Extreme Imaging and Beyond

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I. Introduction

High-speed optical imaging is a powerful tool for blur-free observation of fast transient dynamics in scientific research, industry, defense, and energy [1]. In scientific research, the ability to visualize fast dynamical events such as biomechanical motion in sports, microfluidic flows, and laser ablation enables us to conduct slow-motion analysis of the events and understand their underlying mechanisms that govern the dynamics. Also, high-speed cameras are widely employed in industry, defense, and energy for manufacturing, automobile collision testing, robotic vision for artificial intelligence, real-time tracking of missiles and aircrafts, and monitoring ignitions in nuclear plants.

One of the emerging high-speed imaging methods is optical time-stretch imaging [2, 3]. It is a method for ultrafast imaging with a single-pixel photodetector, instead of a detector array, by spectrally encoding and decoding the spatial profile of the imaging target with dispersive properties of light in both spatial and temporal domains. Since it was originally devised in 2008 [4], it has been shown effective for ultrafast imaging that overcomes what is possible with the traditional high-speed image sensor by replacing it with the single-pixel photodetector and hence overcoming its speed limitations. Due to its inherent affinity with optical signal processing, optical time-stretch imaging can be combined with various optical techniques such as amplification, nonlinear processing, compressive sensing, and pattern correlation to realize unique capabilities.

In this paper, we review the principles of optical time-stretch imaging and its unique application to single-cell analysis. By virtue of its high shutter speed and frame rate, optical time-stretch imaging enables accurate characterization and classification of a large heterogeneous population of cells at single-cell resolution.

II. Optical time-stretch imaging

Optical time-stretch imaging is an imaging method that exploits spatial and temporal dispersion for high-speed image acquisition [2, 3]. A typical setup of optical time-stretch imaging is shown in Figure 1. The optical source is a broadband femtosecond pulse laser with a pulse repetition rate of 10 – 100 MHz (corresponding to the frame rate of optical time-stretch imaging). A pulse from the laser enters the spatial disperser that maps the spectrum into a 2D rainbow pattern which illuminates the sample in such a manner that the different frequency components of the pulse correspond to different spatial coordinates on the sample. The image of the sample is encoded onto the spectrum of the back-reflected pulse which is transformed into a pulse again. The pulse is then time-stretched by the temporal disperser to serialize the pulse spectrum and hence the image into a 1D time-domain waveform. The waveform is detected by the photodetector to convert the optical signal to an electrical signal which is digitized and digitally processed by the signal processor. A 2D image of the sample can be constructed by digitally stacking the 1D images. Noise reduction and image enhancement techniques can also be implemented on the image. Since the laser's pulse repetition rate typically operates at 10 – 100 MHz, the frame rate operates likewise and is tunable, depending on the application. Since the digitizer's sampling rate is 10 – 100 GS/s, the number of pixels is 1,000 – 10,000 pixels/frame.

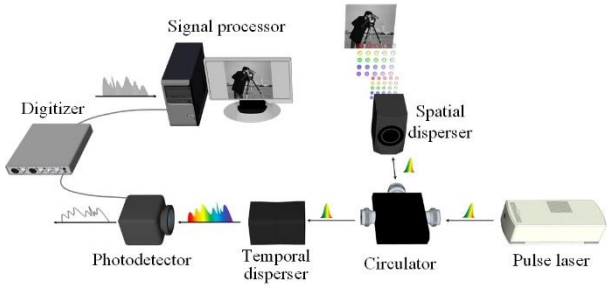

Figure 1: Optical time-stretch imaging.

III. Application to single-cell analysis

One of optical time-stretch imaging's applications is single-cell analysis. Single-cell analysis is the discipline for studying cell-to-cell differences even within the same cellular species and important for cancer biology, immunology, metabolic engineering, and microbiology. When combined with microfluidics, optical time-stretch imaging, which is often called optofluidic time-stretch microscopy, addresses the need and can perform accurate image-based analysis of numerous single cells in a large heterogeneous population.

One example is high-throughput label-free image-based evaluation of a large population of single microalgal cells under different culture conditions. Previously, *Euglena gracilis*, a microalgal species that can produce wax esters (suitable for biodiesel and aviation fuel), has been used for this application [5]. Figure 2 shows image libraries of differently cultured *E. gracilis* cells obtained by an optofluidic time-stretch imaging system at a high throughput of 10,000 cells/s. Nitrogen-sufficient cells look mostly transparent while nitrogen-deficient cells look mostly opaque throughout their entire cell body due to the high concentration of black spots (presumably accumulated lipid droplets and paramylon particles). Based on the information-rich cell images, advanced characterization and classification tools such as machine learning can be used to comprehensively analyze all the features and classify different cell groups with a much higher accuracy.

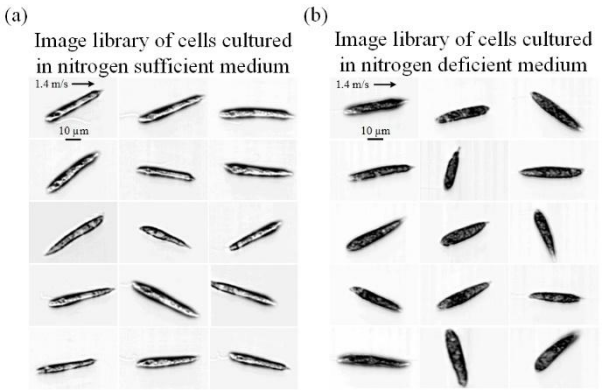

Figure 2: Application to high-throughput image-based analysis of *Euglena gracilis* cells.

Another application of optofluidic time-stretch microscopy is label-free detection of aggregated platelets in blood [6]. Aggregated platelets are known to play an important role in thrombotic disorders, a type of disease that forms blood clots and prevents blood flows in veins. While fluorescence-activated cell sorting can detect them, it suffers from the low labelling efficiency of fluorescent probes. Our detection of aggregated platelets as well as white blood cells and single platelets is shown in Figure 3. Here the throughput is 10,000 cells/s. The image library indicates the diversity of the morphological features of the aggregated platelets as well as their overall differences from other blood cells.

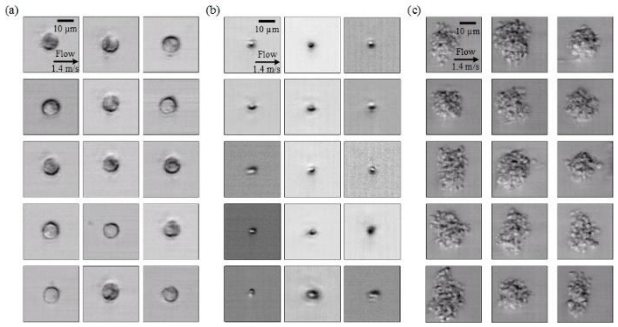

Figure 3: Application to high-throughput image-based analysis of aggregated platelets in blood. (a). White blood cells. (b). Single platelets. (c). Aggregated platelets.

IV. Summary

In this review, we discuss the basic principles of optical time-stretch imaging and show a few applications of the imaging method in metabolic engineering and medicine. We think the method holds great promise for expanding the use of high-speed imaging beyond traditional applications.

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