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Microwave Frequency Dependent Dielectric Properties of Blood as a Potential Technique to Measure Hydration

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ABSTRACT Tissue dehydration is known to have adverse effects on health and is highly challenging to characterize *in vitro* due to the complexity of the cell/tissue organisation. There have been a large number of studies reporting the dielectric properties of animal and human tissue explants or bodily fluids such as urine or blood over a wide frequency range from 10 Hz to 100 GHz. However, variations in blood composition involving the cell type, haematocrit (HCT) protein levels, ionic conductivity, electrolyte or glucose concentration will affect the dielectric measurements. The present study examined the effects of physiological osmotic solutions with NaCl (280 mOsmol/kg to 300 mOsmol/kg), HCT (35% to 50%) and albumin (3.5 g/dl to 5.5 g/dl) isolated from bovine blood on the dielectric properties measured at frequencies spanning from 0.5 GHz to 20 GHz using an open-ended co-axial probe. Measurements demonstrated linear correlations between permittivity and loss factor of blood solutions with varying HCT levels, albumin or osmolality such that a high protein concentration reduced the dielectric response in a dose-dependent manner. Whilst the spectral trends for the permittivity response to HCT and albumin were similar in a concentration-dependent manner, the loss factor profile was influenced by osmolality of the solution. In summary, we characterized the dependence of the microwave dielectric properties of blood on HCT, albumin and osmolality. The dielectric measurement technique has the potential to determine hydration levels for future diagnostic and therapeutic devices.

INDEX TERMS Dielectric measurements, biomedical engineering, open-ended coaxial probe, proteins.

I. INTRODUCTION

Dehydration is a continuing problem in malnutrition and healthcare resulting in critical patients who develop multiple organ failure with annual NHS costs estimated around £13 billion [1], [2]. The subject's hydration levels are determined by urine, blood or plasma osmolality either with freeze-point or vapor pressure depression techniques to quantify electrolyte and fluid ration [3]. However, the methods are time consuming with clinical staff monitoring at-risk patients by body mass, saliva or fluid balance. New approaches that are non-invasive, efficient, comfortable and easy to use are needed to improve prevention of dehydration.

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There have been a large number of studies reporting the dielectric properties of healthy or diseased tissues or bodily fluids from animals and humans over a wide frequency domain of 10 Hz to 100 GHz for medical diagnostics, therapeutics and wearable devices [4], [5]. Indeed, animal or human *in vitro* studies and numerical models have reported the tissue dielectric properties in dehydration, cancer, diabetes, inflammation, skin and lung disease [6]–[16]. However, the variability in the complex permittivity measurements comparing normal with the diseased cell or tissue type makes it difficult to understand the significance of the microwave dielectric measurements. Moreover, the effects of changes in the cell membrane and the extracellular matrix composition will increase blood or plasma osmolality, haemoglobin and haematocrit (HCT) levels, a protein

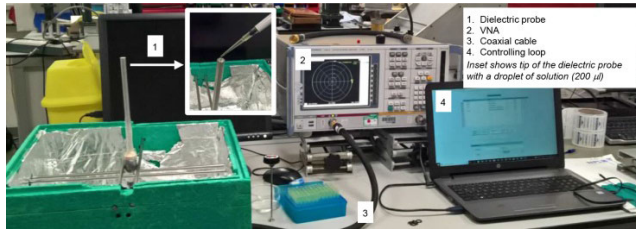


FIGURE 1. The dielectric measurement system. The experimental set-up is composed of a dielectric probe with an open-ended coaxial cable connected to the Vector Network Analyser (VNA), Inset shows the tip of the inverted dielectric probe with a droplet of solution (200 μ l).

well known to represent red blood cell (RBC) or erythrocyte concentration [17]–[19]. Indeed, RBCs isolated from whole blood and diluted in serum are well known to reduce real permittivity at microwave frequencies spanning 0.5 GHz to 20 GHz [15], [20]. At 0.5 GHz to 40 GHz frequency, the levels of hemoglobin were reported to reduce permittivity in whole blood taken from a rodent model [21]. However, plasma consists of multiple cell types such as lymphocytes, thrombocytes or proteins such as albumin or lactoglobulins that will affect blood permittivity measurements due to changes in the osmolality of the plasma solution. Despite the challenges of microwave diagnostics, machine learning models have been designed to predict permittivity by comparing cell types (erythrocytes, lymphocytes) with protein levels (haemoglobin, creatinine) or electrolyte (sodium) and glucose concentrations to broadband permittivity measurements in blood. For example, measurements of the dielectric properties of glucose in blood, plasma or osmotic water was reported to reduce both the real and imaginary part of permittivity at frequencies spanning from 0.5 GHz to 20 GHz in a concentration-dependent manner [5], [22]–[26]. Dehydration and exercise are well known to affect glucose concentration and increase body temperature thereby affecting permittivity measurements [27]–[31]. Whilst the effects of temperature on the dielectric properties of water are well understood, the effects of temperature in blood up to 1 GHz are reported to be more complex [15], [32]. The present study therefore examined the effects of varying levels of HCT, albumin and NaCl osmotic solutions on the dielectric profiles at microwave frequencies spanning from 0.5 GHz to 20 GHz.

II. METHODS

A. PERMITTIVITY MEASUREMENTS

Figure 1 shows the set-up of the broadband dielectric probe (Keysight 85070E, 9.5 mm diameter) and Vector Network Analyser (VNA, Rohde and Schwarz ZVB20) connected via an open-ended coaxial cable (HP 85132E). The dielectric probe was inverted and the tip of the probe pointed upwards (Inset, Figure 1). All permittivity measurements were performed between 0.5 GHz to 20 GHz at 0.1 GHz intervals using NPL proprietary Tkdsen® and Tkcal® software for sample and calibration measurements, respectively (NPL, Teddington, UK) with Full-Wave Modal analysis,

TABLE 1. Uncertainty values of the dielectric system.

Error	Permittivity (%)	Loss Factor (%)
Repeatability error	0.07	0.09
Calibration error	0.43	0.29
Combined Uncertainty	0.04	0.30

Note: The standard deviation of measurements of the dielectric system was examined for frequencies spanning from 0.5 GHz to 20 GHz with NaCl. All values represent the mean and SD of $n=6$ replicates for 0.1 M NaCl solutions equilibrated at room temperature.

as previously described [33]. Data acquisition was controlled via the HS+ GPIB (National Instrument). The operating frequency reflecting the operating band supported by the instrument and the coaxial probe with constrained electrical dimensions set to the current range tested. The dielectric system was calibrated with air, deionised water and a metallic short. A validation measurement was performed with 0.1 M NaCl solution (Sigma-Aldrich, Poole, UK) that had been equilibrated to room temperature of 20.0 ($\pm 0.2^\circ\text{C}$) and used to determine the standard deviation of measurements of the dielectric system with repeatability error, accuracy and total combined uncertainty values detailed in Table 1. All measurements were made with six replicate solutions (200 μ l) from the same test condition.

B. MODELLING THE EFFECT OF SAMPLE VOLUME

The electric field strength and distribution was mapped within a 200 μ l volume size of deionised water by Finite Element Model using a frequency domain CST Microwave Studio™ software and evaluated at 5 GHz and 20 GHz. The probe (150 mm length) was modelled for an inner (0.1 mm diameter) and outer Perfect Electric Conductor (9.5 mm diameter), a Polytetrafluoroethylene (PTFE) lossy insulator (1.6 mm diameter) and a circular base (9.5 mm diameter).

C. SAMPLE PREPARATION OF OSMOTIC FLUIDS

The NaCl solutions were prepared in deionised water with a range of osmolalities of 280, 300, 320 and 350 mOsmol/kg. The osmolality (ℓ) of the solution was determined using Concentration Correction Equation (1) and was prepared by dissolving the correct weight of NaCl (m_{NaCl}) in water ($m_{\text{H}_2\text{O}}$), taking into account the osmotic coefficient of NaCl ($\phi_{\text{NaCl}} = 0.93$) and its molar mass ($M_{\text{NaCl}} = 0.05844\text{kg/mol}$).

$$\ell = \frac{m_{\text{NaCl}} \phi_{\text{NaCl}}}{m_{\text{H}_2\text{O}} \frac{M_{\text{NaCl}}}{2}} \quad (1)$$

Osmolality was measured using an Advanced Instruments 3250 freezing point depression osmometer. The instrument was calibrated with room temperature standard NaCl solution of 280 mOsmol/kg osmolality. All samples were tested with a 200 μ l volume and the system verified within the ± 2 mOsmol/kg range.

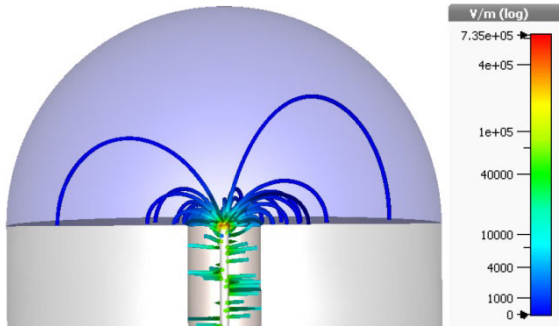


FIGURE 2. Modelling the electric field strength generated by the dielectric probe. The surface of the dielectric probe was modelled in the presence of a droplet of deionised water (200 μ l) and shows the electric field lines within the sample at 0.5 GHz.

D. HCT AND ALBUMIN PREPARATION FROM BLOOD

A bovine red blood cell solution (50%) resuspended in Alsevers solution (50%) was used to prepare the volume of packed RBCs relative to whole blood (Bioivt, West Sussex, UK). The percentage of HCT levels were calculated with the well-established microhematocrit method. Briefly, ten milliliters of whole red blood cell solution was centrifuged for 5 min at 500 g on the Thermo IEC CL 31 Multi Speed centrifuge, and the total length of the RBC solution was measured in the labelled graphic capillary tube. The RBCs (V_{RBC}) were diluted in NaCl solution resulting in a supernatant osmolality of 288 mOsmol/kg osmotic water (V_{OW}) and HCT levels diluted to 35, 40, 45 and 50 % (v/v) as described in Concentration Correction Equation (2).

$$HCT (\%) = \frac{V_{RBC}}{V_{RBC} + V_{OW}} \times 100\% \quad (2)$$

The correct weight of bovine serum albumin (Sigma-Aldrich, Poole, UK) with concentrations of 3.5, 4, 4.5 and 5.5 g/dl were diluted separately in NaCl solution with 288 mOsmol/kg osmolality, using Concentration Correction Equations 1, 3 and 4, where 6 g/dl albumin increased the osmolality (ΔI) of the solution as described in (3).

$$\Delta I = 0.8 + 205 \left(\frac{m_{NaCl}}{m_{H_2O}} \right) \quad (3)$$

The concentration of albumin in osmotic water (ρ_A) was calculated using Concentration Correction Equation (4), where (m_A) is the mass of albumin.

$$\rho_A = \frac{m_A}{V_{OW}} \quad (4)$$

A concentration of 6 g/dl albumin in NaCl solution with 288 mOsmol/kg osmolality was used as a standard. Albumin concentrations were measured with Bromocresol Green (BCG) assay at 620 nm on the SPECTROstar Nano microplate reader (BMG Labtech, Aylesbury, UK).

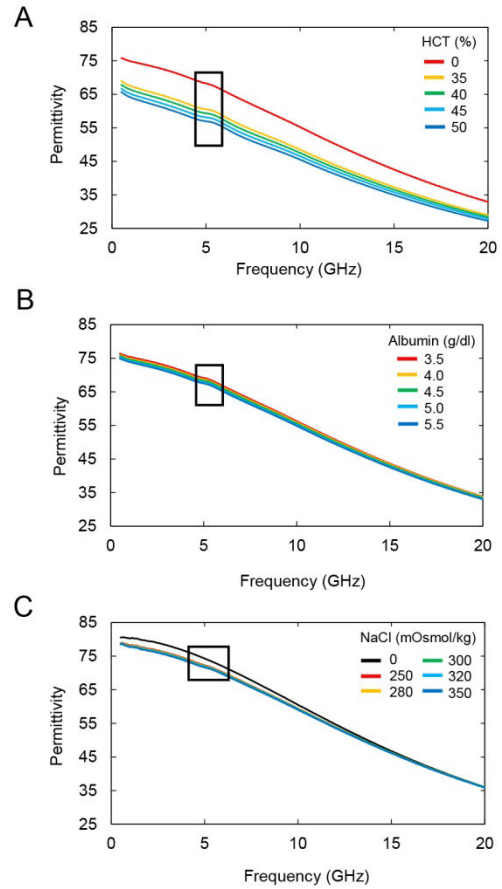


FIGURE 3. Concentration-dependent effects of blood components on the permittivity of osmotic water. Solutions of HCT (A), albumin (B) and NaCl (C) were diluted in osmotic water with concentrations ranging from 35 to 50% HCT, 3.5 to 5.5 g/dl albumin and 250 to 350 mOsmol/kg NaCl. The black boxes highlight bumps in the data caused by the calibration artifacts.

III. RESULTS

A. ELECTRIC FIELD MAPPING WITH MICROLITRE SAMPLE VOLUME

A CST model was designed to examine the effect of 200 μ l sample volume size on the tip of the dielectric probe (Figure 2). At a frequency of 0.5 GHz, the electric field lines at the tip of the dielectric probe have angular symmetry and remain homogenous within the droplet load terminating within the boundary conditions. A similar dielectric field pattern was found at 20 GHz, suggesting dielectric measurements could be performed in microlitre sample volumes.

B. DOSE-DEPENDENT HCT AND ALBUMIN EFFECTS ON PERMITTIVITY IN OSMOTIC SOLUTIONS

Figures 3 and 4 present the effects of HCT levels (35 % to 50 %), albumin (3.5 g/dl to 5.5 g/dl) and NaCl solutions with varying osmolality (250 mOsmol/kg to 350 mOsmol/kg) on the permittivity and loss factor, respectively.

The changes in permittivity were dependent on HCT and albumin concentrations, with a clear reduction in permittivity with increasing levels of HCT (Figure 3A), albumin

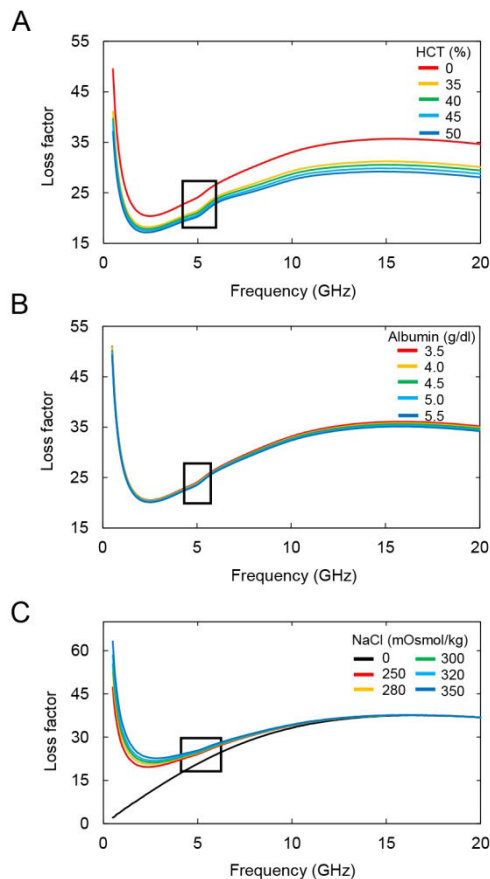


FIGURE 4. Concentration-dependent effects of blood components on the loss factor of osmotic water. Solutions of HCT (A), albumin (B) and NaCl (C) diluted in osmotic water with concentrations ranging from 35 to 50% HCT, 3.5 to 5.5 g/dl albumin and 250 to 350 mOsmol/kg NaCl. The black boxes highlight bumps in the data caused by the calibration artifacts.

(Figure 3B) and osmolality of the NaCl solution (Figure 3C), for all frequencies spanning up to 20 GHz. The permittivity response was paralleled with an increase in the loss factor over a frequency span of 10 GHz to 20 GHz that was dependent on the concentration of protein (Figure 4). In contrast, at a low frequency of 2 GHz, the loss factor was found to have a minimum value.

C. DISPERSIVE EFFECTS OF HCT LEVELS ON THE LOSS FACTOR

The effect of varying HCT levels diluted in NaCl solutions of 288 mOsmol/kg osmolality and a frequency domain from 2 GHz to 17 GHz is shown in Figure 5. At all frequencies examined, the loss factor has a linear relationship with HCT concentration and correlation values ranging from 0.9994 to 0.9995. While six selected frequencies are shown in Figure 5, this trend extends across the different frequency domains from 2 GHz to 17 GHz for all solutions examined.

D. SINGLE FREQUENCY CORRELATION OF HCT AND ALBUMIN EFFECTS

The effect of varying HCT levels and albumin concentrations prepared in NaCl solutions of 288 mOsmol/kg

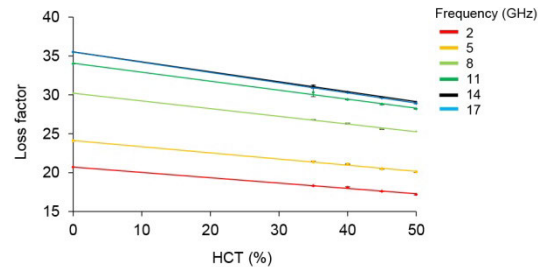


FIGURE 5. Concentration-dependent effects of HCT on the loss factor of osmotic water at frequencies spanning from 2 to 17 GHz. Correlation values ranged from 0.9994 to 0.9999 for all frequencies examined. While six selected frequencies are shown, this trend extends across 2 GHz to 17 GHz ranges for all solutions. Error bars represent the mean and SD values of $n = 3$ measurements.

osmolality on the permittivity and loss factor at 2 GHz is shown in Figures 6 and 7, respectively. At 2 GHz, the permittivity and loss factor have a linear correlation with the concentration of HCT levels, albumin and NaCl (R values = 0.999).

Whilst there was a concentration-dependent reduction in the loss factor with HCT levels (Figure 7A) and albumin (Figure 7B), the linear correlation for NaCl was found to be positive (Figure 7C).

E. PERMITTIVITY SPECTRAL PROFILES AT LOW CONCENTRATIONS

Figure 8 presents the changes in the permittivity and loss factor frequency profiles for HCT levels (5%), albumin (1 g/dl) and NaCl (10 mOsmol/kg) at low, non-physiological concentrations. The osmolality of the NaCl solution at 10 mOsmol/kg has a negligible effect on the permittivity with frequency spanning from 5 GHz and 20 GHz. At all frequencies examined, the loss factor spectra profiles for HCT and albumin are similar, with small differences in the gradients for frequencies less than 5 GHz in contrast to the permittivity which are different. The contribution of NaCl to the loss factor decreased steeply with frequency and is negligible at 20 GHz.

F. PERMITTIVITY MEASUREMENT PROFILES

Unexpected bumps in the spectra trends were observed in Figure 3, 4 and 8 at frequencies less than 2 GHz. These appear to be artifacts of the dielectric system influenced by the type of fluid measured.

IV. DISCUSSION

The present study demonstrated linear relationships between broadband microwave dielectric properties of varying HCT and albumin concentrations in osmotic solutions measured between 0.5 GHz and 20 GHz. We demonstrate that the changes in the real part of the complex permittivity are linearly correlated to HCT and albumin concentrations spanning from 2 GHz to 17 GHz (Figures 5 to 7). Whilst the effect of HCT and albumin concentrations resulted in a similar spectral profile of permittivity or loss factor, there was an

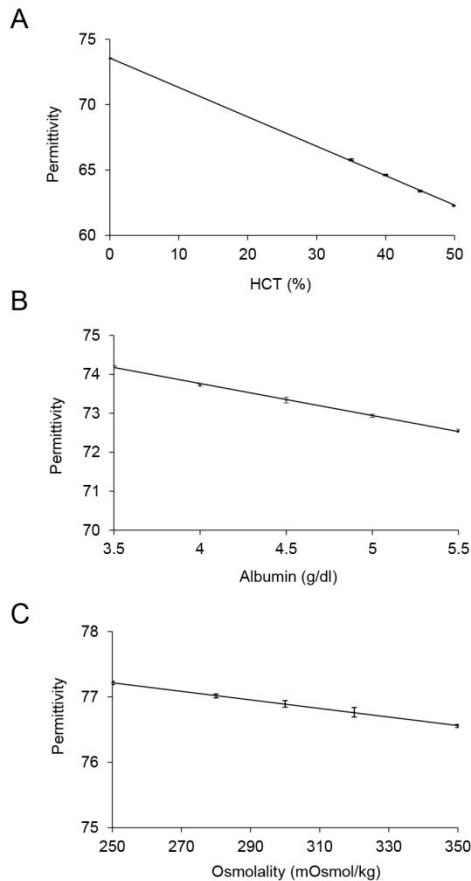


FIGURE 6. Single frequency concentration-dependent effects of blood components diluted in osmotic water on the permittivity. The HCT (A), albumin (B) and NaCl (C) concentrations demonstrate a linear relationship at 2 GHz with R values = 0.999. Error bars represent the mean and SD values of $n = 6$ measurements.

approximate 4.5 % difference in the Concentrations Correction Equation below 5 GHz but not a high frequencies, enabling frequency profiles to be differentiated for each concentration examined (Figure 5). Ionic dielectric polarisation is well known to play a role in the loss factor. The complex permittivity of pure water at microwave frequencies is dominated by the dipolar interactions between hydrogen and oxygen. The addition of NaCl to water disrupts the interactions between the molecules, resulting in the reduced real permittivity [34]. In contrast, the interactions of sodium and chloride ions in an oscillating electric field induce ionic motions that absorb the field energy and dissipate it as heat, resulting in an increase in the imaginary permittivity and thus in the loss factor. The effect of NaCl is therefore frequency dependent with a greater loss at low frequencies and negligible impacts above a frequency of 10 GHz in line with a permittivity response described by the well-established Debye model [21].

In the present study, the changes in the complex permittivity were measured and linear relationships with varying concentrations were found. The presence of haemoglobin, albumin or NaCl diluted in osmotic water is well known to reduce the dipole density and influence the polar interactions per volume resulting in a reduction in the permittivity

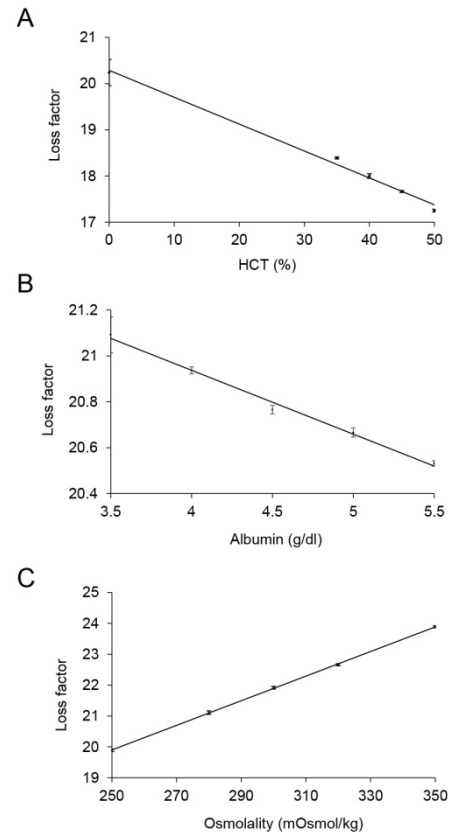


FIGURE 7. Single frequency concentration-dependent effects of blood components diluted in osmotic water on the loss factor. The HCT (A), albumin (B) and NaCl (C) concentrations demonstrate a linear relationship at 2 GHz with R values = 0.999. Error bars represent the mean and SD values of $n = 6$ measurements.

within the microwave region as described previously by the Cole-Cole theory. The changes in the polarisation of haemoglobin or albumin and NaCl electrolyte loss factor therefore enable protein measurements with a single frequency technique (Figure 5), with a clear correlation of the permittivity (Figure 6) and loss factor (Figure 7) at a low frequency of 2 GHz for HCT or albumin. In contrast at 18 GHz, varying HCT levels and albumin could be measured independently of osmolality by using both the permittivity and loss factor. This approach is an alternative frequency measurement domain to be explored at low concentrations.

Whilst RBCs are highly specialized cells, they have no nucleus, mitochondria or endoplasmic reticulum and function as an oxygen transporter in blood undertaken by haemoglobin. Erythrocytes have low permittivity due to the high haemoglobin content, biconcave cell morphology and high surface to volume ratio, which differs from WBC types such as leukocytes or granulocytes which have a nucleus and spherical morphology. The erythrocyte concentration representing HCT levels is well known to take up a large volume fraction of the plasma. In the present study, HCT levels were found to reduce permittivity of the osmotic solution with increased HCT concentration. Furthermore, it has been previously reported that the plasma membrane of erythrocytes

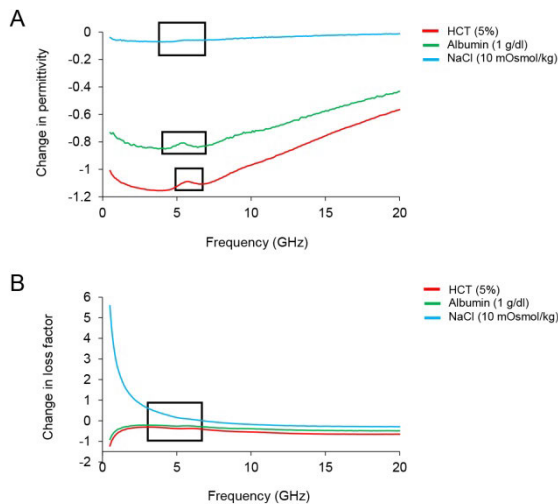


FIGURE 8. The change in permittivity and loss factor in response to low concentrations of HCT (A), albumin (B) and NaCl (C) at different frequencies. The bump seen from 4-8GHz for %HCT and albumin is a continuation of the artifact in figures 2 and 3.

does not exhibit dielectric α -relaxation dynamic process [15]. This phenomenon could likely be caused by counter ion diffusion effects for frequencies less than 100 KHz with similar dielectric properties of erythrocyte to blood proteins and are factors that could influence dielectric profiles [35]. However, albumin and globulin protein structures are species dependent such that the molecular structure could affect binding, folding and dielectric profiles [37], [37]. Erythrocyte concentrations are also species dependent, with humans have a higher HCT level than bovine fluids [38]–[40].

We did not characterize the permittivity response to the multiple cell types (e.g. lymphocytes, neutrophils, monocytes, phagocytes, granulocytes), serum proteins (e.g. globulins, fibrinogens), electrolytes, metabolites, hormones or molecules (e.g. amino acids, fatty acids, cholesterol) found at varying concentrations in human blood. The present study characterized HCT levels which are well known to correlate with erythrocyte cell concentration and are a major component in blood. Indeed, erythrocytes constitute up to 45% of total blood volume compared to less than 1% for WBCs. Due to the low cell concentration and short-term cell viability of WBCs, the cells of the immune system will therefore have a negligible effect on permittivity and uncertainty values of the dielectric system. Indeed, several studies have previously assessed the dielectric properties of metabolites such as glucose, lactate or cholesterol [40]–[44]. The concentration of glucose or lactate in healthy blood is low and will have small effects on permittivity. However, there are several physiological and pathological conditions where the cell type or protein composition in blood may deviate from the normal physiological range. For example, glucose and lactate concentration in blood can reach non-physiological levels that significantly alter gene expression and protein synthesis activating inflammatory mechanisms during stress or dehydration. In order to fully understand the potential application of using dielectrics to characterize hydration, haemoglobin, HCT and lactate of

TABLE 2. Comparison of approaches for osmolality with broadband microwave dielectric measurements.

Criteria	Osmolality	Microwave dielectrics
Technique	Freeze-point depression	HCT or albumin diluted in NaCl
Calibration	30 min daily	10 min daily
Sample preparation	Plasma separation from cells/proteins before testing	Immediate testing
Microliter sample volume	10 μ l to 250 μ l	200 μ l
Sensitivity	+/- 2 mOsmol/kg	+/- 2.5 mOsmol/kg +/- 1.3 % HCT +/- 0.5 g/dl albumin
Measurement time for one sample	Within minutes	Within seconds
Multiplex measurements	No	Simultaneous measurement of multiple factors from a single sample
Non-destructive testing	Sample cannot be re-used for further testing	The technique has the potential to be non-destructive

blood should be monitored during biochemical profiling of blood hydration [45], [46].

In contrast, the differences in the dielectric properties of normal and diseased tissue explants or urine, plasma, blood, saline solutions, deionised water and other interstitial fluids that mimic blood have been extensively reported in the literature [5], [8], [9]. Indeed, many investigators have previously demonstrated glucose-dependent dielectric properties of blood and other liquids with possible developments of microwave wearable devices for glucose monitoring [23]–[25]. The dielectric properties of the blood plasma were previously measured with Agilent’s open-ended coaxial dielectric probe system at frequencies spanning from 0.5 GHz to 20 GHz. For example in a previous study, small changes in physiological glucose concentrations ranging between 72 mg/dl to 216 mg/dl were reported to have negligible effects on permittivity in contrast to high glucose levels of 300 mg/dl similar to a diabetic patient which reduced the relative permittivity [5]. The high sensitivity of the measurement system is required to detect small changes if continuous monitoring is needed but factors such as temperature, frequency, osmolality, cell membrane and protein concentration will affect the plasma dielectric properties. It is clear that the detection of glucose in blood or plasma by dielectric measurements is challenging and systems must be designed accordingly.

Table 2 compares osmolality techniques with broadband microwave measurement systems. Whilst the ideal scenario will be to design an efficient, multiplex system that requires

no sample preparation and measures with accuracy and precision, the reality is that the measurements are affected by the choice of frequency, cost of electronic components and spectra behavior complicated by the protein or molecule being examined. Whilst microstrip or patch antennas for monitoring surface hydration have been previously designed to improve the sensor response in skin, the translation of these devices to the dielectric system will be affected by the selection of frequency which influence penetration depth and spectral behavior [13], [47]–[50]. Thin patches with chemical sensors for assessing metabolites or electrolytes in saliva, sweat or skin may potentially provide an estimation of hydration but the concentration of these factors will be influenced by the individual's biometrics and daily activities [45], [51]. Several whole-body, surface and extremity approaches for microwave assessment have been proposed but it is currently difficult to measure specific changes with a dielectric measurement device [45], [46], [52]. In the future, the development of non-invasive diagnostic or wearable devices will need to adopt a multi-disciplinary approach to overcome the challenges of improving the accuracy, reliability and portability of dehydration detection for successful evolution of current technology.

V. CONCLUSION

The present study demonstrated linear relationships between broadband microwave dielectric properties of varying HCT levels and albumin concentrations in osmotic solutions spanning between 0.5 GHz and 20 GHz. Whilst the spectral trends for the permittivity response to HCT and albumin were similar in a concentration dependent manner, the loss factor profile was influenced by the osmolality of the solution. In summary, we characterized the dependence of microwave dielectric properties of blood on HCT, albumin and osmolality. The dielectric measurement technique has the potential to determine hydration levels for future diagnostic and therapeutic devices.

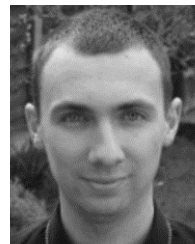
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