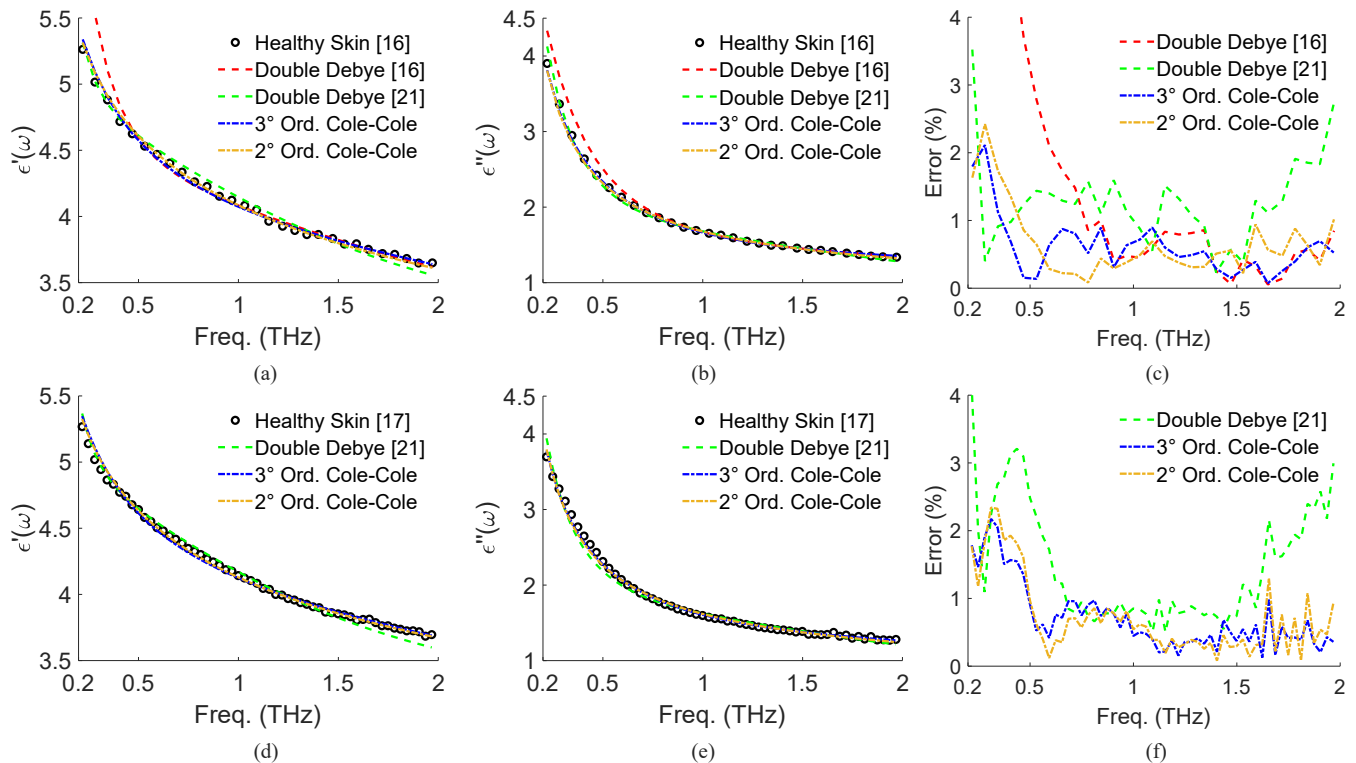


Fig. 1. Approximations of healthy skin permittivity in the THz range, data extracted from [16] (a), (b), (c) and [17] (d), (e), (f). Comparison between the fitting of the second and third order Cole-Cole models and (a), (b) the Double Debye models from [16], [21] and (c), (d) the Double Debye model from [21]. Percentage relative error computed on the module of the relative permittivity $|\epsilon_r(\omega)|$ (c), (f) for the different dielectric models.

is 0.97% on the first dataset and for ϵ'' is 3.31% on the second dataset. The second order Cole-Cole model is characterized by maximum errors of 1.02% of ϵ' on the first dataset and 3.8% of ϵ'' on both datasets. In general the third order Cole-Cole model is able to approximate better the imaginary part of the permittivity of healthy skin. To compare the Cole-Cole models with the Debye it is possible to consider the RMSE as a figure of merit. The third order Cole-Cole model presents RMSEs of 0.0417 and 0.0465 while the second order one 0.0461, 0.0487, for the first and second dataset respectively. Both are an order of magnitude smaller than the RMSE of the DD proposed in [16]. Moreover, there's an approximate mean 38% reduction in the RMSEs compared to the DD model from [21].

Fig. 2 shows the dielectric data relative to the BCC samples from the two datasets, with the comparison between the simulations of the DD and Cole-Cole models. From an analysis of Fig. 2 it is possible to notice similar trends with respect to the healthy skin approximations. The DD model proposed in [16] is not able to track the permittivity of BCC with degrees of accuracy comparable to the other models under 0.5 THz (see Fig. 2a and Fig. 2c) and reaches errors on the module of approximately 17% around 2 THz. The DD presented in [21] manifests errors of roughly 3.5% of $|\epsilon_r(\omega)|$ near 0.2 THz and 2 THz. In this case, it appears that the DD model struggles to accurately track the BCC dielectric data, in particular near the extremes of the interval of interest. On the other hand, the Cole-Cole models exhibit good tracking, as it can be seen from Fig. 2.f especially. For both Cole-Cole models, low errors has

been registered on the real part with a maximum of 2.8% for the second order Cole-Cole model on the second dataset. The fitting of the imaginary part for the second dataset was the most critical one for frequencies higher than 1.5 THz, where the second and third order Cole-Cole model are characterized by errors up to 6.72% and 6.92%, mainly because the experimental data from [17] data shows considerable fluctuations. The third order Cole-Cole model presents RMSEs of 0.0438 and 0.0425 while the second order one 0.0527, 0.0461, for the first and second dataset respectively [16]. It is relevant to note that the error in the second dataset is averaged over nearly twice the number of samples compared to the first one. The RMSE values of the second order Cole-Cole model are approximately 44% and 53% smaller compared with the DD model proposed [21].

IV. DISCUSSION

From the presented results it can be evinced that the third order and second order Cole-Cole model are able to track the permittivity of both skin and BCC in the THz range, with errors always lower than 3% of $|\epsilon_r(\omega)|$. For this reason, the numerical condition (7) is fundamental to ensure a good result of the fitting procedure. Since the multipole Cole-Cole model is used to model materials that exhibits multiple distribution of relaxation times with varying degrees of broadness, it is completely reasonable to expect the resonant frequencies of the poles to be sufficiently distant in the frequency domain. Since the two poles Cole-Cole approximation is definitely comparable to the third order one, while having 3 less unknown

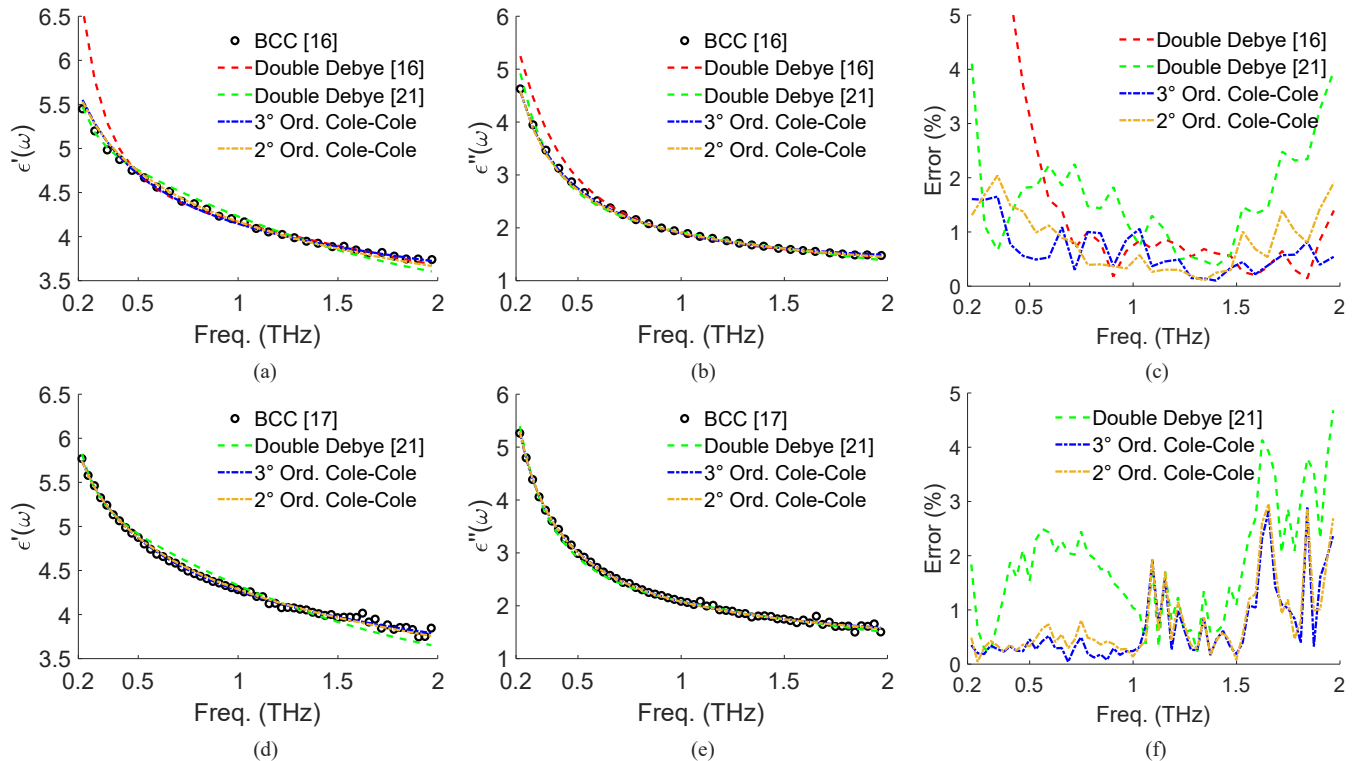


Fig. 2. Approximations of BCC permittivity in the THz range, data extracted from [16] (a), (b), (c) and [17] (d), (e), (f). Comparison between the fitting of the second and third order Cole-Cole models and (a), (b) the Double Debye models from [16], [21] and (c), (d) the Double Debye model from [21]. Percentage relative error computed on the module of the relative permittivity $|\epsilon_r(\omega)|$ (c), (f) for the different dielectric models.

parameters, the most relevant poles are the first two. The first poles are characterized by the largest magnitude, $n_1 = 1$ and are centered at frequencies < 25 GHz, meaning that, in the frequency range of interest, they contribute mainly to the shape of the imaginary part of the permittivity while they almost acts as an offset for the real part. On the contrary, the second poles, with smaller magnitude and centered in the frequency band $[0.2, 2]$ THz, contribute generally to the shape of both the real and imaginary part. Having a Cole-Cole pole inside the band $[0.2, 2]$ THz, with limited slopes ($n_2 < 1$) ensures a good tracking where the DD model falls short, since $\epsilon_r(\omega)$ doesn't vary sharply with frequency. The third pole, if present, contributes slightly to both ϵ' and ϵ'' . Essentially, while the first two poles provide the general shape with good precision, the third pole further enhances the approximation where possible. From the above analysis, while the third order Cole-Cole model reaches numerical errors smaller than the second order one, the improvement of the fitting is not enough to justify the increased computational complexity of the fitting.

V. CONCLUSION

The main objective of this work was to identify an alternative to the Double Debye model for better approximating the permittivity of both skin and BCC in the THz range. Additionally, the study aimed to investigate the feasibility of describing them using a second and third order Cole-Cole model. To achieve this result, starting from dielectric data extracted from the literature, the Cole-Cole parameters of the best fit were obtained

solving a nonlinear least squares problem employing a genetic algorithm routine. Then, the different dielectric models approximations have been quantitatively compared, considering the relative errors as a function of frequency and the RMSE. The results of the numerical analysis indicate that the errors of both Cole-Cole models are similar, while with respect to the DD, the first ones are able to better track the permittivity of both healthy skin and BCC, reaching maximum reductions of the RMSE values of more than 50%. An accurate approximation of the tissues permittivity over the entire frequency band is essential to understand how THz pulses interact and propagate through biological systems, thus allowing for the development of THz technologies for biomedical applications and imaging.

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