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A hardware accelerated system for high throughput cellular image analysis

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HIGHLIGHTS

- A scalable, high speed image analysis algorithm for cell morphological analysis.
- A hardware accelerated system to achieve a high throughput and low latency constraint.
- A demonstration of a proposed system in an end-to-end (CPU- FPGA) machine.
- A flexible hardware design for an FPGA using a high-level synthesis tool.

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ABSTRACT

Imaging flow cytometry and high speed microscopy have shown immense promise for clinical diagnostics, biological research, and drug discovery. They enable high throughput screening and sorting using biological, chemical, or mechanical properties of cells. These techniques can separate mature cells from immature ones, determine the presence of cancerous cells, classify stem cells during differentiation, and screen drugs based upon how they affect cellular architecture. The process works by imaging cells at a high rate, extracting features of the cell (e.g., size, location, circularity, deformation), and using those features to classify the cell. Modern systems have a target throughput of thousands of cells per second, which requires imaging at rates of more than 60,000 frames per second. The cellular features must be calculated in less than a millisecond to enable real-time sorting. This creates challenging computing performance constraints in terms of both throughput and latency. In this paper, we present a hardware accelerated system for high throughput cellular image analysis. We carefully developed algorithms and their corresponding hardware implementations to meet the strict computational demands. Our algorithm analyzes and extracts cellular morphological features from low resolution microscopic images. Our hardware accelerated system operates at over 60,000 frames per second with 0.068 ms latency. This is almost 1400× faster in throughput than similar software based analysis and 335× better in terms of latency.

1. Introduction

Quantitative analysis of cellular properties, such as size, shape, structure, life span, and molecular contents, can characterize cell function, give insight into how it behaves, and provide a technique for cell screening and/or sorting. This is useful for diagnosing disease, monitoring immune systems, screening drugs, and developing regenerative medicine [3,28,23,18]. However, there are strict performance constraints to achieve real-time cellular analysis; the system must have enough processing power to handle a very high cell throughput, and must perform cell feature analysis with a sub-millisecond latency to facilitate sorting.

Our system is capable of analyzing thousand of cells per second based on image based technology, which corresponds to work at over 60,000 frames per second; this is a common goal in imaging flow cytometry [13,34,9]. In our system, a high speed camera images cells at very high frame rate on a specialized experimental setup to catch fast moving target cell features. Camera at such high frame rates have lower resolutions, in our case 64 × 64 pixels. These images may have low contrast; they are sensitive to even a single pixel noise; and the fast movement of the cells within a tiny field of view causes blurring and other optical effects. Furthermore, there are strict latency constraints—real-time cell sorting requires decisions in under 10 ms [25], and ideally under one millisecond.

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Our system processes these noisy, low-contrast, blurry images with very high throughput and minimal latency.

Cytometry systems in such high performance use a specialized sensor, such as a laser, or focus on observing simple properties. However, our cell analysis system computes cellular morphological feature using bright field imaging on a microfluidic device, which gives more sophisticated information of cellular mechanical properties. The system images cells using a high speed optical image sensor, analyzes the resulting video streams, extracts features from the images, and classifies cells based on those observed features. It does not require labeling the cells with fluorescent chromes, which minimizes the preparation time and effort. However, the bright field based images have limited resolution; they are sensitive to variations in lighting; and they easily become blurred or noisy. This makes the accurate extraction of the morphological features difficult, which hinders high throughput massive cell analysis inspite of many other benefits of image based cell analysis system.

In this work, we carefully develop a cellular analysis algorithm to extract their morphological features from microscopic images and build a real-time system using an FPGA device. There are various image analysis approaches for feature detection over low contrast images. However, these approaches are too computationally intensive and hard to achieve such high performance even on a hardware implementation. Most of them have iterative solutions to refine analysis results or use spatial and temporal signatures to estimate target features accurately, which causes longer latency and lower throughput. Our method does not have an iterative process to find a solution and minimizes data dependency for independent operations. It processes input and intermediate data in streaming way, which is intended for an efficient hardware implementation in terms of performance and resources.

The major contributions of our work are:

- Accurate image analysis algorithms for high speed cell morphological analysis.
- Hardware architectural optimizations using high-level synthesis (HLS) code.
- Developing a hardware accelerated system for microfluidic deformability cytometry.
- An in-depth evaluation and end-to-end demonstration of our system using a heterogeneous (CPU–FPGA) compute platform.

The remainder of the paper is organized as follows. We describe background and introduce our target system in Section 2. Section 3 overviews and discusses related works. Then, we explain detailed image analysis algorithms and hardware architecture optimization methods in Section 4. Section 5 presents the system description and experimental results in terms of accuracy and performance. We conclude in Section 6.

2. Background

Cytometry assesses biological, physical, or chemical characteristics of cells using specialized instruments or micro-devices. Imaging cytometry and flow cytometry are the most well known methods of cell analysis.

Imaging cytometry is the oldest and most basic method. It observes cells using a microscope which results in high contrast and high resolution images, yet cannot be performed in a high throughput manner. Imaging cells at the microscopic level commonly requires staining them with a fluorochrome, which binds to a structure within the cell [17,36]. This labeling process highlights particular molecules or cellular structures. For example, it can separate out individual cell features (like the cell membrane or nuclei) and determine interactions between multiple cells [14]. Accurately extracting cell parameters demands significant effort making it difficult to perform high throughput analysis [8,32].

Flow cytometry uses a laser [31,30], an optical device [26,16], or an electrical impedance device [6,10] to extract course features from cells suspended in a fluid. For example, cells are labeled with fluorochromes, which activate when targeted with a particular wavelength of light. A cytometer reads these tagged response signals and determines the cell types or properties. This method is capable of providing high throughput cell analysis, but is not capable of extracting sophisticated cell parameters.

Imaging flow cytometry combines the strengths of flow cytometry (high throughput) and imaging cytometry (high sensitivity) [4,5,1]. Take, for example, the ImageStream by Amnis [34] — a commercial imaging flow cytometer capable of processing 5000 cells per second. It produces 12 images: 10 fluorescent markers in addition to darkfield and lightfield images. The fluorescent images provide higher contrast but require a pre-processing step to add the fluorochromes. On the other hand, the lightfield and darkfield images have no pre-processing requirement, but have reduced image clarity.

Our system targets a particular type of imaging flow cytometry that analyzes cellular mechanical properties using bright-field images. The main idea is to generate a force on a cell in a flowing fluid and determine its physical response. We can analyze the high speed images to determine mechanical properties based upon the cell's shape, size, circularity, and deformability. And then we can use those features to classify the cell.

For example, we can determine the deformability of a cell by analyzing the image. Different cells will deform in different ways. A pluripotent stem cell deforms more than its differentiated progeny; pleural fluid with metastatic cells will deform more than fluid with normal cells [13]; cells susceptible to tumor cell invasion have a changing mechanical behavior [24]; cancerous cells with the highest invasive potential are stiffer than those with lower migrations [33]; and older cells deform differently than younger ones [38]. More generally, recent research states that cells' mechanical properties "play important roles in the regulation of various biological activities at the molecular and cellular level" [39]. Thus, a cellular image analysis system for microfluidic deformability cytometry provides an attractive approach for high throughput cell screening and sorting.

In this paper, we focus on developing a high speed cellular analysis system for microfluidic deformability cytometry. This uses a microfluidic channel to deliver a cell into the center of a stretching extensional flow, which generates a uniform stress on the cell causing a deformation. The cells flow quickly through the microfluidic channel enabling high throughput processing. By imaging the cell in the extensional flow with a high speed image sensor, we can observe the deformation of large population of cells with a high throughput.

Fig. 1 shows the target system that is designed to produce cell stretching in an extensional microfluidic channel. The target system uses a high speed camera to observe cellular deformation. It applies uniform hydrodynamic force to a single cell on the channel, while the fast flowing fluid enters the field of view of the camera. High speed microscopy focuses on the center point imaging cell's movement and its deformation. For example, Fig. 1(d) shows a sequence of a single cell events from entering the field of view to exiting into an outlet for sorting. The resolution of this microscopic image is 64×64 and one cell stays in this view only few microseconds or few frames. Because of the fluid speed in the channel, this hydrodynamic approach is able to assess a large number of cells efficiently. This technique has the potential to process up to 20,000 cells per second. However, it comes with the critical bottleneck of handling the generated image data.

Our target performance is to analyze 2000 cells per second while assuming (1) any frame has no more than one cell (2) one