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ULTRASOUND PULSE-ECHO ANALYSIS OF BLOOD AGGREGATION IN MICROFLUIDICS

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ABSTRACT

Blood aggregation occurs when erythrocytes, red blood cells (RBC), agglutinate together into compact stacks of cells called rouleaux. Blood aggregation can then be compared to a liquid-gel transition that appears at low flow regime, and is responsible of the high value of the blood viscosity at low shear rate. This paper will present a physical device that can detect the appearing of this liquid-gel transition using the transmission and reflection properties of ultrasonic waves.

KEYWORDS: blood, red blood cells, acoustics, ultrasound, pulse echo, aggregation

In order to detect the liquid-gel transition in resting blood we use the property of an ultrasonic shear wave (5 MHz) to be transmitted or reflected at a glass-liquid interface that is populated with RBC. The setup, as sketched in Figure 1, is made of a piezoelectric transducer, a PZT stack that is bonded on the bottom face of a glass cylinder that acts as an acoustic delay line [1]. A burst of signal ($2\mu\text{s}$) is sent by the PZT toward the glass coverslip, travels through the delay line, bounces at the interfaces and returns with a delay to the PZT where it is detected. Amplitudes of the echo is then compared to input signal in order to extract a reflexion coefficient (r).

Experiments are performed both on droplets of healthy blood deposited on glass coverslips and in PDMS microfluidic circuits at low flow strength and at rest. In particular, a spiral shaped microchip, as can be seen in Figure 2, is used both to mimic a vascular network ($160\times 150\mu\text{m}$ section channels) and to expose a large surface (about 25 mm^2) of the sample to the ultrasonic signal [2]. The detection of r over time is coupled with observations of RBCs behaviour during the sample desiccation by optical microscopy to elucidate the dynamics of the drying process of blood. All measurements are carried out at controlled temperature ($25\text{ }^\circ\text{C}$) and relative humidity (30-60%). Note that the acoustic power ($<1\text{pJ}$) sent to the blood is small and does not interact with cells through acoustophoresis mechanisms.

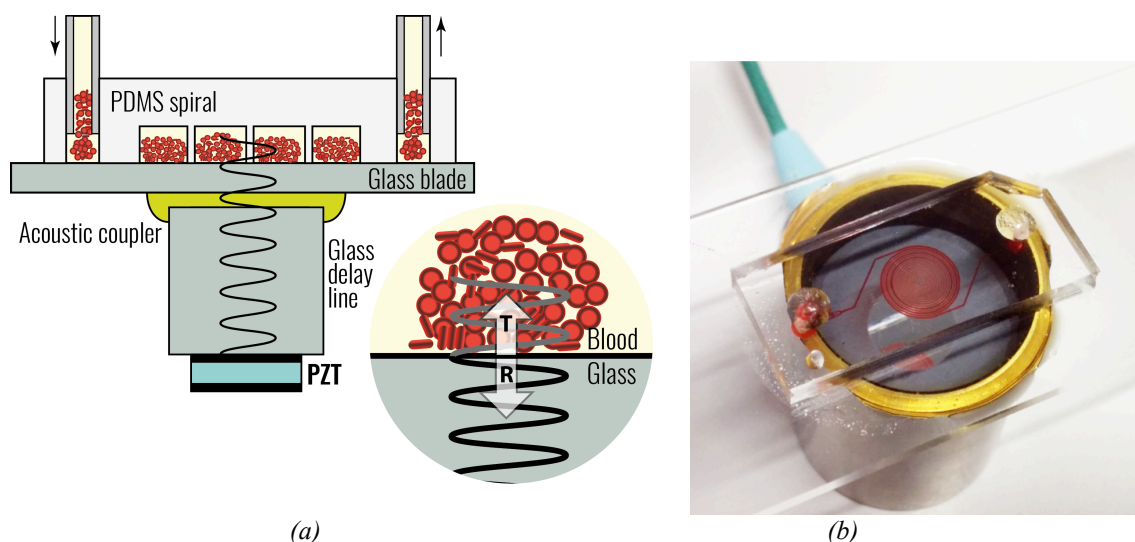


Figure 1: (a) Schematic (not to scale) of the ultrasound pulse echo setup for the analysis of liquid gel transition in steady blood flow due to red blood cells aggregation. (b) Photograph of the spiral shaped microfluidic circuit bonded on a microscope glass blade a coupled to an ultrasonic pulse echo system. The spiral channel is $160\mu\text{m}$ wide, $150\mu\text{m}$ for a total diameter of diameter of 6mm .

Both droplets and RBCs dispersions at rest in the spiral microchip show a comparable behaviour that can be summarized in three main phases (Figure 3). After a preliminary sudden decrease of r due to the attainment of the thermal equilibrium between sample and microdevice and probably to the fast sedimentation of the RBCs on the glass substrate, the value of the reflection index remains almost unchanged for a considerable time. During this long phase, the suspending medium, the plasma, is evaporating. At the same time, RBCs tend to form large aggregates and the macromolecules present in the suspension organize themselves in the form of a dense network on the glass surface, as observed with optical microscopy. Lastly, the cell dispersion shows a gel-like behavior because of the already mentioned evaporation of the plasma and the simultaneous highly compact arrangement of RBCs. The particular mechanical properties of assembled rouleaux confer a given elasticity to the structure that allows the ultrasound to propagate through. Therefore, once the drying process is advanced, the reflection signal drops down to a minimum value that corresponds to the liquid-gel transition (τ_D) and then slightly drops up. This latter part of the curve is characterised by to the onset of cracks in the gel-like blood structure and the following detachment from the surface (Figure 4).

Despite evident analogies from the qualitative point of view, the curves referring to the drying of droplets and in microchips present significant differences in terms of duration of the three main phases. Moreover, the drying process in microfluidic circuits has the handicap to last for even 48 hours and this causes an inevitable scattering of the r curve. In any case, the use of a spiral microdevice shows to be very promising for two fundamental reasons: i) the small volumes of sample necessary for both acoustic measurements and observations; ii) the tighter control on the gel formation and the subsequent cracks formation due to a quite longer liquid-gel phase.

Such an ultrasonic device, thanks to the measurement of r during both the evaporation and the liquid-gel transition phases, allows to estimate some key parameters of blood suspensions, such as the hematocrit and cells aggregability, which are linked to several common pathologies[3].

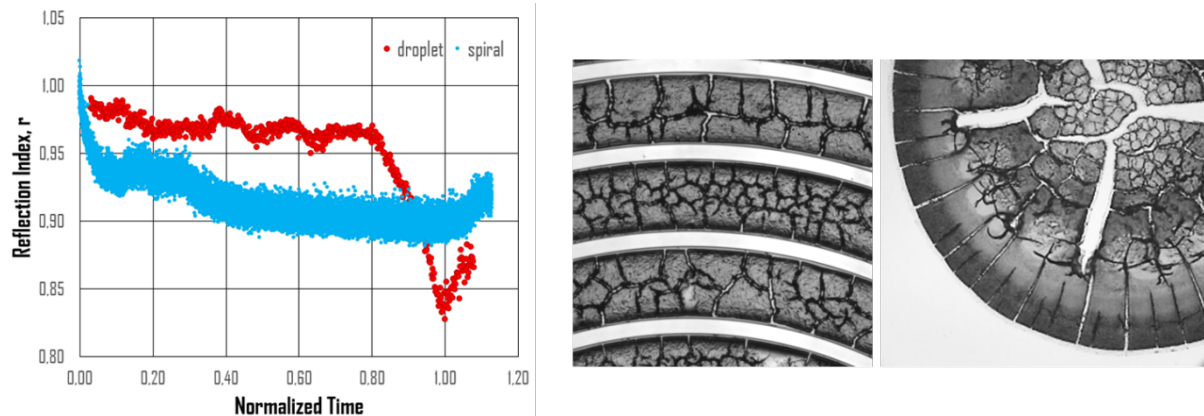


Figure 3. Acoustic reflection index versus time for droplet and spiral and microphotograph of whole blood after complete drying in a microfluidic spiral shaped circuit and in droplet.

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