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Signal-to-noise Enhancement in Optical Detection of Single Viruses with Multi-spot Excitation

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Abstract

We present fluorescence detection of single H1N1 viruses with enhanced signal to noise ratio (*SNR*) achieved by multi-spot excitation in liquid-core anti-resonant reflecting optical waveguides (ARROWs). Solid-core Y-splitting ARROW waveguides are fabricated orthogonal to the liquid-core section of the chip, creating multiple excitation spots for the analyte. We derive expressions for the *SNR* increase after signal processing, and analyze its dependence on signal levels and spot number. Very good agreement between theoretical calculations and experimental results is found. *SNR* enhancements up to 5×10^4 are demonstrated.

Index Terms

Anti-resonant reflecting optical waveguides (ARROWs); biophotonics; integrated waveguides; liquid core waveguides; optofluidics; Y-splitters

I. INTRODUCTION

Optofluidics, which integrates photonics and microfluidics, has led to highly compact and sensitive biomedical sensors [1], [2]. Chip-scale, highly sensitive optofluidic devices using different types of optical waveguides have reached the single bioparticle detection limit for proteins [3], nucleic acids [4], and virus particles [5]–[7].

However, continued improvements in sensitivity remain a major goal as we approach the ultimate limit of detecting individual bio-particles labeled by single or few fluorophores as is the case for antibody-labeled proteins or nucleic acid detection with molecular beacons [7]. Fluorescence spectroscopy is the most popular powerful technique for detecting the presence of a target molecule in a solution while monitoring complex biological processes. When there is only one fluorescence excitation spot, it is often challenging to recover weak signals with very low signal to noise ratio (SNR). One approach to solve this problem is using multi-spot excitation producing temporally encoded signals. As only the targets produce a time-dependent signal that reflects this excitation pattern, detection can be enhanced by a simple signal processing step to drastically increase signal to noise ratios. This method has been implemented for micro-particle detection by exciting particles along a fluidic channel and collecting the fluorescence signal through multiple waveguides or a patterned mask in order to create spatial modulation of the signal [8]–[12].

Here, we systematically investigate multi-spot based SNR enhancement on an LC-ARROW (liquid-core antiresonant reflecting optical waveguide) platform. LC-ARROW devices have proved to enable highly sensitive fluorescence spectroscopy on a chip, by combining good optical confinement with small analyte volumes using well established micro-fabrication procedures [6], [7], [13]–[18]. These devices can also be integrated with optical detection elements such as spectral filters [19], [20], and with sample processing capabilities in a dedicated microfluidic layer [6], [21], [22].

Recently, multiplexed fluorescence detection using multi-spot excitation was demonstrated using a multi-mode interference (MMI) waveguide, demonstrating the potential of this concept [7]. Here, we introduce an alternative approach to creating multi-spot patterns using Y-splitter waveguides. Y-splitters have no spectral dependence, create high quality excitation profiles, and are ideal for systematically varying the number of excitation spots. Specifically, 3 different Y-splitter waveguides creating $N=2, 4$, and 8 spots were fabricated and tested using fluorescently labeled viruses as analytes. A comparison of these devices elucidates the dependence of SNR enhancement on spot number. We show up to 50,000x SNR enhancement by using 1x8 Y-splitter waveguides, in good agreement with the theoretical analysis. The measured SNR enhancement increases with the number of excitation spots.

II. DEVICE DESIGN AND FABRICATION

The new optofluidic analysis chip with Y-splitters is based on LC-ARROW devices that consist of high refractive index dielectric layers which surround a hollow core that can be filled with low-index fluids.

These dielectric layers are designed with appropriate thicknesses to create high optical confinement in the liquid channel, maximizing the interaction between the specimen and the light. These liquid-core waveguides are combined with solid-core waveguides for orthogonal fluorescence excitation and collection with high coupling efficiency. In order to further improve the performance of these devices, we replaced the single solid-core excitation waveguide with Y-splitting waveguides to create multiple excitation spots at the liquid core-solid core intersection (Fig. 1a). Beam propagation software (FimmWAVE, Photon Design) was used to design devices with equal power splitting ratios and minimized propagation loss in the curved waveguide sections. Based on these simulations, the fan-out angle of each splitter is kept below 2° . Fig. 1b shows the design angles for the three separate designs, where $N=2, 4$, and 8 . The difference between each spot is kept at $25\mu\text{m}$ in order to create distinct spot patterns.

Y-splitter devices were created using an optimized fabrication procedure [23], [24]. Dielectric layers, SiO_2 (refractive index $n=1.47$) and Ta_2O_5 ($n=2.107$), with the thicknesses of $265/102/265/102/265/102$ nm starting with SiO_2 in order of deposition, were deposited on Si wafers. A hollow channel, with the dimensions of $5\mu\text{m} \times 12\mu\text{m}$ was defined lithographically using SU-8. A $6\mu\text{m}$ thick SiO_2 layer was deposited in order to create the solid core layers and the top sides of the liquid core channel. The SU-8 was then removed using a mixture of H_2O_2 and sulfuric acid, creating the hollow-core waveguide [25].

The spot patterns created by the Y-splitting devices were characterized by filling the liquid-core channel with quantum dots (Crystalplex) and introducing 633nm laser light into a single waveguide at the edge of the chip. The emitted light from quantum dots is imaged using a custom compound microscope, showing multiple, equally separated spots (Fig. 1c). Compared to MMIs [7], the Y-splitters have a 4 times larger peak to valley ratio in the excitation region, since there is no scattering between the output waveguides.

For single molecule experiments, purified, inactivated H1N1 Human Influenza A/PR/8/34 Virus (Advanced Biotechnology Inc.) was labeled with Dylight 633 NHS ester-activated dye according to manufacturer specifications (Thermo Scientific). Unbound dye was removed by column chromatography using a PD MiniTrap G-25 column and $1 \times$ PBS elution buffer (GE Healthcare Life Sciences), and efficient labeling was verified by TIRF microscopy.

The experimental setup implemented for optical virus detection with multi-spot excitation can be seen in Fig. 1d. A 633nm HeNe laser is coupled into a single-mode fiber, which then butt-coupled into the Y-splitter section of the chip. The fluorescence signals emitted by the labeled viruses are collected orthogonal to the excitation through the liquid- and solid-core waveguides. An avalanche photo diode (Excelitas) is used to detect the fluorescence signal after removing the 633nm excitation wavelength with a band pass filter.

III. SIGNAL PROCESSING ALGORITHM

Each particle traveling down the liquid core passes multiple (N) excitation spots, which creates a time-dependent fluorescence signal $F(t)$ with N peaks that are correlated with the spatial pattern via the particle's velocity (Fig. 2b). A signal processing algorithm is used to increase the SNR of the particle fluorescence by correlating these temporally encoded signals [9]. $F(t)$ is subjected to the following algorithm;

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

where T is the time difference between any two of the N signals. Signals that are correlated by T are enhanced while the random noise, which is not correlated, is filtered out efficiently. The noise background is characterized by its mean value μ and standard deviation σ . SNR is defined as the ratio of P , the average peak value of the particle's signal to the standard deviation of the background signal. The SNR of the original data is then defined as;

$$SNR_o = \frac{P}{\sigma} \quad (2)$$

Mean value and standard deviation for products of multiple independent random variables are defined as,

$$\begin{aligned} \mu_s &= \mu^N \\ \sigma_s &= \sqrt{\langle S(t)^2 \rangle - \langle S(t) \rangle^2} \end{aligned} \quad (3)$$

The standard deviation after the signal processing can be derived as following;

$$\begin{aligned} \sigma_s &= \sqrt{(\sigma_{F(t)}^2 + \langle F(t) \rangle^2) \dots (\sigma_{F(t-(N-1) \cdot \Delta T)}^2 + \langle F(t-(N-1) \cdot \Delta T) \rangle^2) - (\langle F(t) \rangle^2 \dots \langle F(t-(N-1) \cdot \Delta T) \rangle^2)} \\ &= \sqrt{\prod_{i=0}^{N-1} (\sigma_{F(t-i \cdot \Delta T)}^2 + \langle F(t-i \cdot \Delta T) \rangle^2) - \prod_{i=1}^N \langle F(t-i \cdot \Delta T) \rangle^2} \end{aligned} \quad (4)$$

The standard deviation and the mean of the shifted data stay the same, since it is only a temporal shift;

$$\sigma_{F(t)} = \sigma_{F(t-(N-1) \cdot \Delta T)} = \sigma$$

$$\langle F(t) \rangle = \langle F(t-(N-1) \cdot \Delta T) \rangle = \mu \quad (5)$$

Combining equations (4) and (5), the standard deviation of the data after the signal processing becomes;

$$\sigma_s = \sqrt{(\sigma^2 + \mu^2)^N - (\mu^2)^N} \quad (6)$$

The average peak value of the particle signal is enhanced by N times after the signal processing algorithm;

$$P_s = P^N \quad (7)$$

The dependence of SNR enhancement on original mean and noise values is derived by combining equations (2), (6), and (7) to yield;

$$\frac{SNR_s}{SNR_o} = \frac{P^{N-1} \sigma}{\sqrt{(\sigma^2 + \mu^2)^N - \mu^{2N}}} \quad (8)$$

This formula reveals the dependence of the SNR change on the properties of the original signal and the spot number. An SNR enhancement can be achieved for a wide range of σ and μ values. The method works best for large SNR_o and N . The effect can be most dramatic if the background signal contains occasional time points at which the signal level reaches zero. A single zero value is sufficient to render the entire product (1) to zero. Given a probability p_0 of finding a zero in the original signal $F(t)$, the probability of $S(t)=0$ is easily shown to be,

$$p_{S=0} = 1 - (1 - p_0)^N \quad (9)$$

Fig. 1e shows the probability of finding zero for $N-1$ multiplications, for different initial p_0 values (i.e. y-intercepts), from 0.1 to 0.9. Consequently, the SNR enhancement can reach extremely large values as will be discussed below.

IV. RESULTS AND DISCUSSION

A. Enhanced SNR

We first demonstrate the signal to noise ratio enhancement by using a 1x8 Y-splitter waveguide. The labeled H1N1 viruses were introduced to the inlet reservoir with a

concentration of 10^7 per mL, i.e. 0.1 particles per excitation volume. The concentration is kept low enough to avoid multiple particles in the excitation area at the same time. Negative pressure was applied on the outlet in order to pull the particles through the channel and past the excitation area. Viruses traveling in the liquid-core waveguide are exposed to 8 separate laser spots. The particle trace of the raw data, directly obtained by the detector, can be seen in Fig. 2a, demonstrating that single viruses can be detected in flow on this chip. $F(t)$ shows $P=30$ counts per 0.1ms binning time per particle on average, with $\sigma=2.2$ and $\mu=4.2$ counts/0.1ms, leading to average particle signal to noise ratio of $SNR_0=13$. The peak intensities vary between particles due to the variation in dye amounts per particle, location in the channel, and speed in the excitation area [4]. Fig. 2b shows $F(t)$ for one of the detected viruses revealing 8 clear peaks, separated by T . Fig. 2c demonstrates the autocorrelation curve for the single particle in 2b, which exhibits peaks at multiples of T ; here 0.8 ms. The autocorrelation of the complete signal $F(t)$ allows us to determine the average T value which is used to run the signal processing algorithm (1). Fig. 2d shows the processed $S(t)$ for the particle seen in Fig. 2b. On average, we achieve an SNR enhancement of 5×10^4 over the course of this experiment. The initial probability of finding a zero, p_0 for this experiment is 0.019, the ratio of the number of bins with zero counts to total number of bins in the background data. Fig. 2e shows the probability of finding a zero in $S(t)$ according to (9) as function of spot number for this experiment. For the present sample, $N=8$, and $p_{S=0}$ becomes 0.14, in excellent match with the theory (line). Computing the autocorrelation on all individual virus signals allows us to determine the statistical distribution of T and thus the particle velocities. Fig. 2f shows the histogram for the velocities of the detected particles, showing a relative wide variation due to fluctuations in applied pressure and different locations within the Poiseuille flow profile of the rectangular channel.

Fig. 3a shows in more detail how the properties of the background affect the SNR enhancement. In this curve, the variations in SNR_S / SNR_0 according to (8) are depicted by varying the σ and μ , and taking the signal average value ($P=30$) from the experiment. The marked spot represents the experimental (σ, μ) values. An SNR enhancement of 2×10^5 is predicted, which is slightly higher than the experimental result due to variation in peak signal values for each detected particle and the T variation coming from the different particle velocities. Fig. 3b shows the limits of the SNR enhancement, for this experiment. The light region indicates where the SNR enhancement is above 1, and the dark region is below 1. The marked spot shows the value for our experiment.

B. Effect of number of spots (N) on SNR enhancement

We now discuss the dependence of the SNR enhancement on the number of spots. Equation (8) shows that a higher number of peaks leads to a higher enhancement, when the initial particle signal is high enough. In order to prove this experimentally, three different Y-splitter devices with $N=2, 4$, and 8 were fabricated and tested. The same analytes, labeled H1N1 viruses, are introduced to all three devices, with the concentration (10^7 per mL). Viruses were then detected under identical experimental conditions. The excitation power of the laser was adjusted to get the similar average signal value P for the three experiments.

The SNR parameters of these three experiments are shown in the table (Fig. 4a). The experimentally achieved SNR enhancement demonstrates a good match with theoretical calculations. Fig. 4b shows how the SNR enhancement increases exponentially with the number of spots (N) in these three experiments (symbols), providing a good match between the calculation (line) based on average μ and σ values. Due to the different properties of each individual chip, there is a slight variation in the noise (σ), mean (μ) and the average peak (P) values of the experiments, which results in the difference from the theoretical curves. It is evident that using 1x8 Y-splitters creates much higher SNR enhancement compared to 1x4 and 1x2 Y-splitters. The 1x8 Y-splitter is also optimal for ARROW device dimensions because increasing the number of spots further would make the chip larger, and hence, the propagation loss higher. However, this problem can be addressed by replacing the Y-splitters with MMIs which makes it possible to get higher number of spots with significantly smaller dimensions.

V. CONCLUSION

In conclusion, we have demonstrated large SNR enhancement for single virus detection on LC-ARROW chips that use Y-splitter waveguides to create temporally encoded fluorescence signals. Y-splitter waveguides were successfully integrated to a LC-ARROW fluorescence spectroscopy platform, by creating multiple excitation spots at the detection area. The temporally encoded fluorescence signal from single H1N1 viruses was successfully collected and processed with a signal processing algorithm. 50,000 fold SNR enhancement was achieved in good agreement with theoretical analysis. The effect of number of spots in the signal enhancement process has been analyzed. It is shown that, with higher number of excitation spots, the SNR enhancement increases exponentially. Thus, the LC-ARROW platform with integrated Y-splitter solid-core waveguide array provides the best performance if maximizing the signal-to-noise ratio is critical. MMI-based multi-spot excitation is an alternative when using multiple wavelengths or minimizing chip dimensions is the goal.

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References

1. Schmidt H, Hawkins AR. The photonic integration of non-solid media using optofluidics. *Nat Photon.* Oct; 2011 5(10):598–604.
2. Fan X, White IM. Optofluidic microsystems for chemical and biological analysis. *Nat Photon.* Oct; 2011 5(10):591–597.
3. Chen Y-F, Serey X, Sarkar R, Chen P, Erickson D. Controlled Photonic Manipulation of Proteins and Other Nanomaterials. *Nano Lett.* Mar; 2012 12(3):1633–1637. [PubMed: 22283484]
4. Liu S, Wall TA, Ozcelik D, Parks JW, Hawkins AR, Schmidt H. Electro-optical detection of single λ -DNA. *Chem Commun.* Jan; 2015 51(11):2084–2087.

5. Lopez CA, Daaboul G, Vedula R, Özkumur E, Bergstein DA, Geisbert TW, Fawcett HE, Connor JH, Goldberg BB, Ünlü MS. Label-free, multiplexed virus detection using spectral reflectance imaging. *Biosens Bioelectron.* Apr; 2011 26(8):3432–3437. [PubMed: 21342761]
6. Cai H, Parks JW, Wall TA, Stott MA, Stambaugh A, Alfson K, Griffiths A, Mathies RA, Carrion R, Patterson JL, Hawkins AR, Schmidt H. Optofluidic analysis system for amplification-free, direct detection of Ebola infection. *Sci Rep.* Sep.2015 5:14494. [PubMed: 26404403]
7. Ozcelik D, Parks JW, Wall TA, Stott MA, Cai H, Parks JW, Hawkins AR, Schmidt H. Optofluidic wavelength division multiplexing for single-virus detection. *Proc Natl Acad Sci.* Oct.2015 201511921.
8. Kiesel P, Bassler M, Beck M, Johnson N. Spatially modulated fluorescence emission from moving particles. *Appl Phys Lett.* Jan; 2009 94(4):041107–041107–3.
9. Lien V, Zhao Kai, Berdichevsky Y, Lo Yu-Hwa. High-sensitivity cytometric detection using fluidic-photonics integrated circuits with array waveguides. *Sel Top Quantum Electron IEEE J Of.* 2005; 11(4):827–834.
10. Psaltis D, Quake SR, Yang C. Developing optofluidic technology through the fusion of microfluidics and optics. *Nature.* Jul; 2006 442(7101):381–386. [PubMed: 16871205]
11. Kettlitz SW, Moosmann C, Valouch S, Lemmer U. Particle detection from spatially modulated fluorescence signals. *SPIE.* Apr.2014 9129:91291B–91291B–10.
12. Martini J, Recht MI, Huck M, Bern MW, Johnson NM, Kiesel P. Time encoded multicolor fluorescence detection in a microfluidic flow cytometer. *Lab Chip.* Dec; 2012 12(23):5057–5062. [PubMed: 23044636]
13. Yin D, Deamer DW, Schmidt H, Barber JP, Hawkins AR. Single-molecule detection sensitivity using planar integrated optics on a chip. *Opt Lett.* Jul; 2006 31(14):2136–2138. [PubMed: 16794704]
14. Yin D, Lunt EJ, Rudenko MI, Deamer DW, Hawkins AR, Schmidt H. Planar optofluidic chip for single particle detection, manipulation, and analysis. *Lab Chip.* Aug; 2007 7(9):1171–1175. [PubMed: 17713616]
15. Yin D, Lunt EJ, Barman A, Hawkins AR, Schmidt H. Microphotonic control of single molecule fluorescence correlation spectroscopy using planar optofluidics. *Opt Express.* Jun; 2007 15(12):7290–7295. [PubMed: 19547052]
16. Rudenko MI, Kühn S, Lunt EJ, Deamer DW, Hawkins AR, Schmidt H. Ultrasensitive Q β Phage Analysis Using Fluorescence Correlation Spectroscopy on an Optofluidic Chip. *Biosens Bioelectron.* Jul; 2009 24(11):3258–3263. [PubMed: 19443207]
17. Kühn S, Phillips BS, Lunt EJ, Hawkins AR, Schmidt H. Ultralow power trapping and fluorescence detection of single particles on an optofluidic chip. *Lab Chip.* Dec; 2009 10(2):189–194. [PubMed: 20066246]
18. Bernini R, Campopiano S, Zeni L, Sarro PM. ARROW optical waveguides based sensors. *Sens Actuators B Chem.* Jun; 2004 100(1–2):143–146.
19. Measor P, Phillips BS, Chen A, Hawkins AR, Schmidt H. Tailorable integrated optofluidic filters for biomolecular detection. *Lab Chip.* Jan.2011 11(5):899. [PubMed: 21221449]
20. Ozcelik D, Phillips BS, Parks JW, Measor P, Gulbransen D, Hawkins AR, Schmidt H. Dual-core optofluidic chip for independent particle detection and tunable spectral filtering. *Lab Chip.* Aug; 2012 12(19):3728–3733. [PubMed: 22864667]
21. Parks JW, Cai H, Zempoaltecatl L, Yuzvinsky TD, Leake K, Hawkins AR, Schmidt H. Hybrid optofluidic integration. *Lab Chip.* Sep; 2013 13(20):4118–4123. [PubMed: 23969694]
22. Parks JW, Olson MA, Kim J, Ozcelik D, Cai H, RC, Patterson JL, Mathies RA, Hawkins AR, Schmidt H. Integration of programmable microfluidics and on-chip fluorescence detection for biosensing applications. *Biomicrofluidics.* Sep.2014 8(5):054111. [PubMed: 25584111]
23. Hawkins AR, Schmidt H. Optofluidic waveguides: II. Fabrication and structures. *Microfluid Nanofluidics.* Jul.2007 4:17–32. [PubMed: 21603122]
24. Zhao Y, Jenkins M, Measor P, Leake K, Liu S, Schmidt H, Hawkins AR. Hollow waveguides with low intrinsic photoluminescence fabricated with Ta(2)O(5) and SiO(2) films. *Appl Phys Lett.* Feb. 2011 98(9):91104. [PubMed: 21448254]

25. Holmes M, Keeley J, Hurd K, Schmidt H, Hawkins A. Optimized piranha etching process for SU8-based MEMS and MOEMS construction. J Micromechanics Microengineering. Oct.2010 20(11): 115008.

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Fig. 1.

(a) Schematic of ARROW detection platform with Y-splitter. (b) Splitting angles for 3 different Y-splitter chips. (c) Quantum dots filled liquid core section shows 8 excitation spots. (d) Experimental setup consisting of excitation and detection sites. (e) The probability of finding a zero for $N-1$ multiplication, for different initial p_0 values (i.e. y-intercepts), from 0.1 to 0.9.

Fig. 2.

(a) Red-dye labeled H1N1 virus detected by APD. (b) Single virus fluorescence signal demonstrating 8 clear peaks. (c) Autocorrelation curve of the single peak in 2(b), showing that the T is around 0.8 ms. (d) Virus signal from 2(b) after signal processing (8) (e) Probability of finding zero values in noise for N multiplication. The marked spot shows where above experiment corresponds, with the probability of 0.14. (f) Histogram of the particle velocities.

Fig. 3.

(a) Theoretical analysis of *SNR* enhancement varying the noise and mean values using the signal average from the experiment. The marked spot corresponds to the experimental values of μ and σ with an *SNR* enhancement is 2×10^5 . (b) Theoretical analysis of the limits of the *SNR* enhancement. The light region shows the values at which the *SNR* enhancement is above one, and the dark region represents values at which the *SNR* enhancement is below one. The marked spot is the experimental values of μ and σ

Fig. 4.

(a) Table showing the noise, mean, and SNR values of the original data and the enhancement values after the signal processing. (b) Dependence of SNR on the number of excitation spots (N). The line shows the theoretical calculation for average μ and σ values while experimental data is plotted for 3 Y-splitter devices.