Blood screening using a time-stretch camera identifies cancer cells with record sensitivity

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A new liquid-biopsy technique allows identification of abnormal cells in blood with one in a million sensitivity, enabling early cancer detection.

The successful treatment of cancer is contingent on early detection, preferably with a minimally invasive and cost-effective method. A blood test to detect cancer cells would be far less invasive than the standard computed tomography (CT) and positron emission tomography (PET) scans because they expose the patient to high levels of x-ray radiation (CT) or require the injection of radioactive tracers (PET) into the body. Circulating tumor cells (CTCs) are vanishingly rare cells that detach from a primary tumor and circulate in the bloodstream. These rogue cells are believed to seed subsequent growth of additional tumors, leading to metastatic stage of disease that is responsible for 90% of cancer mortalities. Detection and isolation of the few CTCs among a large population of normal cells is extremely challenging, yet important for the early detection of metastatic cancer and monitoring the efficacy of therapy. Being able to identify rare cells in blood and other bodily fluids will not only impact the fight against cancer, but will also influence regenerative medicine (e.g., stem-cell transplantation) and vaccine development as well as offering noninvasive prenatal diagnostics.

Unfortunately, CTCs are exceedingly rare and hard to capture. Their population numbers only a few parts per billion normal blood cells and trying to find them is a classic ‘finding a needle in the haystack’ problem. To overcome Poisson statistics inherent to rare event detection, one must analyze a large number of cells in a short and practical time. Thus, detecting CTCs and other rare cells with good statistical accuracy requires a high-throughput technique that can sift through an enormous population of cells. Furthermore, a high-throughput microscopic blood imaging system can provide a minimally invasive way to detect and monitor cancer, and will usher in a new era in pathology.

Figure 1. Pictorial representation of serial time-encoded amplified microscopy (STEAM), which is based on photonic time-stretch with simultaneous amplification, a process also known as amplified dispersive Fourier transform.

Microscopes equipped with a digital camera are the gold standard for analyzing cells, but are unfortunately too slow to be useful for in high-throughput imaging. To catch the elusive cells, the camera must be able to capture and digitally process millions of images continuously with a very high frame rate. Conventional CCD and CMOS cameras are neither fast nor sensitive enough; time is needed to read the data from the array of pixels and the cameras become less sensitive to light at high speed. Equally important, existing imaging systems are not capable of real-time image processing. The current standard flow cytometry method

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used for routine blood analysis benefits from high throughput, but since it relies on single-point light scattering as opposed to taking a picture, it is not sensitive enough to detect very rare cell types such as those present in patients with pre-metastatic cancer.

We have developed a high-throughput flow-through imaging system for real-time detection of rare cells. The serial time-encoded amplified microscopy (STEAM) flow cytometer is a novel system that integrates a high-speed bright-field imager based on a camera that features time stretching and image amplification and holds the world record in frame rate, shutter speed, and sensitivity for a continuously running camera. The basic principle of STEAM involves two steps, both performed optically (see Figure 1). In the first step, the spectrum of a broadband optical pulse is converted by a spatial disperser into a rainbow that illuminates the target. Thus, the spatial information (image) of the object is encoded into the spectrum of the resultant reflected or transmitted rainbow pulse (although a 2D rainbow is shown in Figure 1, a 1D rainbow is used in flow imaging as the flow causes the cell to be scanned in the second dimension).

In the second step, the spectrum of the image-encoded reflected or transmitted rainbow 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. The amplified time-stretched serial image stream is detected by a single-pixel photodetector and the image is reconstructed in the digital domain. Subsequent pulses capture repetitive frames, hence the laser pulse repetition rate corresponds to the frame rate of STEAM and shutter speed or exposure time corresponds to the temporal width of the rainbow pulse. The extremely fast shutter speed of approximately 30ps eliminates any blurring that would result from high speed cell flow (see Figure 2), and produces 128 × 512 pixel images that are comparable to stationary images captured by the CCD, but at ultrahigh flow speeds of meters per second and beyond.

Figure 2. Comparison of performance between (a) a conventional CCD camera (stationary particles), (b) a state-of-the-art CMOS camera (particle flow at 4m/s), and (c) the STEAM camera (particle flow at 4m/s). CCD camera shutter speed: 17ms, optical image gain: 0dB. CMOS camera shutter speed: 1μs, optical image gain 0dB. STEAM camera shutter speed: 27ps, optical image gain: 30dB. All scale bars=10μm.
With such a high throughput, millions of cells can be imaged and analyzed in seconds to identify rogue cells that are indicative of early stage or pre-metastatic cancer.

The microfluidic chip employs a combination of hydrodynamic and inertial focusing for precise positioning of cells in high-speed flow. The real-time digital image processor is based on a high-speed field-programmable gate array (FPGA) that performs real-time screening of a large heterogeneous population of cells for detection of rare target cells. The integrated system transforms particles in well-controlled microfluidic flow into a series of E-slides—an electronic version of glass slides—on which particles of interest are digitally analyzed (see Figure 3). It consists of a high-speed analog-to-digital converter; FPGA for particle capture, E-slide generation, and coarse particle classification; an on-board memory circuit for storing selected E-slides; and a central processing unit for fine particle classification. With the power of optoelectronic communication and information technologies, this property enables fully automated real-time image recording and classification of a large number of particles through their morphological and biochemical features.

The system performs real-time image-based screening of a large volume of blood with a record high throughput of 100,000 cells/s. It has shown detection of breast cancer cells in blood with a false-positive rate of $10^{-6}$, which is 100-fold better than state-of-the-art flow cytometers. Our proof-of-concept experiments were performed using blood spiked with MCF7 breast cancer cells derived from cell lines and involved acquisition and real-time processing of 100 million image frames at a line scan rate of 37 million frames per second. The next stage in this research is clinical testing to measure the efficacy of this new instrument in analyzing patient blood samples of unknown compositions.

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References


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