



## Measurement of Electrical Conductivity of Human Blood at Frequencies Below 100 kHz with Four-electrode Probe Method

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### Abstract

Electrical conductivity of blood at low frequencies is fundamental for medical electromagnetic applications, such as pulsed field ablation of cardiac tissue. There are several studies in the literature reporting conductivity measurements of blood. However, knowledge of this data at frequencies below 100 kHz is limited due to measurement challenges, including electrode polarization. Electrode polarization is generally reduced by using a four-electrode probe method. For this reason, in this study, we used a low-cost four-electrode probe to measure the conductivity of  $N=9$  human blood samples to electrically characterize human blood between 100 Hz and 100 kHz. The measured conductivity data is in good agreement with the data from the literature, showing that such a low-cost probe is suitable for measurements of blood conductivity. This study introduces a simple and low-cost four-electrode probe as a practical tool for measurements of electrical conductivity of human blood at lower frequencies and helps to fill the gap in the knowledge of electrical conductivity of human blood.

### 1 Introduction

The data for the electric conductivity of human blood at lower frequencies (i.e.  $< 100$  kHz in this study) is very limited. A comprehensive online database hosted and maintained by IT’IS Foundation contains the values for the electrical conductivity of a number of tissues at frequencies up to 1 MHz, including statistical information on the standard deviation and the spread in the values [1]. The value for the electrical conductivity of blood in the database is taken from the previous studies by Gabriel *et al.* in 2009 [2], Geddes *et al.* in 1967 [3], Hahn *et al.* in 1980 [4], and Mohapatra *et al.* in 1975 [5]. The database does not give the values of electrical conductivity for a list of frequencies, but lists only one value for all frequencies below 1 MHz. The reason why the electrical conductivity data at low frequencies is scarce is that there are many challenges when measuring biological tissues at such low frequencies, with electrode polarization (EP) being one of the biggest challenges [6, 7].

EP is the effect caused by the development of ionic double layers at the electrode-sample interfaces under the influence of electric field [7]. EP can depend on many factors, including the conductivity and the temperature of the sample, the structure and the composition of the electrodes and even the roughness of the electrode surface [7]. These effects can be further complicated by electrochemical reactions taking place on the electrode-sample interface [7]. One of the methods of mitigating the effects of EP on the measurement of electrical conductivity is the use of four-electrode probe method in a four-terminal sensing configuration [6, 8]. The four-electrode probe method is often used in galvanostatic regimen, where the sine-wave test current is applied between the working electrode (WE) and the counter electrode (CE), while the voltage is measured between the working sensing electrode (WSE) and the reference electrode (RE) [8]. Since no current is drawn at both WSE and RE, the measured impedance is independent of the electrode-sample interfaces [8].

In their 2009 study, Gabriel *et al.* have implemented the four-electrode probe method in their *in vitro* measurements on porcine blood [2]. In a more recent study by Wolf *et al.* [9], electrical conductivity was measured on human blood *ex vivo*. Wolf *et al.* did not implement the four-probe method in their measurements of electrical conductivity at lower frequencies so their results are likely influenced by the effects of EP. In this study, we have measured the electrical conductivity of human blood *ex vivo* at frequencies from 100 Hz to 100 kHz by implementing the four-electrode probe method in order to avoid the effect of EP. We have developed a low-cost four-electrode probe, with dimensions that allow for measurements of small volumes of blood, e.g. lower than 6 ml.

### 2 Materials and Methods

Measurements of electrical impedance of human blood with four-electrode probe method were performed at both room temperatures and at body temperature. The number of samples measured was thirteen ( $N=13$ ) and the results of ( $N=9$ )

samples were used as the volume of ( $N=3$ ) samples was not sufficient to fill up the measurement cell. The goal of the experiments was to characterize the electrical conductivity of human blood as a function of frequency at frequencies between 100 Hz and 100 kHz. Ethical approval for the study was secured from University Hospital Galway.

## 2.1 Measurements

The measurement setup is described below. Electrical impedance data measured between the WSE and RE was acquired from each sample using the PGSTAT204 potentiostat/galvanostat (Metrohm Autolab B.V., Utrecht, The Netherlands) set to work in galvanostatic mode. Current flowing from WE to CE was set to 10  $\mu$ A RMS. The measurements were performed at  $N=51$  frequency points with a logarithmic distribution across the range from 1 Hz to 100 kHz ( $N=10$  frequency points per decade). The results of the measurement as frequencies below 100 Hz were not consistent and were not included in the data analysis.

## 2.2 Four-electrode probe and measurement setup

A four-electrode probe was assembled with the parts from a standard electronics development kit. Four pins of a gold plated pin header (Harvin, Portsmouth, United Kingdom) were used as four electrodes in a linear array. Four male-to-female breadboard jumper cables (MikroElektronika, Belgrade, Serbia) were used to connect the pins to the PG-STAT204.

Fig. 1 shows the schematic representation and a photo of the probe. The probe is small and it is suitable for measurements on small samples ( $< 6$  ml). The largest dimension is the width of the probe of only 10.16 mm. The distance between the electrodes is 2.54 mm. The length of the electrodes is 3 mm and the width is 0.64 mm. The pins that make the electrodes are gold plated. Total cost of all parts needed to assemble this probe is less than EUR 1.20 per probe (RS Radionics, Dublin, Ireland). The assembly of the probe is simple and straightforward. The probe is designed to be connected to a four-terminal impedance measurement device in a four-electrode configuration. The connections are: WE (red), WSE (purple), RE (blue), and CE (black).

A water thermal bath (Fisher Scientific, Isotemp R , Waltham, MA, USA) was used to control the temperature of the blood samples. The samples were contained in a cell culture tray wells. The rest of the measurement setup consisted of aforementioned PGSTAT204 potentiostat/galvanostat and a computer and is shown in Fig. 2. PG-STAT204 is on one side connected to the probe in a four-electrode configuration and on the other side is connected to a computer. The computer is running NOVA 2.1.4 software with FRA32M impedance analysis module (Metrohm Autolab B.V., Utrecht, The Netherlands). The samples are

brought into contact with the probe by the lift table so there is no need to move the cables or the equipment.

## 2.3 Blood Samples

Venous blood samples were extracted from the antecubital veins of oncology patients approximately 30 minutes before performing the measurements. Whole blood was collected in EDTA tubes, and transferred directly to the laboratory for measurement. Each tube contained approximately 6 ml of blood, which was enough to fill the cell culture well. The first measurement on each sample was performed at room temperature. The second measurement was performed after the sample was brought to the body temperature using a thermal water bath.

Blood from each vial was poured into a small well on a cell culture tray and the temperature of the blood was recorded immediately before we performed the impedance measurements. The size of the samples and the dimensions of the well determined the maximum dimensions of the probe. The temperature of the samples during the first measurements was 22.6  $^{\circ}$ C (SD = 0.8  $^{\circ}$ C). During the second experiment, the temperature was 36.6  $^{\circ}$ C (SD = 0.4  $^{\circ}$ C). The temperatures were measured with DTM 3000 digital thermometer (LKM electronic GmbH, Geraberg, Germany).

## 2.4 Cell constant and calculating electrical conductivity

Impedance data was converted to electrical conductivity of the samples in two steps. The first step is determining the cell constant, which is the factor that relates measured conductance and the corresponding reference conductivity [2]. The second step is calculating the electrical conductivity from the measured impedance data and the calculated cell constant. The cell constant is determined by measuring the impedance of a standard liquids with known electrical conductivity and relative permittivity. In this study we determined the cell constant by using 0.05, 0.1 and 0.15 mol/l aqueous NaCl solution at room temperature as standard liquids. Cell constant is calculated as (1), expressed in metres:

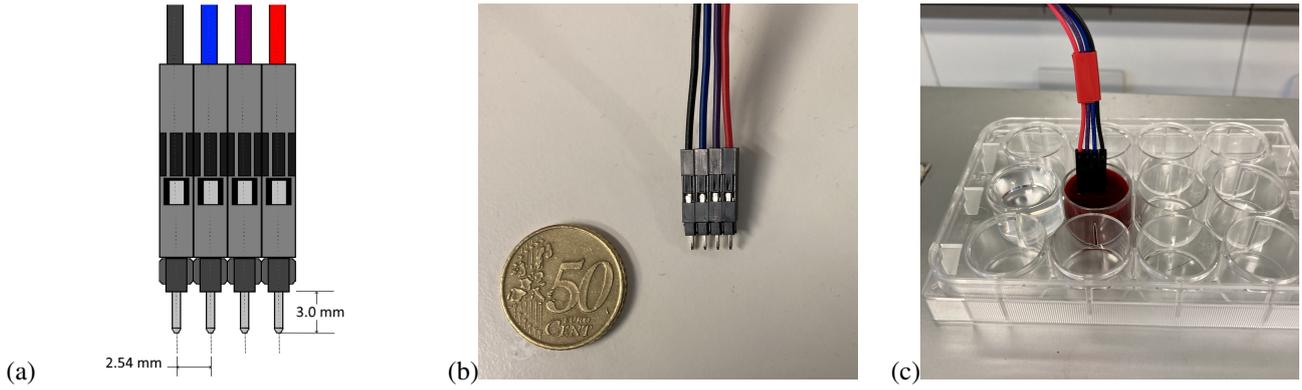
$$k = \frac{G}{\sigma}, \quad (1)$$

where  $G$  is the measured conductance and  $\sigma$  is electrical conductivity of the standard liquid.

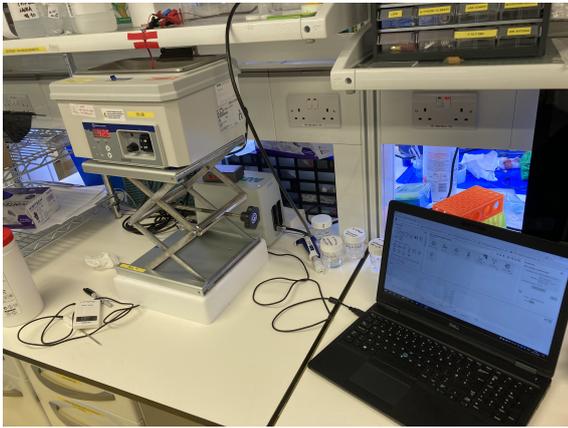
The cell constant of the probe is 0.028 m which is suitable for measurements of biological tissues and is similar in value to the value of cell constant in the Gabriel *et al.* 2009 study (0.02 m) [2].

## 3 Results and Discussion

The results in Fig. 3 show that with our measurement setup comprising a low-cost four-electrode probe we can obtain



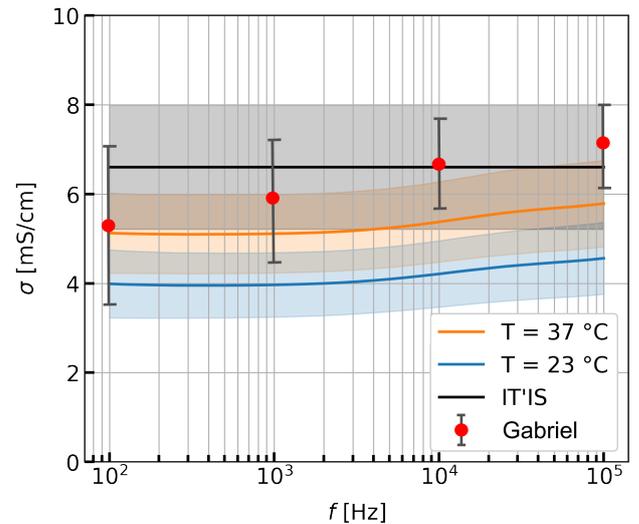
**Figure 1.** Schematic representation (a) and a photo (b) of the probe fabricated from four pin headers and four male to female breadboard wire jumpers. The probe is sufficiently small to measure small samples (< 6 ml), is cheap and easy to make and has shown good characteristics down to 100 Hz. The probe is designed to be connected to a four-terminal impedance measurement device in a four-electrode configuration. The connections are: working electrode (red), working sensing electrode (purple), reference electrode (blue), and counter electrode (black). The distance between the electrodes is 2.54 mm and the length is 3 mm. These dimensions give the cell constant of 0.028 m. A cell culture tray was used as a sample holder (c).



**Figure 2.** Measurement setup with the probe, the samples and the laptop running NOVA software in the foreground. AUTOLAB is in the background. The samples are brought in contact with the probe using the lift table so the probe and the cable could stay fixed. The temperature of the samples is controlled using a water thermal bath.

**Table 1.** Mean conductivity and standard deviation of blood at 1 kHz, in mS/cm. Difference in the mean values is explained by the difference in the temperature of the samples. The higher the temperature of the sample, the higher the conductivity. There is a 20.55% difference between the data from this study and literature data at body temperature [1].

	Conductivity mean (STD) [mS/cm]	Temperature mean (std) [°C]
Room temperature	4.21 (0.74)	22.6 (0.8)
Body temperature	5.37 (0.90)	36.6 (0.4)
IT'IS [1]	6.60 (1.39)	-



**Figure 3.** The results of measurements of conductivity of blood samples. The total number of blood samples that were measured was nine ( $N=9$ ). The values from IT'IS database [1] and from Gabriel *et al.* 2009 study [2] are given as a reference. The values from our experiments and from IT'IS database [1] are given as mean (solid line)  $\pm$  standard deviation (shaded area). The values from Gabriel *et al.* 2009 study [2] are given as points  $\pm$  standard deviation (error bars).

values within the range of those reported in the literature. Table 1 shows numerical values of the electric conductivity for both experiments, at 1 kHz, compared with the value from IT'IS database [1]. The percentage difference between the IT'IS value and the value at body temperature is 20.55%, with IT'IS reporting higher conductivity.

The conductivity that was measured while the samples were at room temperature is lower than the measured conductivity of the samples at body temperature. This is expected at lower frequencies as was shown in a number of studies that were covered in a review on the topic by Rossmann *et al.* in 2014 [10].

Although the measured data is in good agreement with the literature, the data acquisition frequency could be extended (in the lower end) by using platinum coated electrodes, which further minimises the effect of EP [7]. Furthermore, the standard deviation of the blood electrical conductivity could be reduced by increasing the number of measurement samples.

## 4 Conclusion

In this study we performed measurement of electrical conductivity of human blood at frequencies from 100 Hz to 100 kHz with a custom made low-cost four-electrode probe. The probe has shown good performance at frequencies higher than 100 Hz. The difference between the measured electrical conductivity and the values from the literature can be well explained by difference in temperature of the measured samples.

This study shows that electrical conductivity of blood can be measured with custom low-cost probe in a four-electrode configuration. Small probe design changes could improve the performance of the probe significantly without increasing the cost of the probe and give us even better results in the future. The data from these experiments already helps to fill the gaps in the knowledge of low frequency electrical conductivity of human blood. As suggested in Section 3, future studies with the improved version of this probe could provide a more detailed characterization of the electrical conductivity of the human blood, which could then be used in medical electromagnetic applications, such as the simulation of pulsed field ablation of cardiac tissue.

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