Single Particle Detection Enhancement with Wavelet-based Signal Processing Technique

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Abstract: Chip-based single molecule detection requires ultra-sensitive devices and robust signal processing methods. A new wavelet-based signal processing method is introduced that improves detection and error rates on an optofluidic platform by 2x and 3x, respectively.
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1. Introduction

Recent developments in optofluidics have shown sensitivity sufficient for detecting single bio-particles. Devices based on liquid-core anti-resonant reflecting optical waveguides (LC-ARROWs) are good examples of such sensitive bio-detection platforms capable of single nucleic acid detection [1]. Multi-spot excitation utilizing multimode interference (MMI) waveguides provides signal-to-noise (SNR) enhancement up to 5×10^4 [2], and can also be used for spatially and spectrally multiplexed detection [3-4]. Here, we introduce a multiscale signal analysis method based on wavelet transform to further improve particle detection in chip-scale biosensors using multi-spot excitation.

2. Device Design and Experiment

Fig. 1a shows an MMI-generated multi-spot excitation pattern exciting fluorescent particles travelling inside a liquid-core waveguide. Fluorescence signals emitted from labeled particles inside the LC waveguide are collected through the collection waveguide and detected by an APD positioned off chip. Fig. 1b is an example of a time domain fluorescence signal from a tagged E.coli nucleic acid sample with an inset showing a zoomed in view of the 6 peaks produced when a single nucleic acid crosses a multi-spot excitation region [4].

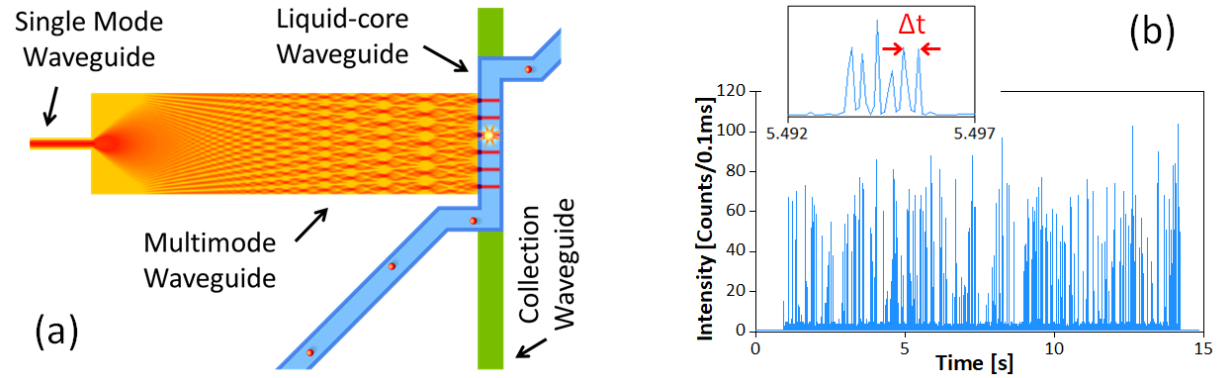

Fig. 1. (a) Schematic of the ARROW optofluidic device. (b) Fluorescence signal from labeled E.coli targets excited at 747nm.

3. Signal Processing Method

A well-stablished approach to analyzing multi-spot signals is based on calculating S(t) as shown in Eq. 1 when the time difference Δt between peaks is known [5]. This method works well in a scenario where the peaks are uniformly distributed and background around and in between the peaks is very low. However, for more realistic signals and imperfect MMI patterns, a noise and deviation tolerant signal processing algorithm is necessary. To this end, we introduce a wavelet based approach.

$$S(t,\Delta t) = \{\prod_{i=0}^{N-1} f(t - i \cdot \Delta t)\}^{\frac{1}{N-1}} \quad (1)$$

The Continuous Wavelet Transform (CWT) is widely used in peak detection algorithms with a significant improvement in single peak detection in comparison to amplitude based peak detection methods [6]. CWT of the function f(t) can be expressed as Eq. 2, where a custom defined wavelet (the blue term), ψ(t), is carefully defined to match the MMI-induced pattern of the fluorescence signal.

$$W_{f(t,\Delta t)} = \langle f, \psi_{t,\Delta t} \rangle = \int_{-\infty}^{+\infty} f(u) \frac{1}{\sqrt{\Delta t}} \psi^* \left(\frac{u-t}{\Delta t}\right) du \quad (2)$$

ψ(t) consists of 6 positive peaks and two negative peaks on both ends (normalized Gaussian functions) as shown in Fig. 2b. CWT is used to map the fluorescence signal from individual particles (Fig. 2a) into a 2D plot of time and Δt, where Δt is a scaling factor determining the temporal width of the wavelet. $W_{f(t,\ \Delta t)}$ is the correlation of the multi-spot

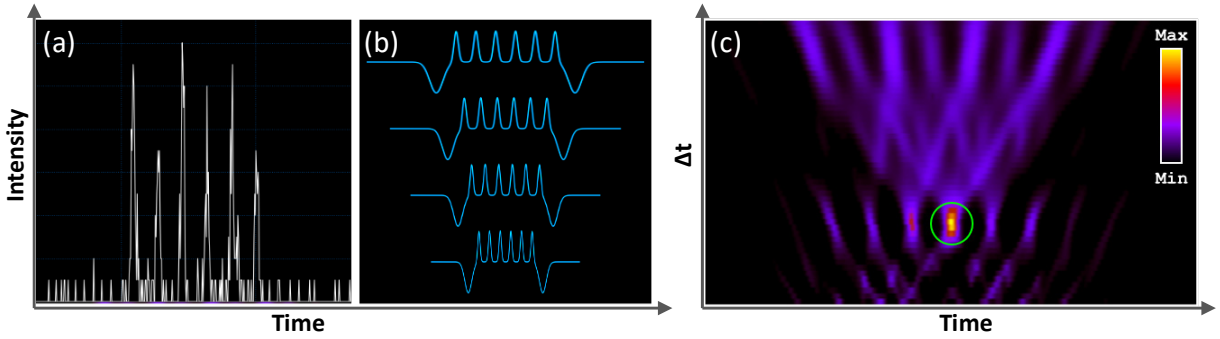

Fig. 2. (a) Single particle fluorescence signal. (b) Custom defined wavelet for four different Δt values. (c) CWT 2D plot with a green circle indicating the local maximum.

signal (f) with the wavelet ($\psi_{t,\ \Delta t}$). Therefore, a match of t and Δt will result in a local maximum in the CWT plot. A moving window technique is used to locate event occurrence in time – Δt space (Fig. 2c). Using this technique, we were able to identify twice as many particles in the trace of Fig. 1a with a 3x lower error rate compared to the algorithm of Eq. (1).

In summary, we demonstrated a multiscale signal processing technique for multi-spot fluorescence signals. Significant improvements in detection rate and accuracy are due to concurrent exploitation of additional information (amplitude, temporal and shape) collected from a multi-spot fluorescence signal.

4. Acknowledgements

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5. References

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