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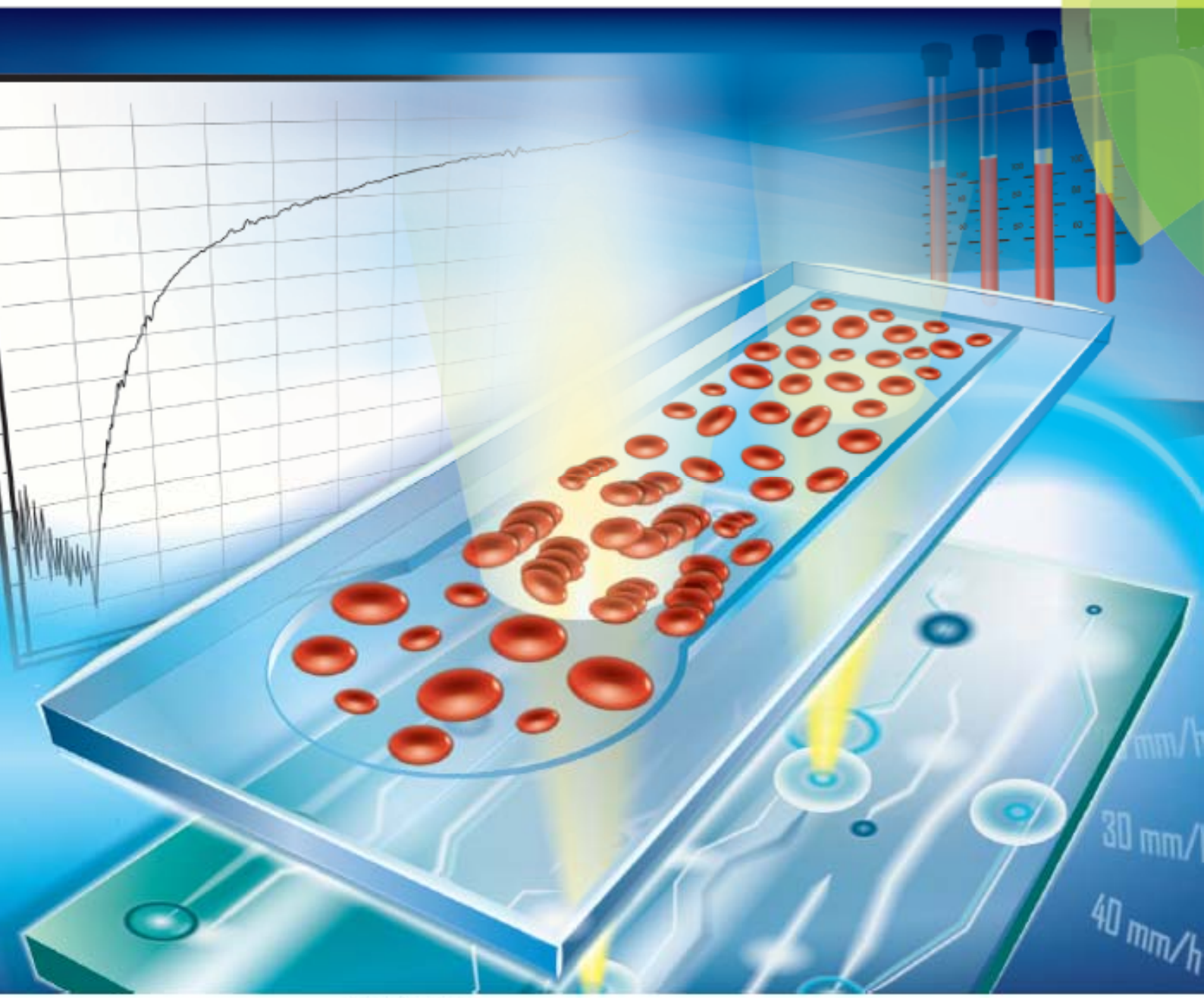

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PAPER
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A portable microfluidic system for rapid measurement of the erythrocyte sedimentation rate

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A portable microfluidic system for rapid measurement of the erythrocyte sedimentation rate

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The erythrocyte sedimentation rate (ESR) is a frequently used 30 min or 60 min clinical test for screening of several inflammatory conditions, infections, trauma, and malignant diseases, as well as non-inflammatory conditions including prostate cancer and stroke. Erythrocyte aggregation (EA) is a physiological process where erythrocytes form face-to-face linear structures, called rouleaux, at stasis or low shear rates. In this work, we proposed a method for ESR measurement from EA. We developed a microfluidic opto-electro-mechanical system, using which we experimentally showed a significant correlation (R^2 = 0.86) between ESR and EA. The microfluidic system was shown to measure ESR from EA using fingerprick blood in 2 min. 40 μl of whole blood is filled in a disposable polycarbonate cartridge which is illuminated with a near infrared emitting diode. Erythrocytes were disaggregated under the effect of a mechanical shear force using a solenoid pinch valve. Following complete disaggregation, transmitted light through the cartridge was measured using a photodetector for 1.5 min. The intensity level is at its lowest at complete disaggregation and highest at complete aggregation. We calculated ESR from the transmitted signal profile. We also developed another microfluidic cartridge specifically for monitoring the EA process in real-time during ESR measurement. The presented system is suitable for ultrafast, low-cost, and low-sample volume measurement of ESR at the point-of-care.

Introduction

The erythrocyte sedimentation rate (ESR), discovered in 1897[1] and widely accepted in 1918,[2] is a simple clinical test commonly used as a sickness index for monitoring several inflammatory diseases such as temporal arteritis[3,4] and polymyalgia rheumatica.[5–8] It is also accepted as a critical prognostic factor in some non-inflammatory conditions including stroke,[9] heart attack,[10] and prostate cancer.[11] ESR reflects the rate of settling of erythrocytes in a vertically placed tube filled with whole blood. The erythrocyte-free plasma height at the top of the tube is measured after 30 or 60 min and reported as the ESR value in mm h^{-1}. The Westergren method is the gold standard method for ESR measurements, in which a tube with a length of 300 mm and an inner diameter of 2.55 mm is used which requires 5 ml of whole blood sample.[12,13]

Erythrocytes form 3D aggregates that resemble rolls of coins at stasis or at low shear rates in plasma or an appropriate suspending medium.[14–16] This reversible process is the main factor for the non-Newtonian nature of blood, and as such, plays a critical role for blood flow.[17–19] EA is affected by (i) intrinsic cellular properties (membrane deformability and surface charge density),[20–22] (ii) suspending medium properties (fibrinogen concentration in plasma or aggregation-inducer macromolecule concentration such as dextran),[23–28] and (iii) shear forces on cells.[29–31] EA is of clinical importance for diseases such as sepsis, thrombosis, and circulatory diseases.[16,32,33] Most studies utilize aggregometers that measure EA using photometric methods that quantify the light beam reflected from or transmitted through a blood sample during the aggregation process.[31,34–40] These aggregometers differ from each other based on their mechanical unit, which creates the shear force required for disaggregation. Image analysis of EA under different dynamic conditions and computational analysis have also been employed for the quantification of EA.[41–44] Custom-made optical systems (microscopes and holograms) are also proposed for erythrocyte analysis. These systems carry out non-invasive single cell investigation such as measurement of morphological properties, volume, and refractive index based on interferometric methods.[45–48] Due to the complexities of the optical systems and image retrieval algorithms, these systems are impractical for rapid and facile monitoring and quantification of the fast aggregation process.[49]

Lab-on-a-chip technologies for blood analysis and their commercialization possess significant potential for healthcare.[50,51] There are studies that led to benchtop

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