The dielectric properties of skin and their influence on the delivery of tumor treating fields to the torso: a study combining in vivo measurements with numerical simulations

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1. Introduction

Measuring the dielectric properties of tissues is important for understanding the interaction of electromagnetic energy with the human body, a topic that is important for safety assessments of human exposure to electromagnetic fields as well as for numerous biomedical applications. Multiple studies have been performed to measure and model the dielectric properties of various tissues (Schwan and Kay 1957, Geddes and Baker 1967, Pethig 1987, Foster and Schwan 1989, Peyman 2011). A well-known study on this topic published two decades ago by Gabriel et al (Gabriel et al 1996a, 1996b, 1996c) contains an extensive database based on impedance measurements and a parametric model that describes tissue properties in the range of 10 Hz–20 GHz. This database has gained large acceptance over the years as a standard reference for determining the dielectric properties of tissues. Within this database, skin is one of the few tissues for which two different values of conductivity and permittivity were reported. The database specifies values for dry and wet skin that are two orders of magnitude apart, indicating that the dielectric properties of skin depend strongly on the surrounding environment. Therefore, when measuring...
different because of their varying water content and composition (McGrath 2010, Sasaki et al 2015). The frequency range of 100–500 kHz by various researchers (Yamamoto and Yamamoto 1976, Gabriel et al 2000, Raicu et al 2007, Giladi et al 2016). Analysis of these studies shows that the TTFields are low-intensity alternating electric fields in the 100–500 kHz frequency range, which have an antimitotic effect on cancerous cells (Kirson et al 2007, Giladi et al 2015). TTFields are approved by the Food and Drug Administration (FDA) for the treatment of glioblastoma multiforme (GBM). In addition, clinical trials testing the feasibility, safety, and efficacy of TTFields for the treatment of lung cancer (ClinicalTrials.gov identifier NCT02973789), pancreatic cancer (NCT01971281), mesothelioma (NCT02397928), ovarian cancer (NCT02244502), and hepatocellular carcinoma (NCT03606590) are ongoing, with robust preclinical data supporting further clinical investigation (Davies et al 2013, Giladi et al 2014, Voloshin et al 2016, Karanam et al 2017). TTFields are delivered via two pairs of transducer arrays (TAs) placed directly on the patient’s skin in close proximity to the tumor (figure 1). The TAs comprise ceramic disks with a high dielectric constant, which are arranged in an almost rectangular shape. Electrical contact between the disks and the skin is through a thin layer of medical gel, which covers the patient-facing facet of the disks. A patch of adhesive tape keeps the arrays fixed to the patient. The sizes of TAs used depend on the specific cancer type, the size of the patient, and the body part on which the TA is placed. Since TTFields are delivered via TAs in electrical contact with the skin, the electrical field penetrating the body is inherently dependent on the dielectric properties of the skin. Consequently, clear understanding of how TTFields distribute within the body requires precise knowledge of the dielectric properties of skin over the frequency range of 100–500 kHz.

The skin consists mainly of two structural layers: the epidermis and dermis. The properties of these layers are different because of their varying water content and composition (McGrath 2010, Sasaki et al 2014). The outermost layer of the epidermis is known as the stratum corneum, a thin dry keratin layer comprising mainly dead cells. The skin layer under the epidermis is the dermis, which mainly consists of connective tissue, blood vessels, and sensory nerve endings. The fatty layer below the skin is known as the hypodermis or subcutaneous adipose tissue (SAT). This layer comprises fat cells, blood vessels, and connective tissue. Since SAT is found under almost the entire skin surface, it is sometimes considered to be part of the skin.

The dielectric properties of either bulk skin or its different layers have been studied at frequencies below 1 MHz by various researchers (Yamamoto and Yamamoto 1976, Gabriel et al 1996c, 2000, Raicu et al 2000, Grimnes and Martinsen 2010, De Santis et al 2015, Wake et al 2016). Analysis of these studies shows that the method of measurement, as well as the source of the sample and sample preparation, may have significant influence on the measured values since different measurement methods and conditions may reflect different properties of the skin. For example, Raicu et al reported a five-fold increase in dispersion magnitude for moistened skin versus dry skin (Raicu et al 2000) and Gabriel et al reported that at low frequencies the conductivity of wet skin was a few orders of magnitude higher than that of dry skin (Gabriel et al 1996c). Gabriel et al suggested that measurements of non-moistened skin may be less sensitive to the dielectric properties of the deeper skin layers (Gabriel et al 2009). Penetration depth is also affected by the dimensions of the probe placed on the skin surface (i.e. an open-ended coaxial probe), where deeper tissues are sampled with bigger probes (Alalen et al 1999, Raicu et al 2000). The composition of the sampled volume is also affected by the thicknesses of skin layers and has a significant effect on the measured impedance. The thicknesses of the different layers change with age, sex, and body.

Figure 1. (a) Model shown wearing transducer arrays (TAs) configured for the administration of TTFields to the abdomen. The TAs comprise capacitive ceramic disks, which are arranged in an almost rectangular shape. Electrical contact between the disks and the skin is made through a thin layer of medical gel, which covers the patient-facing facet of the disks. A patch of adhesive tape keeps the TAs fixed to the patient. When treating pancreatic cancer, one pair of 20-disk TAs is placed on the abdomen and back of the patient, and one pair is placed on the lateral aspects of the patient. (b) NovoTTF-100A system for TTFields administration consisting of a portable electric field generator, TAs, rechargeable batteries, and carrying case. This panel shows the smaller nine-disk TAs used for treating glioblastoma.
mass index (BMI), and vary between different sites on the body surface (Lee and Hwang 2002, Valentin 2002, Gabriel et al 2009, Peyman 2011, Jain et al 2013, Wake et al 2016). Conditions such as temperature and viability also affect skin dielectric properties; for example, lowering skin temperature has been reported to decrease conductivity. Necrotic or excised tissues are reported to have different conductivity and permittivity compared with healthy in vivo tissues due to changes in cell membrane integrity and extracellular water content (Gabriel and Grant 1985, Pethig 1987, Kyber et al 1992, Marzec and Wachal 1999, Martinsen et al 2000, Grimnes and Martinsen 2010). These causes of variability in skin properties emphasize the need to be aware of the application for which the measurements are being performed, make sure that the measurement conditions resemble those imposed by the application, and pay close attention to sample composition.

In this paper, we present a study investigating the dielectric properties of skin and SAT and their influence on the electric field distribution within the body when delivering TTFields to patients. The first part of the study utilized impedance measurements of skin folds around the abdomens of volunteers to derive dielectric properties for skin and SAT. The measurements were performed with electrodes made of the same ceramic disks and medical gel comprising the TAs used for TTFields delivery. This ensured that conditions on the skin during the course of measurement resembled the conditions on the patients’ skin when delivering TTFields. The dielectric properties of skin and SAT were derived by fitting a multilayer model to the measurements. The second part of the study included numerical simulations of TTFields delivery to the abdomen utilizing realistic human computational phantoms to confirm that the newly derived dielectric properties of skin and SAT adequately represent the dielectric properties of these tissues in patients treated with TTFields. A necessary condition for a model to be considered adequate is that its total impedance agrees with the total impedance of the subject being modeled. This implies that when simulating delivery of TTFields to patients, the total impedance of the model must be within the range of total impedance measured on patients. The device delivering TTFields constantly monitors total impedance in patients; however, other means for model validation such as in vivo measurement of the electric field or current density are technically difficult to perform. Consequently, a convenient method for testing whether the computational model is valid is to compare the measured total impedance in patients with the total impedance of a computational phantom. Therefore, to confirm that the measured dielectric properties of skin and SAT are likely representative of the properties of these tissues in the TTFields-treated population, we incorporated the measured properties into a computational phantom and compared the total impedance of the model with the total impedance measured in patients with pancreatic cancer treated with TTFields. We then extended the simulation-based study to include an extensive sensitivity analysis aiming to elucidate the extent to which the dielectric properties of skin and SAT affect the total body impedance and how they affect TTFields distribution within the body.

2. Methods

2.1. Assessment of body impedance in patients
In this study, we assessed the typical electric impedance in patients with pancreatic cancer treated with TTFields. The analysis was based on data from 19 patients with pancreatic cancer treated with TTFields as part of the PANOMA trial (NCT0197128) (Rivera et al 2019). When patients are treated with TTFields, the voltage, current, and absolute electric impedance are logged every 30 min. This log is created so that the treating physician can assess treatment efficiency and patient adherence to treatment protocols. This log also compiles quantitative data on the electric impedance for individual patients. Based on the logs collected from patients, we derived the average impedance of each patient over the first month of treatment and analyzed the distribution of impedance values across this patient population.

2.2. Measuring the dielectric properties of skin
To estimate the dielectric properties of skin, we measured the complex impedance of skin folds around the waists of volunteers (two males and three females). To ensure that the conditions of the skin resembled the conditions when TTFields are delivered to a patient, the impedance measurements were performed using electrodes made of ceramic disks and medical gels (Axelgaard AG625) similar to those present in the TAs used to deliver TTFields. The electrodes were placed on both sides of a skin fold at five to six different locations around the waists of the volunteers. The folds and the electrodes were held in place by a clamp to maintain geometry and pressure during the measurement. A schematic diagram illustrating the measurement setup is shown in figure 2(a). Measurements were taken at room temperature and skin temperature was 30 °C–32 °C. The thickness of each fold was measured using a caliper and documented. Complex impedance was recorded at multiple frequencies in the range of 100 kHz to 1 MHz using a Keysight E4980AL Precision LCR Meter. With this setup, measuring the impedance of a single skin fold took approximately 1 min. After every measurement, the combined impedance of the ceramic disks and gel was measured by sandwiching the layers of gel between the ceramic disks and connecting
the outer surfaces of the ceramics to the LCR meter. The impedance of the gel and disks was subtracted from the total impedance measured on the skin fold to yield the impedance of the tissues alone.

2.3. Modeling and analysis of the impedance measurements

According to the geometry of the measurement setup, only the outer layers of the body are sandwiched between two parallel electrodes (figure 2(a)). In the structure that is formed in the fold, all layers have almost uniform cross-sections and are connected in series. Consequently, a simple multilayer model can be used to analyze the measurements.

The multilayer model of the skin fold used for analysis included five layers of tissue: epidermis, dermis, SAT, dermis and epidermis sandwiched between two layers of medical gel, and two ceramic disks, as shown in figure 2(b). The dermis and SAT layers were considered mainly resistive due to their relatively high water content and their low relative permittivity as reported in the literature (Gabriel et al. 1996c). The epidermis was considered to behave as a capacitor due to its thinness and very low water content, which correlate with high relative permittivity and extremely low conductivity. Using this model, the complex impedance $Z$ for any measurement can be expressed as:

$$Z = Z_{Re} + iZ_{Im}$$  

with:

$$Z_{Re} = Z_0 + 2Z_d = \frac{l_1}{\sigma_1 A} + 2 \cdot \frac{l_2}{\sigma_2 A}$$  

$$Z_{Im} = - \frac{l_c}{\varepsilon_0 \varepsilon_r A \omega}$$

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Figure 2. (a) Skin fold impedance measurement setup: electrodes made of ceramic disks and medical hydrogel placed on either side of a skin fold (epidermis, dermis, and SAT). (b) Multilayer electric circuit model of a skin fold measurement with five tissue layers: epidermis (capacitive); dermis (resistive); SAT (resistive); dermis, epidermis, and two electrodes on each side of the fold made of hydrogel (resistive); and ceramic disks (capacitive).
\[ l_t = l_e + l_d + l_c. \]  

Equations (1)–(4) show that the real and imaginary components of the tissue impedance, \( Z_{Re} \) and \( Z_{Im} \), respectively, depend on six variables: the thickness of the SAT \( (l_t) \), the thickness of the dermis \( (l_d) \), the thickness of the epidermis \( (l_e) \), the total thickness of the fold \( (l) \), the conductivities of the SAT \( (\sigma_s) \) and the dermis \( (\sigma_d) \), and the relative permittivity of the epidermis \( (\varepsilon_r) \). Two constants present in the equations are the vacuum permittivity \( \varepsilon_0 = 8.85 \times 10^{-12} \text{ F m}^{-1} \) and the cross-section of the layers \( A \).

This analysis assumes that the measurement geometry resembles a parallel plate setup in which all layers have the same cross-section as the electrodes. However, during the measurements, the skin fold was stretched to be slightly larger than the electrodes to ensure perfect contact between the medical gel and the skin surface. In addition, the skin fold is connected to a larger body and current can flow through the inner tissues, which may slightly change the uniform cross-section geometry. Therefore, when deriving dielectric properties from the measured data, it is important to use an effective cross-section area \( A_{eff} \), which is different from the cross-section area of the electrode and links the realistic skin fold geometry with the multilayer model. Details on how \( A_{eff} \) was derived are explained in the next section.

It is reasonable to assume that variations in the thicknesses of skin folds are caused primarily by changes in the thickness of SAT at different locations on a single individual and between individuals, and that changes in the thicknesses of the epidermis and dermis are very small relative to changes in the thickness of the SAT. Therefore, we assume constant thicknesses of \( l_e = 80 \times 10^{-6} \text{ m} \) for the epidermis (Zolfaghari and Maerefat 2010) and \( l_d = 2 \times 10^{-3} \text{ m} \) for the dermis. Thus, the relative permittivity of the epidermis can be derived from equation (3) by isolating \( \varepsilon_r \):

\[ \varepsilon_r = \frac{l_e}{|Z_{Im}| \varepsilon_0 A_{eff} \omega}. \]  

Here, \( Z_{Im} \) is the average of the imaginary component of the impedance measured for all skin fold samples.

To calculate the conductivity of SAT and the dermis layers, we applied equation (4) into (2), which after neglecting the epidermis thickness yields:

\[ Z_{Re} = \frac{1}{\sigma_s A_{eff}} \cdot l_t + \left( \frac{2\sigma_s - \sigma_d}{\sigma_s A_{eff}} \right) \cdot l_d. \]  

This equation shows that it is possible to derive values for the conductivity of the SAT and dermis by plotting the real part of the skin fold impedance as a function of total skin fold thickness \( l_t \) and performing a linear regression on the plot. Analyzing the slope and intercept coefficients derived from the regression \( (m \) and \( n \), respectively) yields the conductivity of the SAT and dermis:

\[ \sigma_s = \frac{1}{mA_{eff}} \]  

\[ \sigma_d = \frac{2 \cdot l_d \sigma_s}{\sigma_s A_{eff} n + l_d}. \]

### 2.4. Deriving the effective cross-section area for the skin folds

To derive \( A_{eff} \), we used the following iterative procedure: As an initial estimate, we assumed that \( A_{eff} \) is equal to the cross-section of the ceramic disk \( (2.8 \times 10^{-4} \text{ m}^2) \). Using this value for \( A_{eff} \) and the measured data, we applied equations (5), (7) and (8) to derive the dielectric properties of the epidermis, dermis, and SAT. These dielectric properties were then used to set the properties of epidermis, dermis, and SAT in a simplified computational model of skin fold measurement, which is described in detail below. Following calculation of the electric current in the simplified skin-fold model, the impedance of the model was extracted and analyzed in combination with the assigned dielectric values to yield a modified value of \( A_{eff} \) which was then, in combination with the measured impedance values, reinserted to equations (5), (7) and (8) to derive corrected values for the dielectric properties of the epidermis, dermis, and skin. These values were reassigned into the computational model to yield another modification to \( A_{eff} \). We continued this iterative process of correcting the effective area and dielectric values until the simulation yielded an effective area with corresponding calculated dielectric properties that were within 2% of the dielectric values assigned in that simulation. Convergence occurred after three to four iterative steps.

The simplified skin fold measurement model used for this process is shown in figure 3. The model comprised a large box \((40 \text{ cm} \times 15 \text{ cm} \times 20 \text{ cm})\) representing the torso, with a smaller box attached to the center of one of the faces, representing a skin fold. The small box comprised three segments: epidermis, dermis, and SAT with thicknesses of 0.1 mm, 2 mm, and 9.8 mm, respectively (figure 3(b)). The size of the fold along the Z-axis was 4 cm and the size of the fold pulled outward from the body was 3.5 cm. The large box representing the torso
comprised only two tissue types: SAT as the outermost layer (7 mm thickness) and muscle tissue filling the inner volume. We set the dielectric properties assigned to the epidermis, dermis, and SAT according to the iterative process described in the previous paragraph and the dielectric properties of the inner large box were approximated to those of muscle as reported in the ITIS database 3.1.1 (Hasgall et al 2015). A ceramic disk (19 mm in diameter, 1 mm thick) was attached to each side of the fold through a cylindrical gel (20 mm in diameter, 0.6 mm thick) that adhered to the fold’s surface (figure 3(b)). The dielectric properties assigned to the ceramic disks and gel were taken from the manufacturer datasheet (see next section for values).

To isolate the impedance of the fold from the total impedance of the model, we performed an additional simulation to determine the impedance of the disks and gels alone. For this purpose, a model including only two layers of gel sandwiched between two ceramic disks with the same size as in the skin fold models was created.

All simulations related to the simplified model were performed using Sim4Life v3.2 (ZMT Zurich MedTech AG). To generate current through the model, a constant voltage at 150 kHz with an amplitude of 20 V was set to the outer surfaces of the disks. The total complex impedance of the models was then derived by first calculating the total current flux passing through a plane parallel to the two ceramic disks and located between them, and then dividing the voltage between the two ceramic disks by the total current value.

To calculate the effective cross-section of a skin fold from the real or the imaginary components of the complex impedance of the model, the following equations were used:

\[
A_{\text{eff Re}} = \frac{1}{Z_{\text{Re}}} \left( \frac{I_d}{\sigma_s} + 2 \cdot \frac{I_d}{\sigma_d} \right)
\]

and

\[
A_{\text{eff Im}} = \frac{1}{|Z_{\text{Im}}|} \left( \frac{I_c}{\varepsilon_0 \varepsilon_r \omega} \right)
\]

2.5. TTFields simulations and sensitivity analysis
As part of this study, we performed numerical simulations of the delivery of TTFields to a realistic human computational phantom. These simulations were performed with three goals:
1. To confirm that assigning the dielectric properties derived from the measurements to computational phantoms was likely to be representative of patients treated with TTFields (for this we compared the model total body impedance with patients’ body impedance data).
2. To test the sensitivity of the total body impedance to skin and SAT dielectric properties.
3. To test the sensitivity of the electric field distribution that developed within the computational phantom to the dielectric properties assigned to the skin and SAT.

2.5.1. Simulations setup
To simulate the delivery of TTFields to the abdomen, a realistic computerized model of a human male (DUKE 3.0 from ZMT) was used (Christ et al 2010). The simulations were performed at 150 kHz using Sim4Life v3.2 (ZMT) electro-quasi-static solver. Two TAs were placed on the phantom. Each array comprised 20 ceramic disks (20 mm in diameter, 1 mm thick), which made electric contact with the phantom skin through a thin layer of medical gel (20 mm in diameter, 0.5 mm thick). The TAs were placed on the back and on the stomach of the computational phantom (see figure 4) using a semi-automatic algorithm reported elsewhere (Bomzon et al 2015).

As a baseline, all tissue properties were assigned to the phantom utilizing the ITIS database 3.1.1 (Hasgall et al 2015), which is based on the Gabriel dispersion relationships (Gabriel 1996). The values of skin, SAT, liver, and pancreas were then changed as described below. The dielectric properties of ceramic disks ($\sigma = 0$ S m$^{-1}$, $\varepsilon_r = 1000$) and medical gels ($\sigma = 0.1$ S m$^{-1}$, $\varepsilon_r = 100$) were obtained from the manufacturers’ specification sheets. To deliver TTFields to the phantom, a constant voltage was imposed between the outer surfaces of the ceramic disks in the two TAs (Dirichlet boundary conditions). The voltage was normalized to simulate a current of 4 A peak to peak flowing through the model. The model was voxelized with a maximum voxel size of 3 mm$^3$. To reduce computation time while minimizing errors, the model was truncated at the neck and below the waist of the phantom where the average electric field falls to 10% of its minimum value in the middle of the torso. It is worth noting that other human models and software simulation packages that could be suitable for studies such as this do exist. Information about other available human models and software simulation packages can be found in (Makarov et al 2017).

2.5.2. Applying measured dielectric properties to the computational model
A challenge associated with applying the measured dielectric properties of the dermis and epidermis to the model is that in the computational phantom, skin is segmented as a single layer that does not reflect the electrical variability between the anatomical layers. Therefore, it is necessary to derive effective skin properties from the measured values such that the impedance of the phantom’s single-layer skin will be equivalent to realistic two-layer skin impedance.

This was done using the following equations:

$$\varepsilon_{\text{eff}} = \frac{d_{\text{skin}} |Z_{\text{Im}}|}{\omega A \left( |Z_{\text{Re}}^2 + Z_{\text{Im}}^2| \right)} \frac{1}{\varepsilon_0}$$

(11)
\[ \sigma_{\text{eff}} = \frac{d_{\text{skin}} Z_{\text{Re}}}{A \left( Z_{\text{Re}}^2 + Z_{\text{Im}}^2 \right)}. \]  

(12)

Here, \( \varepsilon_0 \) is the vacuum permittivity, \( \omega \) is the angular frequency, \( A \) is the cross-section of the electrodes, and \( d_{\text{skin}} \) is the average skin thickness of the phantom. \( Z_{\text{Re}} \) was calculated using equation (2) and the dermis conductivity extracted from the measurements. \( Z_{\text{Im}} \) was calculated using equation (3) and the epidermis relative permittivity extracted from the measurements. For these calculations, the dermis thickness was taken as the average thickness of the phantom’s skin, which was found by measuring the thickness of the skin at multiple sites around the phantom’s abdomen, and then averaging these measurements. The epidermis thickness was considered to be \( 80 \cdot 10^{-6} \) m, similar to the thickness used to derive the epidermis permittivity from the measurements. The cross-section \( A \) was taken to be the cross-section of the electrodes.

2.5.3. Sensitivity analysis

For most biological tissues over the frequency range of 100 kHz – 1 MHz, the conductivity has a stronger influence on the electric field and current density distribution than relative permittivity. Therefore, our major simulation sets tested the sensitivity of the computational phantom total impedance to the conductivity values assigned to the SAT and skin. We varied the conductivity of the skin from a low value of 0.0007 S m\(^{-1}\) (conductivity of dry skin reported in Gabriel database (Hasgall et al 2015)) to a maximum value of 0.3 S m\(^{-1}\), and varied the conductivity of the SAT between 0.04 S m\(^{-1}\) (fat conductivity in Gabriel database (Hasgall et al 2015)) and 0.45 S m\(^{-1}\). In this analysis, relative permittivity of the skin was set to either the nominal value derived from our measurements or to the values reported in the Gabriel database for dry and wet skin (1100 and 10 000, respectively). The relative permittivity of the SAT was set to 82 (Hasgall et al 2015) in all simulations. The total impedance of the model was then calculated, and the differences resulting from the different settings were examined.

Another set of simulations compared the contribution of the dielectric properties of the internal organs with the total impedance of the body versus the contribution of the outermost layers. In these simulations, skin and SAT were assigned with the dielectric values extracted from our measurements and the liver and pancreas were assigned with conductivity values that were either half or double the values in the Gabriel database (Hasgall et al 2015).

Finally, we tested the sensitivity of the electric field to all of the mentioned changes in dielectric properties by comparing the distribution of the field intensity in the pancreas for all settings. In order to gain additional insight into how the skin contributes to the total impedance of our models, we considered a simple electrical circuit representing delivery of TTTFields to the body. In this circuit, each tissue layer/component is represented as a resistor–capacitor unit, with all units connected in series, as shown in figure 5. The center unit represents the internal organs of the body, which are sandwiched between units representing the outer body layers (skin and SAT) and the gels and disks comprising the TAs. To calculate the contribution of the skin unit to the total impedance of the body, we calculated \( Z_{\text{Re}} \) and \( Z_{\text{Im}} \) for the skin:

\[ Z_{\text{Re}} = \frac{d \sigma}{\left( \sigma^2 + \varepsilon_0 \varepsilon_r \omega^2 \right) A}. \]  

(13)

\[ Z_{\text{Im}} = \frac{d \varepsilon_0 \varepsilon_r \omega}{\left( \sigma^2 + \varepsilon_0 \varepsilon_r \omega^2 \right) A}. \]  

(14)

Here, \( \sigma \) and \( \varepsilon_r \) are the conductivity and relative permittivity assigned to the phantom’s skin in the simulations, \( \omega \) is the angular frequency, \( d \) is the average thickness of the phantom’s skin, and \( A \) the total effective cross-section of the disks in a TA. This approximation is valid because the current in the skin just below the arrays is mostly concentrated to the regions under the disks, before it spreads out in the torso volume. The absolute value of skin impedance was calculated for all skin properties used in the simulations and the contribution of the skin to the total impedance of the models was evaluated.
3. Results

3.1. Patients’ total body impedance

Figure 6 shows a histogram of the average absolute impedance measured on 19 patients with pancreatic cancer participating in the PANOV A trial during their first month of TTFields treatment. The measured impedance varies between a minimum of 21 \( \Omega \) to a maximum of 49 \( \Omega \), with an average value of 34. The standard deviation is 7 \( \Omega \), and the 15th and 85th percentiles are 25 and 41 \( \Omega \), respectively.

3.2. Impedance measurements and analyses of skin folds

Figure 7(a) shows a plot of \( Z_{\text{Re}} \) versus fold thickness for all skin fold measurements at 150 kHz. A linear regression of this plot yields a slope of \( m = 12720 \) and intercept of \( n = 73.1 \) with a goodness of fit \( R^2 = 0.74 \) and root mean square error of 32 \( \Omega \). Similar analysis performed at other frequencies yielded linear fit curves with goodness of fit \( 0.74 < R^2 < 0.77 \) from which frequency-dependent conductivities of SAT and dermis can be derived using equations (7) and (8). The average value of \( Z_{\text{Im}} \) across all samples versus frequency is presented in figure 7(b) with an average of 92.6 \( \Omega \) and a standard deviation of 8.7 \( \Omega \) at 150 kHz.

Figure 7(c) shows the frequency–dependency of SAT conductivity (filled squares), dermis conductivity, and the relative permittivity of the epidermis (unfilled markers), calculated utilizing measured values of \( Z_{\text{Re}} \) and \( Z_{\text{Im}} \) and equations (5), (7) and (8) in combination with the effective cross-sections \( 4 \times 10^{-4} \) m\(^2\) for \( Z_{\text{Re}} \) and \( 3.5 \times 10^{-4} \) m\(^2\) for \( Z_{\text{Im}} \). These effective cross-sections were extracted from the iterative analysis of the simplified skin fold simulations results and equations (9) and (10). It is evident from the figure that at 150 kHz, dermis and SAT conductivities are 0.1 S m\(^{-1}\) and 0.2 S m\(^{-1}\), respectively, and the relative permittivity of the epidermis at this frequency is 592.

Combining epidermis and dermis to a single layer of skin with an average abdomen skin thickness of 2.4 mm, which is the skin thickness in the abdomen of the DUKE model, yielded an effective conductivity of 0.07 S m\(^{-1}\) and an effective relative permittivity of 5675 at 150 kHz. These values were used as nominal values in the simulations. The effective conductivity and relative permittivity of a single skin layer at other frequencies are presented in figure 7(c) (filled circles); all measurements over the frequency range (100 kHz–1 MHz) show conductivity values for SAT that vary very little (0.2–0.22 S m\(^{-1}\)). Effective skin conductivities increase from 0.09 S m\(^{-1}\) at 100 kHz to 0.15 S m\(^{-1}\) at 1 MHz. These values are in agreement with conductivity values reported by Wake et al (2016), who reported 0.12 S m\(^{-1}\) at 150 kHz for bulk skin (0.09–0.32 S m\(^{-1}\) at 100 kHz–1 MHz) and conductivity of 0.14 S m\(^{-1}\) for SAT at all frequencies below 1 MHz. The Gabriel database (Gabriel et al 1996c) reported conductivity of 0.09 S m\(^{-1}\) for wet skin with relative permittivity of 11 362, which is slightly higher than the values we found.

When simulating the delivery of TTFields at 150 kHz delivered to DUKE’s abdomen after assigning the nominal conductivity and permittivity to the phantom, the absolute impedance of the model was 35 \( \Omega \), which is in the mid-range of the impedance measured in patients. This simulation provides additional validation that our measurements are applicable to the clinical setting.
3.3. Results of sensitivity analysis

The absolute value of impedance extracted from TTFields simulations with various combinations of dielectric properties for skin and SAT are presented in Table 1. Each column in the table is related to simulations performed with the same skin conductivity and each row is related to simulations performed with the same SAT conductivity.

It is evident from Table 1 that assigning low conductivity and low permittivity to the skin (0.02 S m\(^{-1}\) and 1100, respectively) resulted in much higher impedances compared with all other combinations, regardless of SAT conductivity. In addition, for combinations with higher skin conductivity and/or permittivity, the total impedance did not change much (<20%), regardless of the magnitude of assigned values. Assigning Gabriel database (Gabriel et al. 1996c) values for dry skin yielded total impedance of 75 Ω, which is out of the range of impedance measured in patients.

A better understanding of these results can be achieved using equations (13) and (14) to estimate the impedance of the skin when delivering TTFields to the torso. For the lowest conductivity and permittivity values (0.02 S m\(^{-1}\), 1100) and an effective cross-section of 20 disks (80 \(\cdot\) 10\(^{-4}\) m\(^2\)), the absolute value of the skin impedance was about 27 Ω. This value was almost half of the total impedance calculated in the simulation, suggesting that skin impedance determined the total impedance of the model. However, when higher conductivities and permittivities were assigned to the skin, the contribution of the skin to the total impedance dropped (less than 7 Ω), so the total impedance of the model was determined by the internal organs. Thus, once the conductivity and/or permittivity of the skin exceeded a certain level (close to the average properties of the internal organs), further increases in either value had little effect on the total impedance of the model.

After establishing how the dielectric properties of the skin and SAT influenced the model impedance, we fixed the dielectric properties of the skin and SAT to the properties obtained from our measurements and altered the conductivity of the liver and pancreas. Total impedances of 35–32 Ω were calculated for simulations where we assigned these organs conductivity values equal to 50% and 200% of the value reported in the Gabriel databases (Gabriel et al. 1996c, Hasgall et al. 2015). These results clearly show that the conductivity of the liver and pancreas had a negligible effect on the total impedance of the model. This is probably due to lower current density in the internal organs compared with the skin. Once the current flux passes the outer layer of the body, it spreads out to

![Figure 7](image_url)

Figure 7. (a) \(Z_{\text{Re}}\) measured at 150 kHz for each skin fold sample versus fold thickness. (b) Absolute value of the average \(Z_{\text{Re}}\) versus frequency measured for all skin fold samples. Error bars represent the standard deviation at each frequency. (c) SAT, dermis, and bulk skin (2.4 mm) conductivities (blue, primary axis) and epidermis and bulk skin relative permittivity (orange, secondary axis) calculated from measured data for all frequencies tested in this study.
fill the entire torso volume, and current density at any point is significantly reduced. Consequently, changing the conductivity of a part of the internal volume has very little effect on the impedance of the entire volume. Therefore, the total impedance of the model was relatively insensitive to changes in the conductivity of specific organs.

3.4. The effect of skin properties on electric field intensity

The electric field intensities in the torso were extracted from all the simulations described in the sensitivity analysis after normalizing the current applied to the models to 4 A peak to peak. Figures 8(a)–(d) shows coronal and axial views of the electric field intensity in the abdomen (field amplitude) through the pancreas for simulations where skin and SAT properties were assigned with our nominal dielectric properties at 150 kHz and pancreas and liver conductivities were assigned with 50%, 100%, or 200% of their conductivity values as reported in the Gabriel database (Hasgall et al 2015). Intensity maps of all other combinations of dielectric properties for skin and SAT yielded very similar maps to figures 8(a) and (d), and therefore are not presented. Figure 8(e) shows a histogram plot of field intensities in the pancreas of the simulations mentioned above, as well as two in which extreme conductivity values were assigned to skin and SAT (0.0007, 0.04] S m\(^{-1}\) and [0.45, 0.3] S m\(^{-1}\), respectively), and a simulation in which skin and SAT conductivity were set to nominal values and the current was set to 2A peak to peak.

It is evident from figure 8(e) that for a given current, the median electric field within the pancreas changed very little (less than about 10%), even when the skin and SAT properties changed by one and two orders of magnitude. However, changing the conductivity assigned to the pancreas had significant influence on field intensity within this organ: the higher the conductivity, the lower the electric field. These results can be explained by examining the field intensity maps shown in figures 8(a)–(d). Once the current penetrates the skin, it spreads out in the body, and only a small fraction of the current passes through any specific organ. Therefore, while changing the conductivity of a specific organ causes only small changes in the distribution of the current, changes in the electric field in that organ are proportional to the changes in conductivity. This is because the electric field intensity equals the unchanged current density divided by the conductivity.

4. Discussion

The purpose of this study was to elucidate the role of the outer-body layers (skin and SAT) in shaping the intensity and distribution of TTFields in the clinical setting by combining measurements with numerical simulations. The study comprised two parts: In the first part, we measured the dielectric properties of the skin under conditions similar to those imposed on the skin when delivering TTFields to patients with cancer. In the second part, we performed computational simulations to evaluate how the dielectric properties of the skin influence the intensity and distribution of TTFields.

To measure the properties of the outer-body layers, we placed electrodes on either side of skin folds at several locations around the waists of volunteers and measured the impedance of the folds. Assuming that the tissue in the skin fold comprised three layers (epidermis, dermis, and SAT) and analyzing the linear relationship between fold thickness and impedance, we derived dielectric properties for the three tissue types in the model. The calcu-

| $\varepsilon_r$, skin | $\sigma$ skin (S m\(^{-1}\)) | $\sigma$ SAT (S m\(^{-1}\)) | 0.02 | 0.07 | 0.11 | 0.3 |
|---------------------|-----------------------------|-----------------------------|------|------|------|------|
| 1100                | 0.08                        | 57                          | 39   | 36   | 30   |
|                     | 0.2                         | 53                          | 36   | 33   | 28   |
|                     | 0.36                        | 51                          | 34   | 32   | 27   |
|                     | 0.45                        | 50                          | 34   | 31   | 27   |
| 5396                | 0.08                        | 41                          | 37   | 35   | 30   |
|                     | 0.2                         | 37                          | 35   | 32   | 28   |
|                     | 0.36                        | 36                          | 33   | 31   | 27   |
|                     | 0.45                        | 35                          | 32   | 30   | 26   |
| 10 000              | 0.08                        | 36                          | 35   | 34   | 30   |
|                     | 0.2                         | 33                          | 32   | 32   | 28   |
|                     | 0.36                        | 32                          | 31   | 30   | 27   |
|                     | 0.45                        | 31                          | 30   | 30   | 27   |
lated effective dielectric properties of the bulk-skin were in good agreement with values reported by studies that characterized skin as one layer.

The electrodes we chose for the measurements were made of ceramic disks and medical gel similar to those found in the TAs used to deliver TTFields to patients, ensuring that conditions on the skin during the measurements were similar to those imposed on the skin in the clinical setting. This is important in skin measurements because the dielectric properties of the skin are sensitive to the environment. Measurements were performed in vivo on volunteers to ensure that the tissue being measured was viable and that its properties were not influenced by loss of blood flow and fluids, necrosis, or tissue death that can occur in excised samples. We note that during measurements, pressure was applied to the skin folds. This pressure may have resulted in small systematic errors in our measurements due to tissue compression. However, the pressure was necessary to obtain stable and consistent measurements.

The thickness of the medical gel used for the measurements was 0.6 mm, which is non-negligible. Thus variability, in the properties of the gel samples used for the individual measurements could lead to non-negligible variability in the measured properties of skin folds. To minimize this source of measurement error, the impedance of the disks and gels used for each specific measurement was measured separately, and subtracted from the total impedance measured for the skin-fold-ceramic disk-gel complex, to yield the net impedance of each skin fold. This methodology enabled us to account for variability in the properties of the gel samples used for each measurement thereby minimizing the measurement error.

Unlike experiments performed in vitro, when measuring samples in vivo it is impossible to accurately characterize sample geometry including the cross-sections and the thicknesses of the various layers. However, using an iterative process combining numerical simulations and linear regression on the measured data, we were able to derive an effective cross-section for the skin folds, which yielded consistent results, minimizing systematic errors in the values of the dielectric properties that we derived from the measurements. Since it was not possible to characterize tissue layer thickness in each fold, we assumed that the thicknesses of the epidermis and dermis were the same for all measurements and that the differences in the thicknesses of the various folds were only due to changes in the thickness of the SAT. This assumption is reasonable because the thicknesses of the epidermis and dermis of adults reported in the literature are 0.035–0.09 mm and 1–2.5 mm, respectively (Lee and Hwang 2002, Valentin 2002, Gabriel et al 2009, Peyman 2011, Jain et al 2013, Wake et al 2016). These ranges are small relative to the changes in the thicknesses of the skin folds we measured (4–24 mm). Therefore, the recorded differences in the various folds’ thicknesses were mainly due to changes in the thickness of the SAT. Our linear model connecting conductivity of the SAT and dermis to the measured impedance fits the data with a high goodness of fit ($R^2 > 0.74$). Thus, it is likely the intersample variability manifests itself as random noise in the model, which is averaged out by the curve-fitting procedure we applied. As such, the values that we derived from the model represent average values across the population of subjects on whom measurements were performed. In future studies, the magnitude of intersubject variability could be addressed by measuring the thicknesses of the various layers in
the field using imaging modalities such as optical coherent tomography and high-frequency ultrasound (Laurent et al 2007, Sattler et al 2013).

For an electrical model to be considered representative of the subject it simulates, it is necessary that the total impedance of the model matches that of the subject. Since other methods for validation such as in vivo measurement of the electrical field or current within the subject are more complicated and often not feasible, at present, comparing total impedance may be the only practical method for testing the reliability of computational models simulating delivery of TTFIELDS. Therefore, total body impedance was used to indicate that the dielectric properties of skin and SAT that we measured were representative of the dielectric properties of these tissues in patients treated with TTFIELDS. For this purpose we incorporated the measured dielectric properties into a realistic human computational phantom by calculating effective permittivity and conductivity for the single-layer phantom skin, which generated impedance equal to the impedance of a two-layer skin. The effective skin conductivity and permittivity derived for the model (0.07 S m\(^{-1}\), \(\varepsilon_r = 5340\) at 150 kHz) are within the low range of values previously reported for skin (Wake et al 2016): 0.1 ± 0.017 S m\(^{-1}\), Gabriel wet skin: 0.094 ± 0.013 \(^1\) S m\(^{-1}\), \(\varepsilon_r = 11362\), Gabriel dry skin: 0.0007 ± 0.0001 S m\(^{-1}\), \(\varepsilon_r = 1111\) (Gabriel et al 1996c, Andreuccetti et al 1997). The lower values derived from our measurements compared with wet skin may arise from the medical gel used in our study as a moistening agent versus saline solution that was used in other studies.

The conductivity for SAT tissue derived from our study (0.2 S m\(^{-1}\)) is in the higher range of conductivity reported by Wake et al (2016) (0.15 ± 0.02 S m\(^{-1}\)) and is about 2.5 times higher than the conductivity reported for fat by Gabriel et al (2009) (0.08 S m\(^{-1}\)). These differences may be due to different origins of the skin samples and different water content in the samples used in the different studies, which are known to influence fat conductivity (Wake et al 2016). Differences in the composition of this layer and the relative volume fraction of connective tissue in the sample (conductivity of 0.39 S m\(^{-1}\) at 150 kHz (Hasgall et al 2015)) may also increase the measured conductivity of the discussed layer of interest. This suggests that the values extracted from our measurements are valid for the subcutaneous tissue layer in computational phantoms.

When we applied SAT conductivity and skin effective dielectric properties to the phantom abdomen, the total impedance of the model was within the mid-range of values measured on patients. In previous studies involving TTFIELDS delivery to the abdomen, lower conductivity values were assigned to the skin and SAT (0.02 S m\(^{-1}\) and 0.08 S m\(^{-1}\), respectively). The typical impedance of the models in these studies was around 57 \(\Omega\), which is in the higher range of impedance measured on patients. Thus, the conductivity values derived in this study yield a better representation of the average patient treated with TTFIELDS than the conductivity values used in previous studies. Of note, the impedance measured on a single patient may vary by more than 10 \(\Omega\) over a single month. It is unlikely that this large variation arises from changes in the resistivity of the internal organs and tissues; it most likely originates from changes in skin conductivity and contact between the arrays and the skin. Understanding the exact causes for this variation is beyond the scope of this study and may be examined in detail in future studies.

The second part of this study focused on a sensitivity analysis in which we examined the degree to which variations in the dielectric properties of skin and SAT influenced the model impedance and field intensity of TTFIELDS delivered to computational phantoms. We showed that skin properties contributed significantly to the total model impedance when they were below a threshold value of about 0.05 S m\(^{-1}\) and relative permittivity of 5000. However, once they exceed these values, skin impedance drops to a level where it is small relative to the impedance of the rest of the body, and the total impedance of the body is insensitive to further increases in these properties. The dielectric properties we measured for skin and SAT placed these layers in the region where their contribution to the overall impedance was small relative to the contribution of the inner-body tissues. Therefore, our body model was relatively insensitive to the dielectric properties of these layers, and even an increase of over 100% in skin and SAT dielectric properties due to inaccuracies in the measurements or realistic physiological changes that may increase skin conductivity may not be reflected in measurements of the total body impedance.

In this context, it is interesting to note that according to our simulations, for a given current applied to the TAs, the field distribution within key organs (liver and pancreas) was only affected minimally by skin conductivity, even when the conductivity was below the threshold. This is because the current flowing through any plane crossing the body between the TAs is equal to the applied current regardless of skin properties. Thus, the current density in different regions of the body is largely unaffected by skin conductivity. Since the electric field is proportional to the current density, it is also mostly unaffected by skin conductivity. However, since the electric field intensity in any material is inversely proportional to its conductivity, field intensities within the organs are highly sensitive to the organs’ conductivities, as shown in this study. In addition, applying higher currents results in higher electric fields. Therefore, when studying TTFIELDS distribution within the body, accurate determination of the skin properties is only of secondary importance relative to accurately setting the properties of the organs of interest. In particular, the field intensity within tumors will strongly depend on the electric properties

\(^1\) The error was calculated based on Gabriel et al reporting a 15%–25% spread in measured values (Gabriel et al 1996b).
of the tumor and its surrounding tissues. Since reliable information on the electric properties of tumors in the frequency range of 100 kHz–1 MHz is scarce, studies focusing on measuring tumor properties within this range are warranted.

5. Conclusions

In this paper we presented a comprehensive study investigating the dielectric properties of skin and SAT under conditions similar to those imposed on the skin of patients during the delivery of TTFields. The findings of this paper are relevant to a wide range of low-frequency electro-therapeutics such as electric muscle stimulation and neurostimulation. This paper combined experimental work with simulations to derive dielectric properties for skin and SAT, then examined the influence of these properties on the total body impedance and the distribution of TTFields within the body. When applying the measured dielectric properties to computational models and simulating the delivery of TTFields to patients, the total impedance of the models matched well with patient data, suggesting that the dielectric properties of skin and SAT reported in this study should be used as standard values in future studies on the delivery of TTFields to the torso. Our results also suggest that the dielectric properties of skin and SAT are within a range where they have a relatively small influence on the total impedance of bodies to which TTFields are delivered and on the distribution of the electric field within the body. However, the simulations also show that the properties of internal tissues and the applied current play a major role in determining the field intensity within these tissues. Since the efficacy of TTFields increases with field intensity, and information on the dielectric properties of tumors in the frequency range of 100 kHz–1 MHz is scarce, future experimental studies focusing on the measurement of tumor properties within this frequency range are required. These studies will enable a better understanding of the interaction between TTFields and the human body, ultimately leading to better patient outcomes.

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