

# A NOVEL MODEL OF BLOOD IMPEDANCE FOR INDIRECT VISCOSITY MEASUREMENT

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*Recent studies have shown the existence of a remarkable strong correlation between electrical impedance and viscosity of blood. Because of possible application for indirect viscosity measurement, impedance-measurement techniques have been investigated. In this paper two measurement techniques to measure blood impedance are discussed. These are the two-electrodes and the four-electrodes technique. The results show the advantages and drawbacks of both these techniques, which appear to depend on the frequency range and the electrodes contact of the electrode-blood interface. Based on experimental results, a novel model for blood impedance has been developed. As compared to existing models, the novel model is valid for a wider frequency range.*

## 1. INTRODUCTION

When blood is centrifuged one can distinguish three components (figure 1), namely: plasma (55%), buffy coat (1%) and red blood cells or erythrocytes (44%). If a person has an inflammation, then there is an increased risk that the red blood cells will aggregate. This aggregation increases the risk for occurrence of thrombotic events such as heart infarcts or strokes. An important parameter for aggregation is viscosity. Therefore for certain patients it could be worthwhile to monitor blood viscosity in vivo. However, up to now this is not possible.

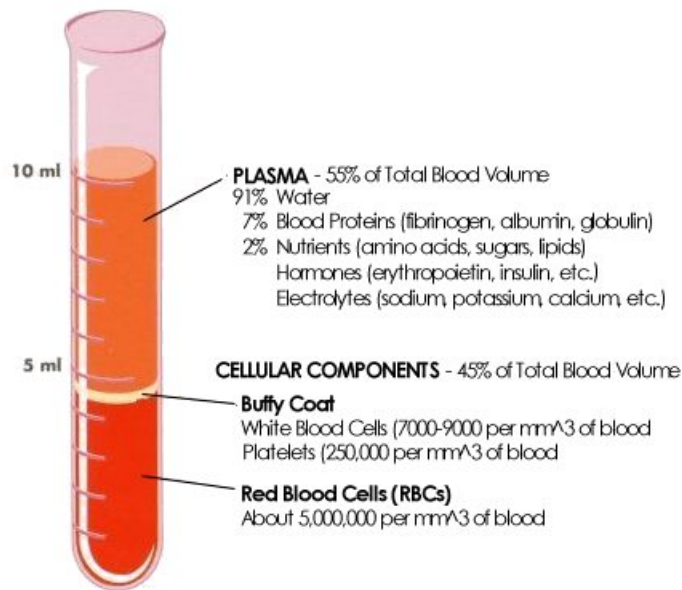


Fig. 1. Content of whole blood after centrifuge.

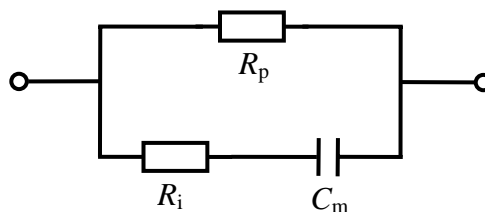
Recent studies of Pop *et al* [1] showed that there is a remarkable strong correlation between the viscosity and the electrical impedance of blood. A possible explanation for this correlation is, that clattering of red-blood cells gives rise to an increase of both: viscosity and impedance of blood.

The existence of this phenomenon makes it worthwhile to investigate the possibilities of viscosity measurements in an indirect way, by performing impedance measurements.

In this paper two measurement techniques to determine the blood impedance are compared: the two-electrodes and the four-electrodes technique. Using both types of measurement techniques characteristic impedance properties of blood can be found. The blood characteristics will be modeled over the frequency range up to 100 MHz. These results will be used to find the requirements for practical measurement setups for in-vitro and ultimately in-vivo blood-impedance measurements.

## 2. IMPEDANCE MEASUREMENT SETUP

Figure 2 shows a commonly used model for the blood impedance [2]. It concerns a lumped model for whole blood, where  $R_p$  represents the plasma resistance in presence of red blood cells,  $C_m$  represents the cell membrane capacitance and  $R_i$  represents the interior resistance of the red-blood cells.



*Fig. 2. The electrical model of whole blood impedance, according to [2].*

Preliminary measurements have shown that [1] both parameters  $R_p$  and  $C_m$  are affected by blood viscosity. For further investigation a measurement setup has been developed, which was required to measure at least the parameters  $R_p$  and  $C_m$  and to enable a check of the model validity for frequencies up to 100 MHz.

The impedance measurements have been performed with a four-electrodes and a two-electrodes setup, respectively. Figure 3 shows the front-end measurement circuit used for the four-electrodes setup. The output voltages  $V_{O,ref}$  and  $V_{O,DUT}$  are connected as input voltages for a gain-phase analyzer HP4192A (not shown in the figure) to obtain the impedance results. The measurement cell is filled with blood. This cell is implemented with the four measurement electrodes. Two instrumentation amplifiers,  $A_{I,1}$  and  $A_{I,2}$ , and two Opamps,  $OA_1$  and  $OA_2$  have been used. The capacitors  $C_{d1}$ ,  $C_{d2}$  and  $C_{current}$  are used for DC decoupling, while resistor  $R_b$  is needed for proper biasing of the Opamps.

The principle of this front-end circuit is as follows: when applying a constant AC voltage over the resistor  $R_{\text{current}}$  (neglecting  $C_{\text{current}}$ ), an almost constant current will flow through the electrodes number 1 and number 4. This voltage is amplified by the instrumentation amplifier and generates the output voltage  $V_{O,\text{ref}}$ , which is a measure for the current. With the two sense-electrodes 2 and 3 the voltage across the inner part of the electrode configuration is measured, This voltage is also amplified and results in the  $V_{O,\text{DUT}}$ . From these two voltages the Gain and Phase are obtained and the modulus and the argument of the impedance are calculated.

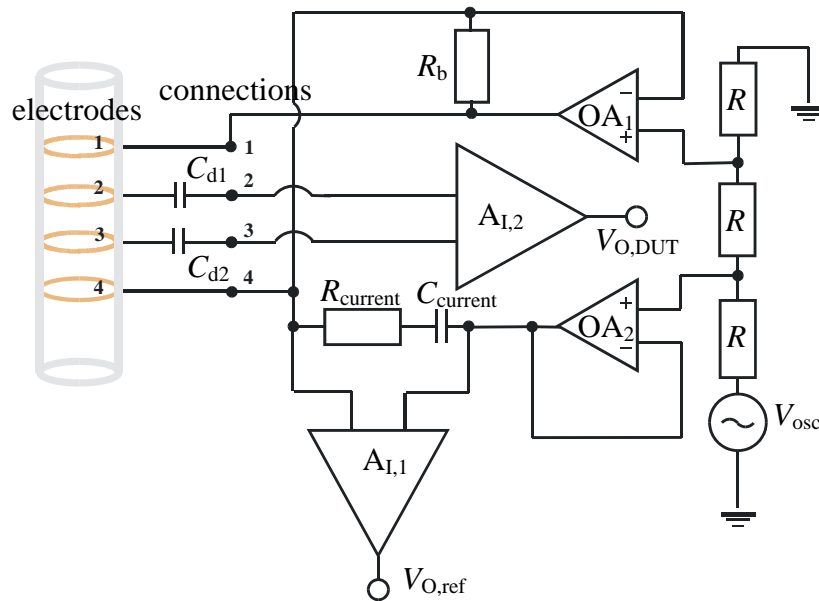


Fig. 3. Front-end measurement circuit of the four-electrodes measurement setup.

For the two-electrodes measurement setups an Agilent 4294A precision impedance analyzer has been used. This analyzer has been connected straightforward with the electrodes 1 and 4, without using any additional electronic means. When using the two-electrodes technique to measure the blood impedance, in series with this impedance the polarization impedance of the electrode/blood interface will also be measured. Especially, in the low-frequency region this polarization impedance is important. Figure 4 shows a model for this polarization impedance. The capacitor  $C_{\text{dl}}$  represents the double layer capacitance and  $R_{\text{ct}}$  the charge transfer resistance. Further in Figure 4 the Warburg-element and the contact potential ( $V_{\text{contact potential}}$ ) are shown.

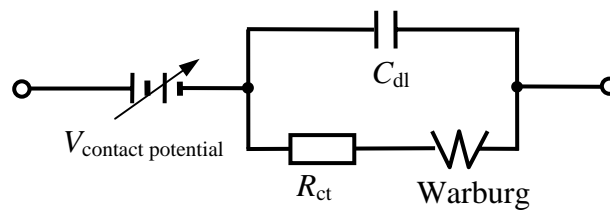


Fig. 4. Electrical model for the polarization impedance.

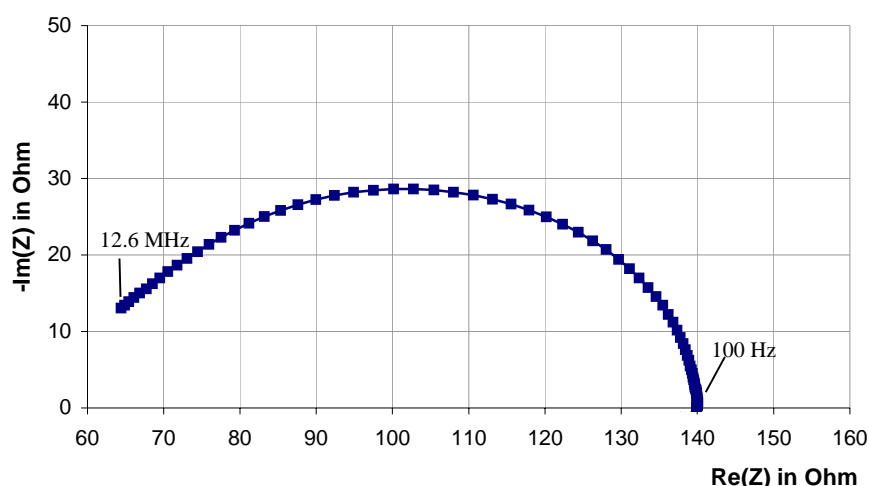
For in-vivo measurements, for safety reasons, the signal frequency should be higher than 20 kHz in order to prevent interference with the heart rhythm. As will be shown, in our setup the polarization impedance at these frequencies was negligible. However, in practical circumstances, due to the effects of corrosion, oxidation and growth of an endothelium layer, at the long term contact resistance will cause unreliability of the measurement result. Therefore, to avoid the affects of contact resistance and polarization impedance, people usually prefer to use the four-electrodes technique.

On the other hand it is not so easy to implement the four-electrode setup for the higher frequency range ( $>10$  MHz). This problem is caused by the effect of parasitic capacitances, which cause phase shift and current loss, and which at high frequencies results in an inaccuracy of the impedance measurement. Therefore, for the purpose of characterization and modeling we combine the results of both methods. Moreover, to compensate for the residual errors a good calibration setup is required.

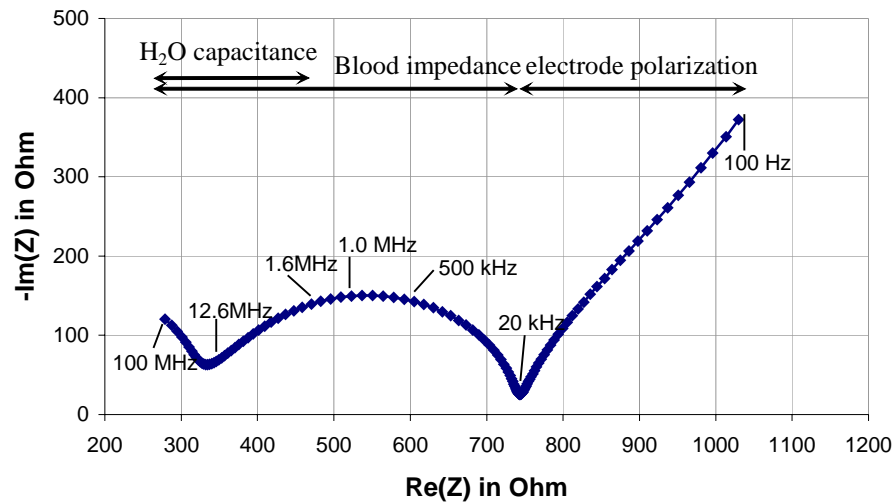
For short-term blood-impedance measurement in our measurement setup we have used both stainless-steel and gold-coated electrodes. However, when applying these two types of electrodes, no significant difference in the impedance measurements has been found.

### 3. RESULTS OF THE MEASUREMENTS

Blood of a volunteer was collected and anti-coagulated with Heparin. Next, the blood was put in a cylindrical-measurement cell with a diameter of 9.52mm. The measurement result of the four-electrodes measurement is shown in figure 5. For the same blood figure 6 shows the result for the two-electrodes measurement. Because of the difference in the cell constants, for the two techniques the values along the axis are different.

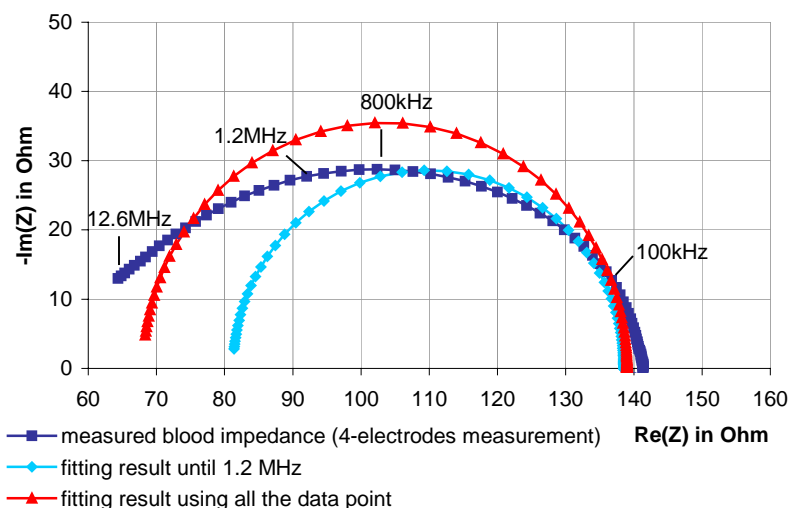


*Fig. 5. Nyquist plot of blood impedance using four-electrodes technique, heamatocrit (% red blood cells)  $H_t=45\%$ ,  $T=24^\circ\text{C}$ .*



*Fig. 6. Nyquist plot of blood impedance using two-electrodes technique, heamatocrit (% red blood cells)  $H_t=45\%$ ,  $T=24^\circ\text{C}$ .*

It can be observed, that for the frequency range from 20 kHz to 12.6 MHz both methods give similar results. Moreover, figure 6 shows that the electrode polarization is only significant for two-electrode technique, for frequencies below 20 kHz. Around 12.6 MHz (figure 6) we observe a valley in the graph and an increase for higher frequencies. This indicates the presence of a capacitive element in the high frequency region; it can be identified as the dielectric capacitance of water. When examining the electrical model for blood (figure 2) this capacitance is missing.

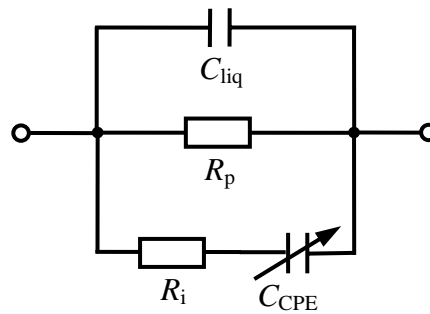


*Fig. 7. Using the model in figure 2 to fit data on the measured impedance of blood shown in fig. 5.*

Another remark is that the Nyquist plot of the measured blood impedance does not show a semi-circle but instead more an elliptical form. This indicates that the cell membrane capacitance cannot be fully modeled with a capacitor  $C_m$  in the lumped model. Fitting results confirm this mismatch, see figure 7. However, for measurement frequencies below 1 MHz the simple model in figure 2 is still feasible.

### 3.1 A novel model for blood impedance

Having identified two types of deviations in the model of Fig. 2, in this paragraph we introduce a novel model (figure 8), which gives a much better curve for blood impedance over a wide frequency range.



*Fig. 8. Novel electrical model of blood.*

In figure 8 the capacitor  $C_{liq}$  represents the dielectric capacitance of water in blood and  $C_{CPE}$  is a so-called **C**onstant **P**hase **E**lement with impedance:

$$Z_{CPE} = \frac{1}{(j\omega)^n C} \quad (1)$$

where  $\omega=2\pi f$ , and the exponent  $n$  is a constant smaller than one. If the exponent  $n=1$  then  $Z_{CPE}$  behaves as a normal capacitor.

### 3.2 Fitting result for the novel model of blood impedance

Figure 9 shows the fitting result obtained with the novel model (Fig. 8) in series with the model of figure 4 for the polarization effects. From figure 9 we can conclude that the novel model of blood impedance has a much better fitting than the conventional model (figure 2). Even at frequencies up to 100 MHz a good fitting is achieved.

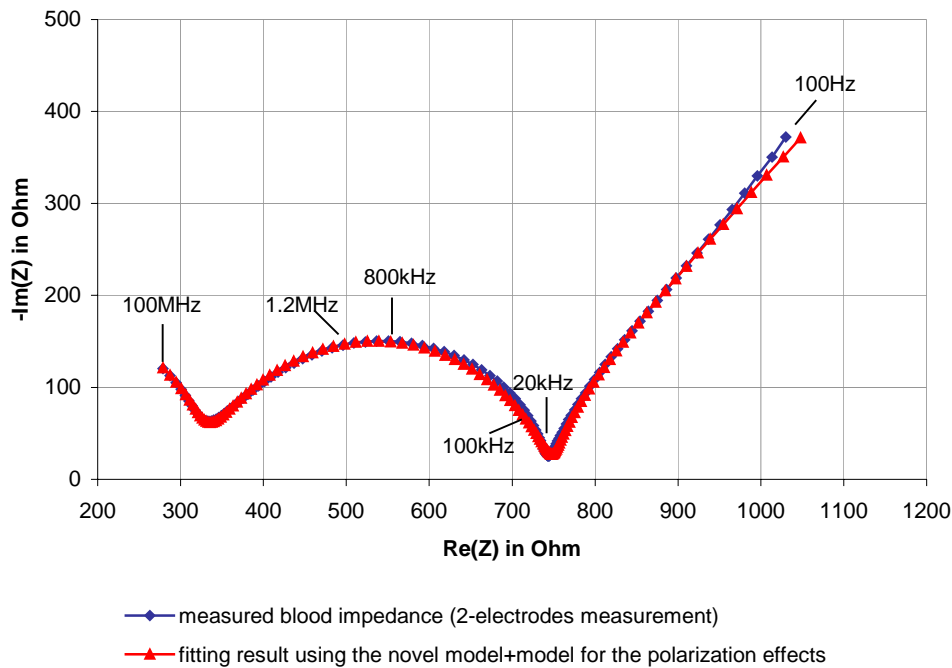


Fig. 9. Fitting results of the novel model including the fitting for the polarization effects using the model in fig. 4.

#### 4. CONCLUSIONS

With clean electrodes and measurement frequencies above 20 kHz the two-electrodes technique is very suited to measure blood impedance. When corrosion and formation of an endothelium layer has to be taken into account, the four-electrodes technique should be preferred. A disadvantage of this four-electrodes technique is that parasitic capacitors in the measurement setup will limit the applicable frequency range. However, with a good calibration setup our setup was found to be suited for a frequency range up to 12 MHz.

A novel model of blood impedance was found and verified for the frequency range up to 100 MHz. This novel model shows a much better fitting than the conventional one. In the novel model the dielectric capacitance of water has been modeled. Moreover, a Constant Phase Element has been used to replace the cell-membrane capacitance.

#### 5. REFERENCES

- [1] G.A.M. Pop, W.J. Hop, M. van der Jagt, J. Quak, D. Dekkers, Z. Chang, F.J. Gijzen, D.J. Dunncker, and C.J. Slager, *Blood Electrical Impedance Closely Matches Whole Blood Viscosity as Parameter of Hemorheology and Inflammation*, Appl. Rheol. 13:6 (2003) 305-312.
- [2] Fricke, H., *The Electrical Resistance and Capacity of Blood for Frequencies between 800 and 4.5 million cycles*, J. Gen. Physiol., 1925-26, ix,153.