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High-Throughput Image Cytometry for Rare Cell Detection

Keisuke Goda[1,2], Genshun Yu[1], Yoshifumi Wakisaka[1], and Hirofumi Kobayashi[1]

[1] Department of Chemistry, University of Tokyo
[2] Department of Electrical Engineering, University of California, Los Angeles
E-mail: goda@chem.s.u-tokyo.ac.jp

1. Introduction

The detection of rare cells in a large heterogeneous population of healthy cells has become an extremely important task in medical diagnostics, regenerative medicine, and drug discovery. The types of such rare cells include antigen-specific T cells, hematopoietic stem cells, fetal cells in maternal blood, and circulating tumor cells (CTCs) in blood. Particularly important among these cells are CTCs – precursors to cancer metastasis that circulate in the bloodstream of cancer patients [1, 2]. Unfortunately, conventional cell-screening methods fall short of providing sufficient sensitivity, specificity, and throughput required for identification of these cells with a reasonable statistical accuracy in a practical period of time. Next-generation medical instruments that should satisfy these requirements are expected to play a critical role for reducing medical costs (especially for the elderly) and hence improving their quality of life.

2. High-Throughput Image Cytometry with STEAM

High-throughput image cytometry is an attractive approach to addressing this issue. Recently high-speed optical imaging combined with microfluidics and digital signal processing has been shown to be effective for real-time detection of rare cells in blood. This high-throughput image cytometer is capable of performing continuous non-stop blur-free image-recording and image-based evaluation of fast-flowing cells for identification of rare cells with a high capture efficiency of nearly 80% and an unprecedented throughput of 100,000 cells/s [3], which corresponds to screening of 10 mL of blood in less than 15 min. Rare cells are identified by the image cytometer via their morphological and biochemical phenotypes. The multi-parameter evaluation of cells enables screening of cells with a record low false positive rate of one in a million – roughly 100 times better than conventional methods.

Specifically, this method is based on the use of an ultrafast optical imager known as serial time-encoded amplified microscopy (STEAM) [4] which runs with shutter speed of ~10 ps at ~10 MHz frame rate (Fig. 1). Here the principle of STEAM is the spatiotemporal mapping of broadband optical pulses into a 1D digital signal by using spatial dispersive elements and a dispersive fiber (known as dispersive Fourier transformation [5]). 2D images that are encoded into the spectrum of each optical pulse are reconstructed from the 1D signal by re-mapping it into a 2D matrix in the digital domain. The key component of STEAM is its optical image amplifier that circumvents the trade-off between sensitivity and speed – a predicament that exists in nearly all optical imaging systems. Also used in this high-throughput image cytometer is a self-focusing microfluidic chip that focuses and orders cells into a single stream with inertial lift forces [6]. Furthermore, a high-speed digital image processor which consists of a field-programmable gate array (FPGA) is employed together with the STEAM imager and microfluidic chip to digitally analyze and classify a large number of cells in real time.

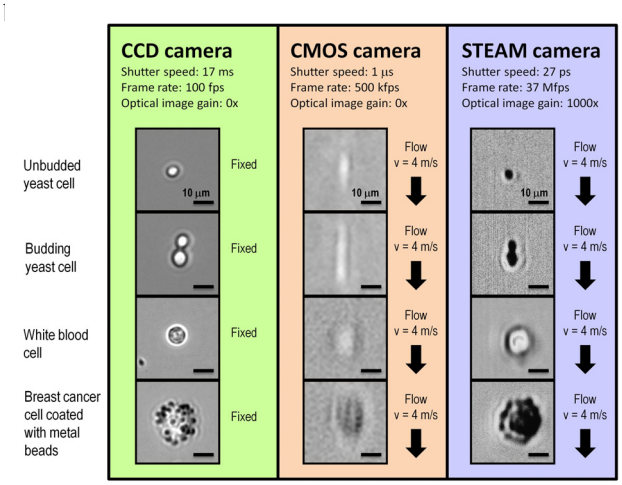

Fig. 1. STEAM's superior imaging performance compared with CCD and CMOS cameras. STEAM enables sensitive blur-free imaging of cells in high-speed flow. Here the flow speed of 4 m/s corresponds to a throughput of 100,000 cells/s.

3. Conclusion

Our high-throughput image cytometry technology is expected to be effective for early, noninvasive, low-cost detection of cancer and evaluation of chemotherapy. Furthermore, this method can be applied to real-time identification of other types of rare cells.

4. Acknowledgements

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5. References

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