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Xu Tieying, Maria Lizarralde, Wassim El Nemer, Bruno Le Pioufle, Olivier Français. Microfluidic device using reusable parylen-pdms packaging for the red blood cell transit time analysis in mechanical constrictions, using impedance measurement. *MicroTAS*, Nov 2018, Kaohsiung, Taiwan. hal-01972640

HAL Id: hal-01972640

<https://hal.science/hal-01972640>

Submitted on 7 Jan 2019

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MICROFLUIDIC DEVICE USING REUSABLE PARYLEN-PDMS PACKAGING FOR THE RED BLOOD CELL TRANSIT TIME ANALYSIS IN MECHANICAL CONSTRICTIONS, USING IMPEDANCE MEASUREMENT

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ABSTRACT

In this paper, a micro-device dedicated to the analysis of the Red Blood Cell (RBC) deformability is proposed. It is based on PDMS microfluidic channels mimicking the flowing in the capillary vascular network. The RBC transit time within the capillary is electrically sensed using embedded electrodes on glass associated to current blockage analysis. To get reusable device, a specific PDMS coated by parylen has been developed. In this way, the PDMS porosity to gaz is drastically reduced which permits to used depressurization for both controlling the biological sample flow and the non-permanent bonding of the device for reusable capability.

KEYWORDS: RBC deformability; Microfluidic; Bioimpedance; Reversible Packaging

INTRODUCTION

In case of diseases affecting RBC, its deformability may be altered, which can induce vaso-occlusive crises or hemolytic anemia. These consequences are the main clinical features of malaria or sickle cell disease for example [1]. This loss of deformability changes the capability for the RBC to travel across the capillary vascular network. Thus, monitoring the RBC transit time can be a direct measurement indicator of its rigidity and as a consequence a degree of pathology.

Nowadays, microfluidic technologies offer easy way to mimic the flowing of RBC by reproducing the vascular network [2]. Permanent bonding of PDMS (using O₂ plasma) with other substrates, such as Glass or Silicon, enable association with electrical functions to achieve smart devices. But the alignment between the PDMS channels can be difficult to obtain as it is a single try. In addition, the cleaning of the chip becomes complicated if non-contamination is needed between experiments or if clogging events occur. Thus, the chip is one time used which increased the cost of the experiment.

In this paper, a microfluidic device devoted to the red blood cell (RBC) transit time analysis is presented. For an easy way of practical use, an original reusable packaging has been developed between the fluidic part, made of parylen coated PDMS, and the electrical part for the transit time measurement using impedance sensing (Fig. 1.A).

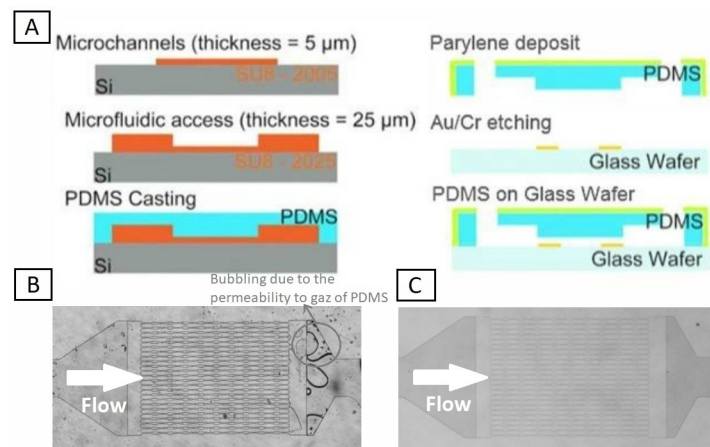


Figure 1: A. device fabrication process; B. air bubbles within microchannels; C. after parylen coating

Thanks to this strategy, simple alignment between microfluidic channels and electrodes is achieved with reversible assembly of both parts. The biological sample is flowed using negative pressures (up to 600 mbar) at the outlet of the fluidic network, while being deposited in a very low quantity (few microliters) at the inlet. The parylen coating of the PDMS avoids the air-flow through the PDMS, that otherwise might occur due to its permeability to gaz (Fig. 1.B and 1.C to be compared). The parylen coated PDMS fluidic part is thus maintained on the substrate thanks to de-pressurization during the experiment, resulting in that no permanent bonding is required (Fig. 1.B), offering an easier reuse.

DESIGN OF THE MICROFLUIDIC DEVICE

In order to mimic the flowing of RBC in the capillary vascular network, with sections of the capillary that are smaller than the cells, we fabricated 2 levels 5 μ m/25 μ m SU8 mold for the fluidic network (Fig. 1.A). This network contains a 10 x 24 capillaries array in which their diameter reduces from 20 μ m down to 5 μ m for high throughput capabilities. After casting PDMS and depositing parylen layer of 1.25 μ m, the fluidic part can be reversibly aligned with the electrical part for impedance measurement. RBC deforms while passing through the capillaries because of the membrane flexibility that directly affect the transit time.

The transit time is electrically measured thanks to thin Cr/Au electrodes patterned on a glass wafer. Applying an AC electrical signal, current blockade appears as RBC locates in the capillary corresponding to impedance variations [3]. Electrical modelling of the device is presented taking into account the polarization effect on the electrodes, ionic conductivity (σ) of the medium, dielectric properties of the RBC and dimensions of the microfluidic device (Fig. 2). Due to reduced size of the electrodes, the double layer capacity (C_{DL}) can not be neglected. A value of $C_{DL}=1 \mu\text{F}/\text{cm}^2$ has been used. The electrode surface in contact with the medium is : 40 μm x 20 μm . The medium is here considered as a pure conductive liquid ($\sigma=1.44 \text{ S}\cdot\text{m}^{-1}$). The cell is divided in two parts: its membrane (5 nm) which behaves like a shell ($\sigma=10^{-5} \text{ S}\cdot\text{m}^{-1}$, $\epsilon_r=11$) and its cytoplasm similar to a polarizable medium ($\sigma=0.9 \text{ S}\cdot\text{m}^{-1}$, $\epsilon_r=50$).

Optimal frequency for the current blockade detection can be selected from the simulated impedance spectrum, in order to get the highest sensitivity. A frequency of 30 kHz has been chosen in correlation with the impedance variation between the measuring electrodes (Fig. 2).

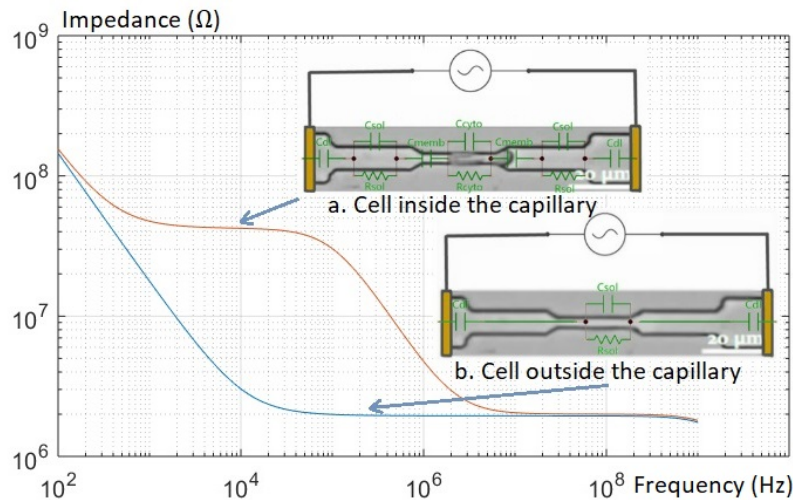


Figure 2: Matlab bioimpedance evolution in function of frequency with different cell position

RESULTS AND DISCUSSION

First results of current blockade are presented in Figure 3, associated with impedance value measured versus time. The frequency used for the excitation is 30 kHz and the impedance values are in the range of the modeling (Fig. 2). The impedance baseline value, with no cell in the microfluidic part between the electrode, is around 1.2 M Ω . The crossing of cells increases the impedance value up to 4.2 M Ω with an average value at 3 M Ω . Due to the electrodes localization, several cells can be sensed at the same time but the events can be separated. This situation

occurs in figure 3 around $t=29s$ where a first cell is measured ($t=28 s$) within the microcapillary and is directly followed by a second cell at $t=29s$.

Using a negative pressure of 590 mBar, the transit time obtained is in the range of 100ms which imply to choose a sampling time below 1ms in order to detect variation. Other strategies to improve the sensibility to transit time variation can be to increase the length of the mimicking capillary channel or to reduce the pressure used.

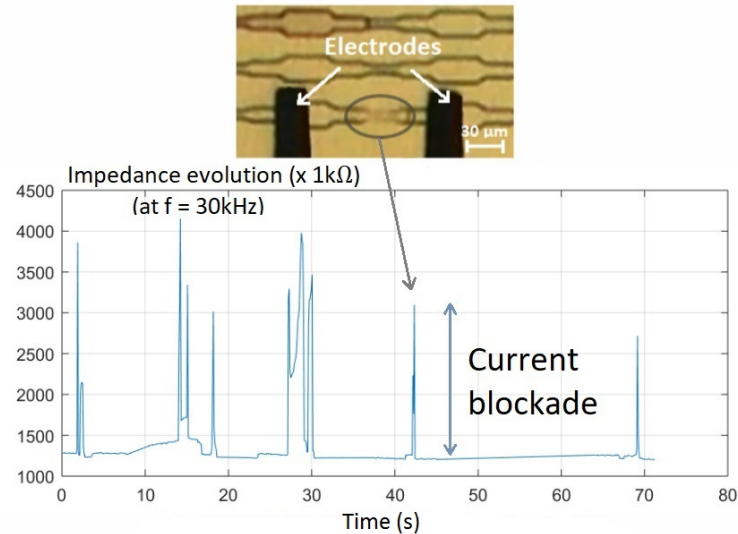


Figure 3: Impedance variation within the microchannel due to the cell transit (for the excitation frequency at 30 kHz)

After each experiment, the chip has been cleaned as the bonding is non-permanent and controlled by the pressure applied during the experiment. More than 10 different experiments have been achieved using the same chip (glass part with electrodes and PDMS microfluidic level) with reproducible results.

CONCLUSION

Here, the working of a reusable microfluidic device for RBC transit time monitoring using bioimpedance measurement has been demonstrated. Based on PDMS coated parylen and depressurization for fluid handling and device sealing, electrical sensing has been associated to the mimicking vascular network for current blockade detection.

Based on these first results, genetic mutation of RBC like the Sickel Cell Disease should be sensed in such device, as the rigidity of the cell is altered, altering the transit time that can be electrically measured [4].

ACKNOWLEDGEMENTS

The authors acknowledge the Labex LaSIPS (ANR-10-LABX-0040-Lasips), the “Ecole Doctorale EOBÉ” of Université Paris-Saclay, the “Institut d’Alember” and the “CNRS” for project foundings.

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