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High-throughput Volume Refractive Index Distribution Measurement Through Mechanical Deformation of Single Cells

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Abstract—This paper reports a high-throughput microphotonic biosensor measuring volume refractive index distribution through mechanical deformation of single cells. Preliminary results suggest that different cell states can be distinguished. This feature could readily add novel parameters for cell analysis without resorting to nucleic acid dyes.

Keywords—Optical microcavity, microphotonics, biomedical sensor, biological cells.

I. INTRODUCTION

A large part of biomedical research focuses on detection of micrometer sized particles for very large populations. For instance, flow cytometry and Fluorescence Activated Cell Sorting (FACS) use scattered light and selective fluorescence, respectively, to investigate cellular populations comprised within thousands or million individual cells. It represents one of the most cutting-edge technology for cell population identification. However, some cell states or types are still not easily identifiable and require either costly fluorescent probes and/or time-consuming experiments.

Recent studies have shown that previously unexploited properties could be used for cellular identification. Indeed, mechanical properties, such as cellular deformability [1], or optical properties, such as refractive index (RI) [2], are both being measured in a consistently more sensitive manner. Furthermore, it has been shown that during progression through cell cycle, the cytoskeleton and the osmotic pressure undergo changes generating different mechanical properties and volume, respectively [3]. This paper reports preliminary results on a high-throughput microphotonic biosensor measuring volume refractive index distribution through mechanical deformation of single cells. We suggest that mechanical and optical properties can be measured by our device with a sensitivity high enough so that they may be correlated to cell cycle phases within a single cellular population. To our knowledge, it is the first time a high-throughput microdevice combining mechanical and optical properties measurements in a single optical resonant cavity is reported.

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II. MATERIALS AND METHODS

Microfabrication of the Fabry-Perot resonant cavity was conducted on a Silicon-On-Insulator wafer with a 15 μm thick device layer following the technique previously presented in [4]. Rib waveguides were designed to approach a single-mode like behavior [5]. Altogether, the microdevice yields a sensitivity of 1392 nm per Refractive Index Unit (RIU) and a resolution of 1.1×10^{-5} RIU. T lymphocyte cells, Jurkat clone E6-1, were cultured following standard protocol. Cells were resuspended in Phosphate Buffured Saline (PBS) at a concentration of 6×10^6 cells/ml prior to measurement. Viability of Jurkat cells was assessed to 97% through hemocytometer counting.

Individual cells are hydrodynamically focused in the center of the resonant cavity, causing a red shift of the resonance peak as presented in Fig. 1 [4]. A fast infrared photodetector records optical intensity variations at a fixed wavelength and relays it to a high speed digitizer. The experimental setup enables measurement rate of 1000 cells/s which is comparable to a flow cytometer.

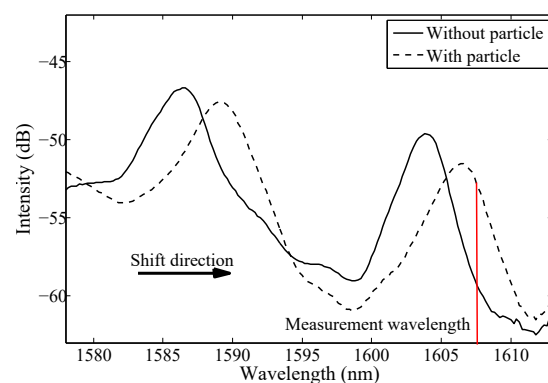


Fig. 1. Fabry-Perot resonance peaks red shift due to the presence of a particle.

III. RESULTS AND DISCUSSION

A spherical homogeneous capsule yields a symmetric displacement of the resonance peak in time. This precept transposes to a Jurkat cell since its nucleus takes most of the cell volume. However, microfluidic

forces tend to deform the cell's shape more or less depending on the surface capillary number (Ca_s). The surface capillary number represents the ratio of the viscous forces over the elastic forces. Since the nucleus is stiffer, most of the deformation is expected to come from the membrane's elasticity and microtubules stiffness. Consequently, for high value of Ca_s , shear stress pulls cell membrane closest to the walls backwards whereas fluid flow pressure pushes on the back and pulls in the front of the cell to create a bullet-like shape [1]. Similar deformation has been observed with homogeneous capsules [6]. Considering the small dimensions of the microfluidic channel ($15\mu\text{m} \times 35\mu\text{m}$) and the high mean cell velocity (0.3 m/s), it is reasonable to assume that the capillary number allows for significant cellular deformation. Fig. 2 presents a typical asymmetric intensity measurement over time for a deformed Jurkat cell. Insets present schematized turning points of a cell's transition in the resonant cavity.

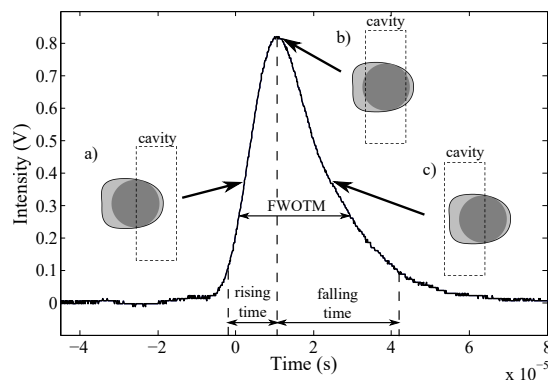


Fig. 2. Typical asymmetric intensity measurement over time for a deformed Jurkat cell. Inset a) cell entering the cavity, b) cell's nucleus centered in the cavity and c) cell leaving the cavity.

From the intensity curve in Fig. 2, the ratio of rising time over falling time is introduced to quantify its degree of asymmetry. This parameter represents the volume RI distribution through cellular deformation. Moreover, the Full Width at One Third of the Maximum (FWOTM) has proven to be a discriminant parameter related to the RI and size of the cell [2], [4]. Fig. 3 compares Jurkat cells based on their FWOTM and the ratio of rising time over falling time values in logarithmic scales. Results suggest that multiple cellular sub-populations can be distinguished in this single type cell solution. Each sub-population is gated using a free-drawing method. Colored isodensity contour lines enclosing 50% of the cells in each sub-population are shown. Hypothetic cell cycle phases G_0/G_1 , S, G_2 and M are displayed next to each sub-population.

The G_0/G_1 phases (red) are considered resting states and include most of the cells. In the S phase (blue), DNA replication occurs increasing the nucleus size but not significantly changing the cell's volume, conferring a more symmetrical signal. In the G_2 phase (green), cell volume increases significantly leading to

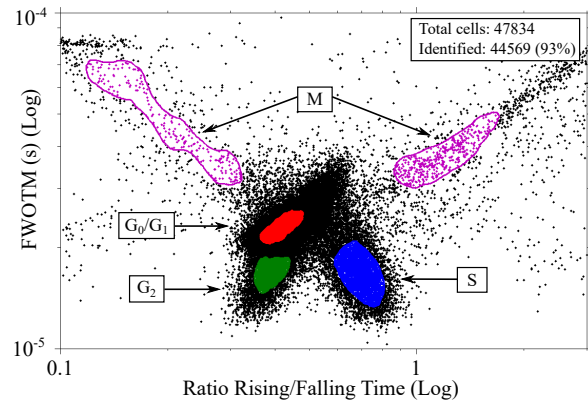


Fig. 3. Scatter plot of measured Jurkat cells compared on the basis of their FWOTM and ratio rising time over falling time values. Colored isodensity contour lines enclosing 50% of the cells sub-populations are shown. Hypothetic cell cycle phases are displayed next to each sub-population.

a more deformable cell and conferring a more asymmetrical signal. Finally, in the M phase (violet), cells divide and produce a double peak if their separation is not completed. Distribution of cell cycle phases calculated from data is $G_0/G_1 = 68.1\%$, $S = 13.8\%$, $G_2 = 8.7\%$ and $M = 2.6\%$. Comparatively, a triple staining method [7] reported $G_0/G_1 = 46.1\%$, $S = 22.7\%$, $G_2 = 14.8\%$ and $M = 1.7\%$. Results are in relatively good agreement with this technique. Thus, this device potentially holds a novel optical measurement technique providing discriminant parameters for cellular analysis.

IV. CONCLUSION

We presented preliminary results on volume refractive index distribution correlated to deformability of single cells. Among potential applications, this device could allow cell cycle analysis in a short time period without resorting to nucleic acid dyes.

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