

Planar Sensor Structures for Whole Blood Viscosity Measurements

A. Firouzian, D. Tanase, B. P. Iliev, Z. Chang, W. A. van Duyl, and P. J. French

Abstract—The focus of this work is to investigate a number of planar sensor structures (electrodes) in order to measure whole-blood viscosity. As a first step, the parameters, which should be taken into account in designing planar electrodes, have been studied. Prototype sensors were fabricated in IC technology for preliminary measurements. The final goal is to integrate the electrodes on a medical probe, which contains pressure, and flow sensors in order to measure cardiac output.

Index Terms— Bio-impedance, blood viscosity, four-point measurement.

I. INTRODUCTION

BLOOD is a non-Newtonian fluid because its viscosity depends on shear rate. At low shear rates, the red blood cells aggregate and cause the blood resistance to decrease [1]. Low shear rate can be found in veins and arteries [2]. Red blood cell aggregation causes inflammatory activities, which is important at low shear rates. Therefore, low blood viscosity at low shears rates, can be a sign of inflammatory disease.

Red blood cell aggregation is determined by haematocrit, which is the most important determinant of blood viscosity. In patients with clinical signs of the hyper-viscosity syndrome, hemodilution has proven to be a simple but effective method to improve tissue perfusion by lowering blood viscosity. Several studies [3], [4] have shown that there is an optimal hematocrit for tissue perfusion. Hematocrit also affects thrombosis [5].

Since the work of Frick [6] numerous studies [7], [8] have demonstrated a strong correlation between the electrical resistivity of blood at low frequencies (20-50 kHz) and the hematocrit of blood. More recently, in vitro studies have also shown a correlation between electrical resistivity and fibrinogen, which is another important determinant of blood viscosity [9]. Other studies have shown that there is a strong correlation between the electrical impedance of blood and the whole-blood viscosity [10].

According to these considerations, the aim of the present study is to fabricate a sensor with a planar structure, which is able to measure the electrical impedance of whole blood by using the four-point measurement technique. Two prototype

sensors were used as a starting point and preliminary measurements for further sensor characterization have been performed. These sensors were fabricated in IC technology with a goal of being integrated with flow and pressure sensors in order to measure cardiac output (Fig.1).

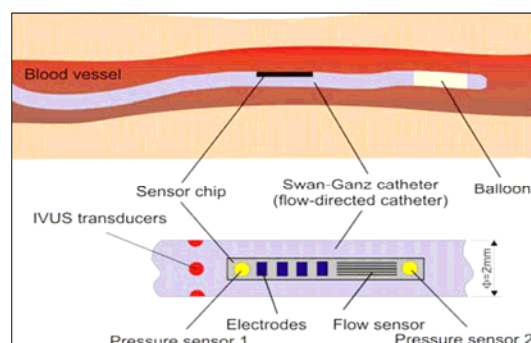


Fig. 1. The medical probe with three sensors

II. SENSOR STRUCTURES

The sensors consist of an array of four rectangular electrodes. An AC current is injected into the sample through the outer electrodes while the resulting potential is measured differentially across the inner electrodes. An investigation was performed into optimizing the current electrode configurations considering measurement accuracy and vessel-wall proximity. In the first step a number of simulations were performed to find out the effect of each parameter on the measured resistance.

A. Measurement Technique

In order to measure the electrical impedance of whole blood, the four-point measurement technique was chosen. In this technique when the input impedance of the voltage acquisition system at inner electrodes is very high, the polarization effect will be minimized. In the ideal situation when the input impedance is infinite, the polarization effect does not play any role in the measurement [11].

B. Area of the Electrodes

If the impedance at the electrodes is low (especially at the outer electrodes) and the impedance of the inner electrodes is equal, the errors in the measurement caused by the electrode-electrolyte impedance will be minimized. So the

A. Firouzian is with TU Delft, Faculty of Electrical Engineering, Mathematics and Computer Science, Department of Micro-electronics and Computer Engineering, Electronic Instrumentation Laboratory (phone: +31(0) 152786432; fax: +31 (0) 85755; e-mail: a.firouzian@ewi.tudelft.nl).

electrodes should be as large as possible. The material and process to fabricate the electrodes should be in a way that they lead to low interface impedance as possible.

C. Distance Between the Electrodes

There are some parameters that should be taken into account while choosing the distance between the electrodes:

1) *Distance between the Inner electrodes:* A large distance between the inner electrodes has a number of advantages. If the voltage drop between the inner electrodes for a given sample and current is high, we will get a good signal-noise ratio and the errors caused by the non-uniformity of the sample will be minimized [12]. It is better to take the distance between the inner electrodes considerably larger than the maximum cellular size of the sample, which in case of whole blood is 7 μm .

2) *Distance Between the Inner & Outer electrodes:* Placing the inner electrodes closer to the outer ones is beneficial in terms of signal to noise ratio and spatial resolution.

Starting from the theoretical aspects, a number of simulations were performed to establish the optimal sensor configuration.

D. Material of the Electrodes

The material and the process to make the electrodes, should lead to as low electrode-electrolyte impedance as possible. Platinum electrodes have been used frequently because of their biocompatibility and their low half-cell potential compared to other materials such as stainless steel or silver [13].

III. READ-OUT ELECTRONICS

The readout circuit consists of a simple relaxation oscillator, which converts the measured quantity into a period (Fig.2). The three-signal method used in this circuit eliminates the influence of parasitics and ensures long-term temperature stability [14].

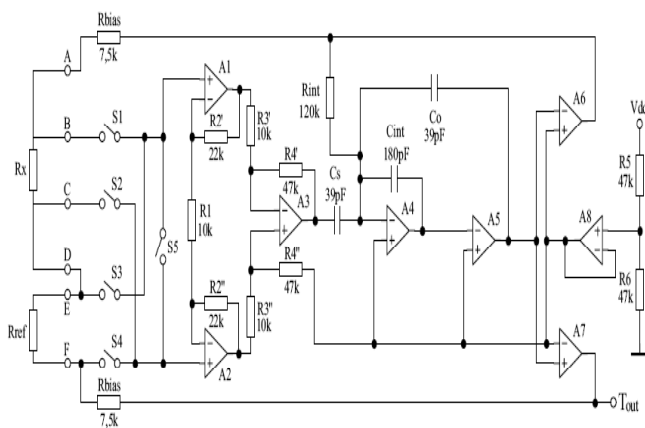


Fig. 2. The circuit diagram of the oscillator

IV. WALL PROXIMITY

As the final sensor is going to be placed either in the right atrium or in the pulmonary artery, the effect of the wall of the

vessel or atrium on the measurement results should be taken into account. When the sensor enters the heart, due to heartbeat the place of the sensor will change and if it gets too close to the wall then no reliable measurement data can be obtained. Therefore, the sensor should be designed in such a way to reduce the wall-proximity effect. This effect happens because the distance to the vessel wall affects the field distribution around the sensor [15].

In order to study the influence of this effect on the geometry of the sensor, different simulations have been performed. From the simulation results the following can be concluded:

- 1) Increasing the size of the electrodes, results in a greater sensitivity of the sensor to the wall.
- 2) The larger the distance between the inner electrodes, the lower the sensitivity to the wall.
- 3) By increasing the distance between the inner electrodes and the outer ones, we will increase the sensitivity to the wall.

The above points, more or less agree with the rules mentioned at the sensor-structure part except for the size of the electrodes.

V. EXPERIMENTAL RESULTS

In order to see if theory matches the real situation, some measurements were performed in saline solution. These measurements were done with the two prototype sensors previously fabricated in our laboratory (Fig.3). For convenience we called these sensors MP1 and MP2 (MP stands for Medical Probe). Their geometry is as follows:

1) *MP1:* The size of the electrodes is 150*700 μm , the distance between the inner electrodes is 1100 μm and between the inner and outer electrodes is 700 μm .

2) *MP2:* The size of the electrodes is 125*760 μm , the distance between the inner electrodes is 550 μm and between the inner and outer electrodes is 250 μm .

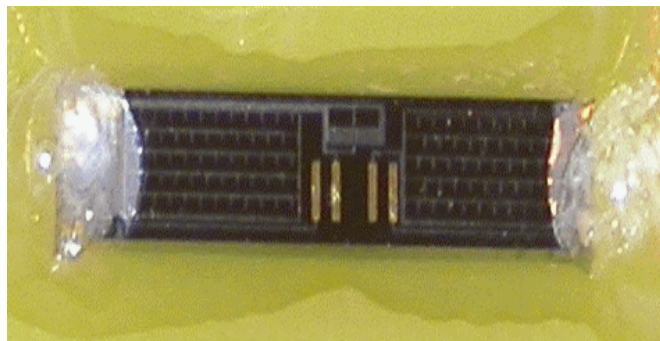


Fig. 3. The medical probe, which is fabricated in our laboratory

Two kinds of measurements were performed. Initially, we did not consider the wall effect and only wanted to make sure that our device is able to cover the whole range of blood resistivity, which is between 50-250 Ohm-cm. The resistance

between the inner electrodes was measured for different conductivities of saline solution (Fig.4a and 4b). As the graph shows, the cell constant is constant through the whole range.

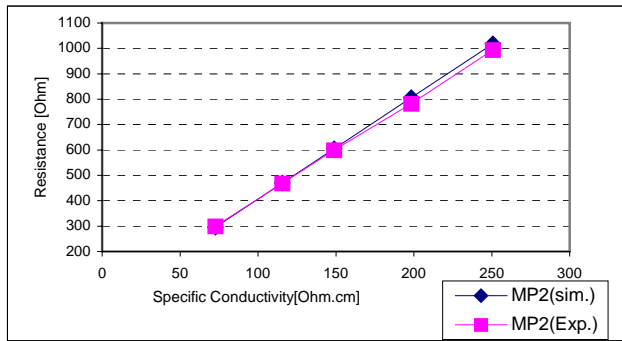


Fig. 4a. Resistance versus specific conductivity of the medium; experimental and simulation results for MP2

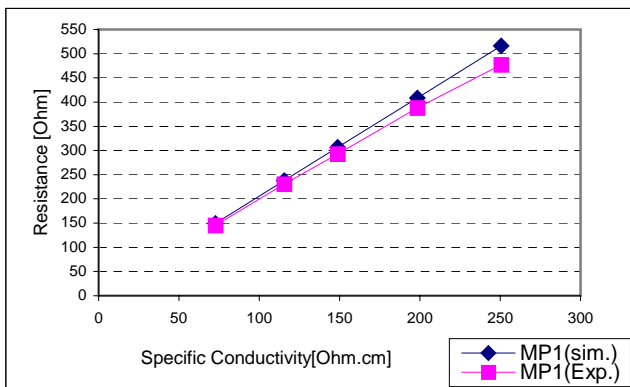


Fig. 4b. Resistance versus specific conductivity of the medium; experimental and simulation results for MP1

For the in-vivo measurement, the cell constant can be measured in a saline solution with a defined conductivity and be used to calculate the specific resistivity of blood and as a result the blood viscosity.

The second set up was made to study the effect of wall on the output signal (Fig.5). A glass plate was considered as a wall and the resistance was measured at different distances from the glass wall (Fig.6).

The two sensors have different configurations and as a result the point where the effect of the glass wall can be measured is different for each. The larger the sensor, the more sensitive it is to the wall. There is proportionality between the length of the electrode array and the distance at which the effect of the wall starts. MP1 is about two times larger than MP2 therefore the effect of the wall shows up in the output signal at a larger distance comparing to MP2. This is due to changes in the field distribution. The field distribution is an important parameter in the measurement results. Therefore, the optimum sensor configuration should minimise field disruption. Schwan [16] suggested that the inner electrodes should be small enough in

order not to disturb the field. Fig.7 shows how the inner electrodes can affect the field distribution.

As the distance between the outer electrodes increases, the field will spread further and the wall can disturb it at a larger distance.

Work is underway to fabricate new sensor structures with different geometries and continue testing on these structures.

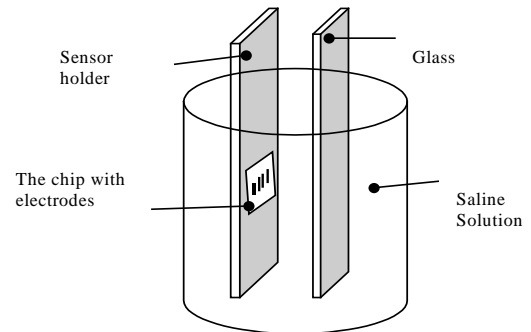


Fig. 5. Measurement setup to investigate the wall effect

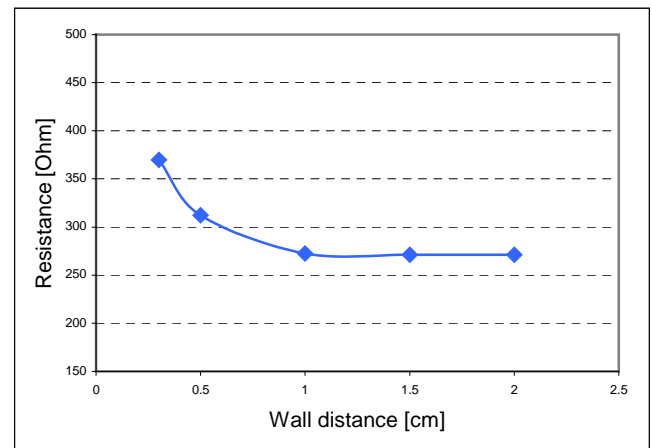


Fig. 6a. Resistance changes due to wall effect (MP1)

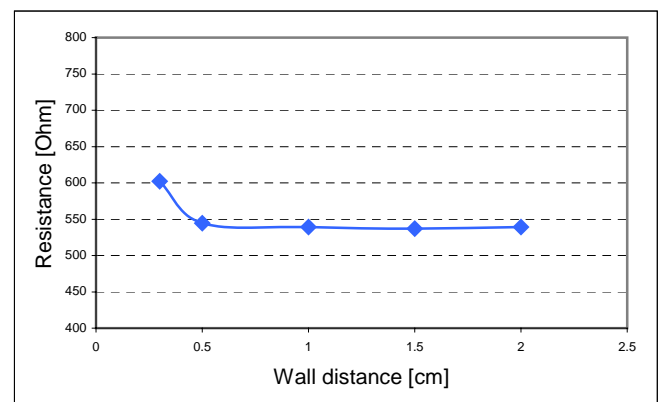


Fig. 6b. Resistance changes due to wall effect (MP2)

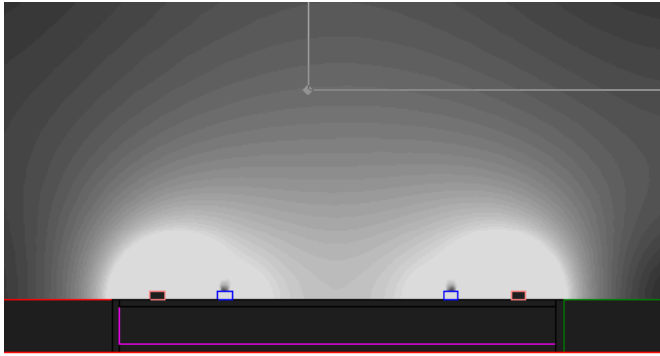


Fig. 7. Current field distribution in the cross section area of the chip

VI. CONCLUSION AND FUTURE WORK

The basic guidelines in order to design a planar probe to measure blood impedance have been described.

The introduced experimental setup will be improved and preparation for in-vivo testing will be done.

A number of sensors with different configurations will be made to find the optimum one considering the size, reliability, biocompatibility, fabrication process and the wall proximity.

REFERENCES

- [1] H. Schmid-Schonbein, P. Gaethgens et al., "On the shear rate dependence of red blood cell aggregation in vitro", *J Clin Invest*, vol.47, 1968, pp. 93-107.
- [2] Kroon de MGM, C. J. Slager et al., "Cyclic changes of blood echogenicity in high-frequency ultrasound", *Ultrasound in Med. & Biol.*, vol.17, pp. 723-728, 1991.
- [3] J. Crowell, E. Smith, "Determinant of the optimal hematocrit", *J. Appl. Physiol.*, vol. 22, Issue 3, pp. 501-504, 1967.
- [4] S. Lee, R. Heros, J. Mullan et al., "Optimum degree of hemodilution for brain protection in a canine model of focal cerebral ischemia", *J. Neurology*, vol.80, pp. 469-475, 1994.
- [5] H. Goldsmith, E. Kaufer, F. McIntosh, "Effect of haematocrit on adenosine diphosphate -induced aggregation of human platelets in tube flow", *Biorheology*, vol.32, pp. 537-552, 1995.
- [6] H. Frick, "Relation of the permittivity of biological cell suspensions to fractional cell volume", *Nature*, vol. 4381, pp. 731-732, 1953.
- [7] L. Geddes, L. Baker, "The specific resistance of biological material: a compendium data for the biomedical engineer and physiologist", *Med. Biol. Eng.*, vol.5, pp. 271-293, 1976.
- [8] D. Hill, F. Thompson, "The effect of hematocrit on the resistivity of human blood at 37 C and 100 kHz", *Med. Biol. Eng.*, pp. 182-185.
- [9] G. A. Pop, Z. Chang et al., "Catheter-based impedance measurement in the right atrium for continuously monitoring hematocrit and estimating blood viscosity changes; an in vivo feasibility study in swine", *Biosensors and bioelectronics*, vol. 19, 2004, pp. 1685-1693.
- [10] G. A. M. Pop, W. J. Hop, L. Moraru et al., "Blood electrical impedance closely matches whole blood viscosity as parameter of hemorheology and inflammation", *Applied Rheology*, vol. 13, Issue 6, pp. 305-312, 2003.
- [11] H. P. Schwan, *Ann. Acad. Sci.*, 1968, vol. 148, pp. 191.
- [12] B. J. Roth, "Interpretation of skeletal muscle four-electrode impedance measurement using spatial and temporal frequency-dependent conductivities", *Med. Bio. Eng. Comput.*, vol. 27, pp. 491-495, 1989.
- [13] L. A. Geddes, "Electrodes and the measurement of bioelectric events", Wiley-Interscience, John Wiley & Sons, Inc., New York, 1972.
- [14] B.P. Iliev, G.A.M. Pop, G.C.M Meijer, "Low cost system for measuring plasma resistance", *Proceedings of the Electronics conference, Bulgaria*, 2001, pp.44-47.
- [15] N. Kordas, Y. Manoli, W. Mokwa et al., "A CMOS-compatible monolithic conductivity sensor with integrated electrodes", *Sensors and Actuators*, 1994, vol. 43, pp. 31-37.

- [16] H. P. Schwan, "Electrode polarization impedance and measurements in biological materials", *Ann. New York Acad. Sciences*, vol. 148, pp. 191-209, 1968.

Azadeh Firouzian was born in 1979 in Tehran (Iran). She got her bachelor degree in Biomedical Engineering from Shahid Beheshti Medical University in Tehran in 2002. Then she worked for the research Institute in Imam Khomeini Hospital in Tehran for a year. She started her Master of Biomedical engineering in TU Delft in February 2004.

Dafina Tanase received her Mechanical Engineering Degree from Transylvania University Brasov, Romania, in 1995 and her MSc. Degree in Applied Computer Science from Free University, Brussels, in 1998. In 2003 she received her Ph.D. from Delft University of Technology on the development of a magnetic-based navigation system for endovascular interventions. Currently, she is working as a post-doc being involved in the development of sensors for medical applications.

Blagoy Iliev was born in Smolyan, Bulgaria in 1976. He studied in Technical University - Sofia, Branch Plovdiv, Bulgaria in Faculty of Electronics and Automatics, where he received his M.Sc. degree in 2000. His subject of education was Automatics, Information and Control Systems. He spent 3 months at the Technical University of Delft, The Netherlands where he did his diploma thesis on " Interface System for Impedance Measurement Based on a Relaxation Oscillator ". Since December 2000 he is a Ph.D. student in Electronic Instrumentation Laboratory in Delft University of Technology. His interests now are focused on impedance measurement systems.

Zu-yao Chang was born in China Zhejiang came here in the Netherlands at the age of eight. He finished secondary school and went to the university here in Delft. He has worked for a few years and is now trying to graduate. His graduate assignment is to design an optimal signal processing for bio-impedance equipment. In spare time he studies philosophy, theology and Tao.

Wim van Duyl was born in Rotterdam in 1939. He has got his BSc in Electrical Engineering, Technical College Rotterdam in 1960, MSc-Electrical Engineering, Technical University Delft in 1968. PhD-Erasmus University Rotterdam 1977, From 1968-1972 part time assistant-professor at Erasmus University Rotterdam/Dept. BioMedical Physics and Technology and at Technical University Delft/Group for Medical Electrical Engineering. After 1972 full time assistant-professor at Erasmus University Rotterdam/Dept. BioMedical Physics and Technology, since 1984 as associate-professor "Medical Technology". Since 1973, he is a consultant in academic hospital Rotterdam (Querido-fund). In 1987 registered as a Clinical Physicist. Main field of teaching: medical physics, technology and system analysis for medical students. From 1984-1991 lecturer at Technical College Utrecht, evening-courses in Control Engineering and Digital Signal processing. From 1991-1993, he was a guest lecturer Medical Technology at Technical University Delft. Since 1998 lecturer at Technical University Delft/ Electrical Engineering/ Biomedical Engineering; Since 2001 retired from Erasmus University Rotterdam and next joined to Electronic Instrumentation (E.I.) Laboratory. He is still a member of different international clinical organisation and of IEEE and of the editorial board of "Klinische Fysica". Current interest at E.I.: development and application of smart sensors in medicine in cooperation with clinical partners.

Paddy French received his B.Sc. in mathematics and M.Sc. in electronics from Southampton University, UK, in 1981 and 1982, respectively. In 1986 he obtained his Ph.D., also from Southampton University, which was a study of the piezoresistive effect in polysilicon. After 18 months as a post-doc at Delft University, The Netherlands, he moved to Japan in 1988. For 3 years he worked on sensors for automobiles at the Central Engineering Laboratories of Nissan Motor Company. He returned to Delft University in May 1991 and is now a staff member of the Laboratory for Electronic Instrumentation with interests in micromachining and process optimisation related to sensors. In 1999 he was awarded the Antoni van Leeuwenhoek chair and in June 2002 he became head of the Electronic Instrumentation Laboratory.