Chapter 2
Time Stretch

Time stretch is the leading technology in ultrafast big-data acquisition. Here we introduce time stretch technique and highlight its applications in the context of imaging.

2.1 Time Stretch Imaging

High-throughput optical sensing are indispensable tools to acquire large data sets for detection and classification of rare events. As noninvasive instrument, high-speed optical sensing are widely used in scientific, industrial, military, and biomedical applications. However, as the acquisition speed increases, the signal energy collected in single measurement drops. This leads to a reduction in the signal-to-noise ratio of the measurement, which ultimately limits the resolution and sensitivity of the sensing or imaging application. For optical instrument like camera, one way to collect more photons in each measurement is to increase the intensity of the illumination or the interrogation light, but this is often undesirable in biological applications because the biological samples can easily get damaged by the intense light, especially when an objective lens is focusing the light on the specimen.

Enabled by the photonic time stretch and optical amplification, a new class of instruments with record throughputs have led to the discovery of optical rogue waves, detection of rare cancer cells with record accuracy, and the highest analog-to-digital conversion performance ever achieved. One example of these instruments is the time stretch microscopy, an imaging and sensing modality that features continuous operation at about 100 million frames per second and shutter speed of less than a nanosecond.

Telecommunication systems routinely generate, capture, and analyze data at rates exceeding billions of bits per second. Interestingly, the scale of the problem is similar to that of blood analysis. With approximately 1 billion cells per milliliter

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of blood, detection of a few abnormal cells in a blood sample translates into a "cell error rate" of 10^{-12}, a value that is curiously similar to the bit error rate in telecommunication systems. This suggests that data multiplexing, capture, and processing techniques developed for data communication can be leveraged for biological cell classification.

Time stretch dispersive Fourier transform is a method for real-time capture of ultra wideband signals. It allows acquisition of single shot optical spectra continuously and at tens to hundreds of million frames per second. It has led to the discovery of optical Rogue waves [7] and, when combined with electro-optic conversion, to record analog-to-digital conversion performance [8]. Combination of the telecommunication technique of wavelength division multiplexing (WDM) and the time stretch technique [9], the time stretch camera known as STEAM [10–16] has demonstrated imaging of cells with record shutter speed and continuous throughput leading to detection of rare breast cancer cells in blood with one-in-a-million sensitivity [16–20]. A second data communication inspired technique called fluorescence imaging using radio frequency-tagged excitation (FIRE) is a new approach to fluorescent imaging that is based on wireless communication techniques [21]. FIRE has achieved real-time pixel readout rates one order of magnitude faster than the current gold standard in high-speed fluorescence imaging [21]. Producing data rates as high as one tera bit per second, these real-time instruments pose a big data challenge that overwhelms even the most advanced computers [22]. Driven by the necessity of solving this problem, we have recently introduced and demonstrated a categorically new data compression technology [23, 24]. The so-called Anamorphic (warped) Stretch Transform is a physics based data processing technique that aims to mitigate the big data problem in real-time instruments, in digital imaging, and beyond [22–26]. This compression method is an entirely different approach to achieving similar functionalities as compressive sensing [27, 28] and is more amenable to fast real-time operation.

The operating principle of time stretch imaging is shown in Fig. 2.1. First, the object image is encoded in the spectrum of ultrafast optical pulses. Then, pulses are stretched in time by dispersive Fourier transformation, so that different wavelength components reach a single-pixel photodetector at different times. The time stretch function allows ultrafast image frames to be digitized in real-time. Images are optically amplified before detection and digitization to overcome the thermal noise. The basic principle of time stretch imaging (STEAM) involves two steps both performed optically. In the first step, the spectrum of a broadband optical pulse is converted by a spatial disperser into a rainbow that illuminates the target. Therefore, the spatial information (image) of the object is encoded into the spectrum of the resultant reflected or transmitted rainbow pulse. A one-dimensional or two-dimensional rainbow is used to acquire a line-scan. The 2D image is obtained by scanning the one-dimensional rainbow in the second dimension or by a two-dimensional rainbow. In the second step, the spectrum of the image-encoded pulse is mapped into a serial temporal signal that is stretched in time to slow it down such that it can be digitized in real-time [9]. This optically amplified time stretched serial stream is detected by a single-pixel photodetector and the

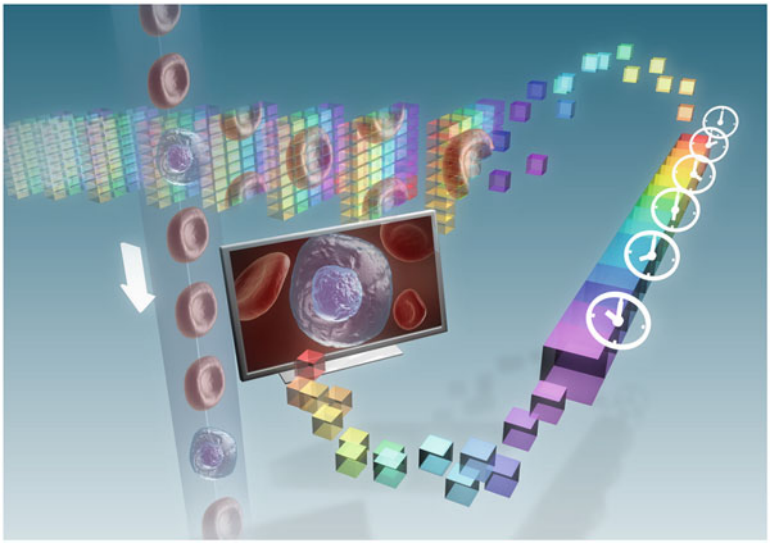

Fig. 2.1 Operating principle of time stretch imaging. The key innovations in STEAM that enable high-speed real-time imaging are photonic time stretch for digitizing fast images in real-time and the optical image amplification for compensating the low number of photons collected during the ultra-short shutter time

image is reconstructed in the digital domain. Subsequent pulses capture repetitive frames. The laser pulse repetition rate corresponds to the frame rate and the temporal width of the pulses corresponds to camera's shutter speed (exposure time). The key innovations in STEAM that enable high-speed real-time imaging are photonic time stretch for digitizing fast images in real-time and the optical image amplification for compensating the low number of photons collected during the ultra-short shutter time [29].

2.2 Cell Classification Using Time Stretch Imaging

Using time stretch imaging, we demonstrated high-throughput image-based screening of budding yeast and rare breast cancer cells in blood with an unprecedented throughput of 100,000 particles/s and a record false positive rate of one in a million [30]. Our first rare cancer cell detection method was based on imaging metal beads conjugated to cells expressing specific surface antigens [30]. However, when downstream operations such as DNA sequencing and subpopulation regrowth are desired, the negative impacts of biomarkers on cellular behavior are often unacceptable.

2.3 Label-Free Phenotypic Screening

Phenotypic screening has been the basis for the discovery of new drugs and has also been widely used in biological research. High-throughput label-free cellular imaging leads to large scale and high dimensional phenotyping of cells in their natural conditions without biomarkers, enabling applications in circulating tumor cell detection when certain biomarkers are absent [31], as well as downstream analysis for studying the stochasticity in gene expression [32].

Imaging flow cytometry overcomes the throughput bottleneck in microscopic imaging as well as the low-content issue in conventional flow cytometry, making it a perfect candidate for label-free phenotypic screening. When combined with image analysis [33], it enables recognizing and quantifying multiple informative measures of cells, including morphology, protein localization, cell cycles, DNA content, etc.

2.4 Warped Time Stretch for Data Compression

Using warped group delay dispersion, it has been shown that one can reshape the spectro-temporal profile of optical signals such that signal intensity's time-bandwidth product is compressed [22–26]. The compression is achieved through time stretch dispersive Fourier transform in which the transformation is intentionally warped using an engineered group delay dispersion profile. This operation causes a frequency-dependent reshaping of the input waveform. Reconstruction (decoding) method depends on whether the information is in the spectral domain amplitude, or in the complex spectrum. In the time stretch camera, the image is encoded into the amplitude of the spectrum of a broadband optical pulse, and reconstruction consists of a simple nonuniform time-to-frequency mapping using the inverse of the warped group delay function.

To illustrate the concept in the context of time stretch imaging, we can consider a microscopic field of view consisting of a cell against a background such as a flow channel or a microscope slide (Fig. 2.2). In the time stretch imaging, the object is illuminated by an optical pulse that is diffracted into a 1-D rainbow. This maps the 1-D space into the optical spectrum. The spectrum is then linearly mapped into time using a dispersive optical fiber with a linear group delay. The mapping process from space to frequency to time is shown in Fig. 2.2a. The linearly stretched temporal waveform is then sampled by a digitizer resulting in uniform spatial sampling. This uniform sampling generates redundant data by oversampling the sparse peripheral sections of the field of view. Such a situation evokes comparison to the mammalian eye where central vision requires high resolution while coarse resolution can be tolerated in the peripheral vision. In the eye, this problem is solved through nonuniform photoreceptor density in the retina. The Fovea section of the retina has a much higher density of photoreceptors than the rest of the retina and is responsible for the high resolution of central vision.

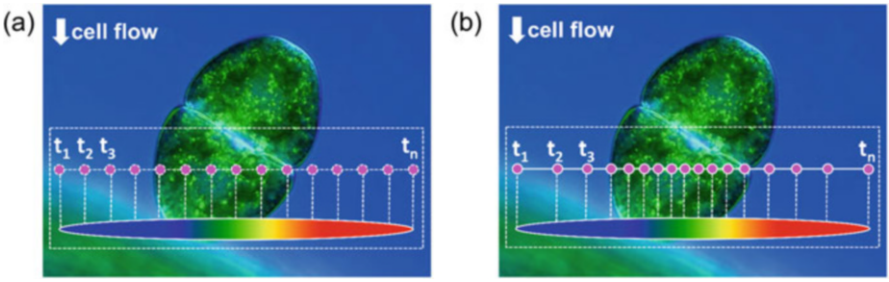

Fig. 2.2 Illustration of warped-stretch transform in imaging. (**a**) In conventional time stretch imaging (STEAM), the spectrum-to-time mapping is uniform, and the pixels are assigned equally distanced across the field of view. (**b**) Using a nonlinear group delay profile in the spectrum-to-time mapping process results in a nonuniform sampling of the line image, assigning more pixels to the information-rich central part of field-of-view and less to the low-entropy peripherals

We solve this problem by nonuniform mapping of spectrum into time via a warped group delay. The warped (anamorphic) space to frequency to time mapping is illustrated in the dotted box in Fig. 2.2b. After uniform sampling in time, this leads to higher sampling density in the central region of the field of view and lower density in the sparse peripheral regions. The reconstruction is a simple unwarping using the inverse of the group delay.

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