A Bio-molecular Sensor Based on Optical Weak Measurement

Nian Xiong 1, Xiangnan Wang 2, Lixuan Shi 2, Yang Xu 2, Tian Guan 2 and Yonghong He 2

1 College of Information Science and Technology, Jinan University, 601 West Huangpu Ave, Guangzhou, China;
2 Institute of Optical Imaging and Sensing, Shenzhen Key Laboratory for Minimal Invasive Medical Technologies, Graduate School at Shenzhen, Tsinghua University, Xili University Town, Shenzhen, China;
Email: heyh@sz.tsinghua.edu.cn

Abstract: We developed a phase-sensitive sensor based on the optical weak measurement for label-free detection of biomolecular interaction. The weak value amplification system can be implemented in common-path with total internal reflection structure. The phase difference between p and s polarizations caused by biomolecular recognition is measured by the central wavelength shift of the frequency domain weak measurement system. Structure of p and s polarizations in common-path makes system robust and stable. The applicability is illustrated by real-time monitoring interaction of biomolecules.

1. Introduction

There are many methods for quantitative analysis of proteins, such as absorption photometry, fluorescence analysis, capillary electrophoresis analytical method, chemiluminiscence, and resonance light scattering method. However, these methods include complex sample preparation, lack of real-time functionality, and need expensive devices. The type of reflection optical biosensors which is sensitive to phase, such as surface plasmon resonance (SPR) and total internal reflection (TIR) sensors have been researched intensively because it can realize high sensitivity and label-free biomolecular determination with simple setup [1-3]. TIR biosensors is easily implement in fiber with simple setup and can be employed in various conditions. However, their resolution were limited because of rather smooth phase response [4]. So it is difficult to realize high sensitive biomolecular detection. Surface plasmon resonance (SPR) sensors can realize better resolution [5] because p polarization component can induce sharper phase shift against the coupled resonance of surface plasmon and light. It is important to realize the optimization of wavelength and the incident angle and the accurate control of gold film thickness [6]. Recently, optical weak measurement based on the amplification mechanism of signal has emerged as a promising method because it was reported to realize the phase measurement on the basis of imaginary weak value which performs better than the standard interferometry method by some orders of magnitude [7].

The quantum weak measurement methods were first proposed in 1988[8]. The eigenvalue can be amplified multiple times by appropriately adjusting the preselected state and the postselected state. The pointer system and measurement system are weakly coupled. With the interaction process completed, the values containing the pointer state are defined as the weak value, which was originally implemented by Ritchie et al. in 1991 [9]. This process is called Weak Value Amplification (WVA), which offers a deeper interpretation of weak measurement and shows the potential for accurate measurements. The HSA amplification mechanism has high precision and measurement potential for observing physical
phenomena and detecting physical parameters. Based on different application requirements, time domain, spatial domain, polarization angle distribution and frequency domain are widely used in the implementation of weak measurement. Time domain applications include single photon tunneling time [10] and speed [11]. Applications in the spatial domain are as follows: Goos-Hänchenshift [13], ultra-sensitive beam deflection measurements [12] and weak measurement techniques to improve SPR resolution [14]. Polarization rotation [15] is the main application of polarization angle measurement. Temperature measurement [17] and sub-pulse width time delay [16] are applications of frequency domain. The application of weak measurement techniques in these fields has shown great applicability while achieving high precision.

In this paper, we present a label-free sensor which is sensitive to phase for biomolecules detection based on the optical weak measurement. Biosensors with weak measurement in common-path configuration can be implemented in reflection type, which offers the real-time and high precision biomolecular determination for various applications.

2. Experimental Setup

2.1. Weak Measurement System

Figure 1 shows the system model diagram of the weak measurement system based on TIR. Incident light, which is from SLD (IPSD0803, 5mW, Inphenix), with the central wavelength at 830 nm and propagated through a Gaussian filter with the bandwidth of 10 nm. After that, the angle $\alpha$ is preselected by the first linear polarizer (Thorlabs Inc., LPVIS050-MP2, extinction ratio 100000:1) and it is the angle between the horizontal direction and the polarization axis of the first polarizer. The beam then passes two quarter-wave plates, with the fast axis being vertical and vertical for the purpose of continuous phase adjustment. We placed the SF6 prism under the SF6 substrate with an index matching liquid. The light is then reflected by the SF6 substrate and is post-selected by the second linear polarizer. Finally, the spectrometer (Ocean Optiocs, HR2000) collects the output spectral signals.

Figure 1. The schematic diagram of the weak measurement system.

The SLD is a super light-emitting diode and has a center wavelength of 840 nm and a bandwidth of 50 nm. The lens is a collimating lens. The GF is a 830 nm Gaussian filter with a bandwidth of 20 nm. Pre and Post are used to select the front and back polarizers, respectively. The substrate and prism are SF6 prisms and a substrate having an index matching liquid. The QWP is a pair of quarter wave plates and their fast axes are perpendicular to each other. The plane of the first wave plate is inclined at the angle of $\chi$ with regard to the second wave plate.

On the surface of the substrate, there was some interactions of the sample which would make a change of the refractive index. Achieving by two orthogonal polarizations to introduce the phase difference of the eigenstates of the weak measurement system, the total internal reflection (TIR) at the substrate interface was used. The spectrum which could collect the central wavelength shift of the output spectrum was connected to a computer. Hence, the central wavelength shift of the output spectrum reflects the reaction process in real time by monitoring the liquid sample.
The refractive index of the liquid sample changed due to the interaction of the sample on the surface of the substrate. The phase difference of the eigenstate of the weak measurement system was introduced by total internal reflection (TIR) at the substrate interface and it is achieved by two orthogonal polarizations. The spectrometer was connected to a computer to collect the center wavelength shift of the output spectrum in real time. Thence, we can monitor the reaction process of the liquid sample in real time through the center wavelength shift of the output spectrum.

This system has better anti-interference capability in comparison with non-common path system like Mach-Zehnder. It suits for general path implementation. The surface was as a detection zone so that real-time and label-free detection of tumor marker measurements could be easily achieved. Besides, in comparison with the SPR sensor, even there is no accurate gold film coating, the immune response on the reflective prism surface could be directly monitored by the TIR-based weak measurement biosensor.

2.2. Weak Value Amplification System

The weak measurement system was well demonstrated by Figure 1. The pre-selection can be presented as... Fast axes of two quarter-wave plates are perpendicular to each other, which the light passes through. The phase difference between the V and H polarization would be changed when the quarter-wave plates are inclined. By inclining the first wave plate at a small angle, the phase difference between H and V polarizations was increased because of the use of two quarter-wave plates. The equation between the inclination angle and the phase difference can be acquired as:

\[ \delta = \pm \frac{\pi(n_g - n_o)h\lambda^2}{\lambda} \]  

(1)

\( n_g \) represents the refractive index for extraordinary component and \( n_o \) for ordinary in equation (1). \( \lambda \) represents the wavelength and \( h \) represents the thickness of waveplate.

In this paper, the refraction index of the prism was 1.75 RIU. So, with the expression \( \sin^{-1}(1/n) \), the angle of total internal reflection of the prism is 49.46°. And the angle of incident light is 50°. The refraction index in terms of substrate surface will change while the solution flows through the substrate surface. Thus, the phase difference varies with the light. The phase difference caused by change of refraction index is shown as:

\[ \Delta = 2\tan^{-1}\sqrt{\frac{(n_{eff}/n_g)^2 \sin^2 \theta_2 - 1}{n_{eff}/n_g \sin \theta_2 \tan \theta_1}} \]  

(2)

\( n_{eff} \) and \( n_g \) represent the refractive index of the surface of substrate and the prism respectively. \( \theta_2 \) represents the incident angle. So, the total phase difference could be shown as \( \Delta + \delta = \delta + a\lambda^2 \).

The state of the post-selection was set at angle of \( \pi/2 + \beta \), with the axis of first polarizer. The state of post-selection is calculated by \( |\psi_i\rangle = \cos(\alpha + \beta) |H\rangle + \sin(\alpha + \beta) e^{i(\Delta + \delta)} |V\rangle \).

The observable operator was \( \hat{A} = [H]H - [V]V \). \( \hat{A}_w \), which represent the weak value can be shown as:

\[ A_w = \frac{\langle \psi_f |\hat{A}|\psi_i \rangle}{\langle \psi_f |\psi_i \rangle} = \frac{\sin a \cos(\alpha + \beta) + \cos(\alpha + \beta) e^{i(\Delta + \delta)}}{\sin a \cos(\alpha + \beta) - \cos(\alpha + \beta) e^{i(\Delta + \delta)}} \]  

(3)

We define \( \gamma = \cotan(\alpha + \beta) \) so its imaginary part could be shown as:

\[ \text{Im}A_w = \frac{1 + y e^{i(\Delta + \delta)}}{1 - y e^{i(\Delta + \delta)}} \approx \frac{2y \sin(\Delta + \delta)}{1 + y^2 - 2y \cos(\Delta + \delta)} \]  

(4)

Depending on the relationship between the momentum and the imaginary part of the weak value \( \delta \), the expression of the shift of central wavelength can be achieved by introducing \( P = 2\pi/\lambda \) with regard to the phase change.
According to $\Delta + \delta = \Delta + \delta x^2$, the relationship between the quarter-wave plate dip angle and the center wavelength could be shown as:

$$\delta \lambda = -\frac{2\pi k (\Delta \lambda)^2}{\lambda_0} \text{Im} A_w = -\frac{4\pi k (\Delta \lambda)^2 y \sin(\delta + \Delta)}{\lambda_0 (1 + y^2 - 2y \cos(\delta + \Delta))}$$  

(5)

The initial phase difference $\Delta$ can be altered by refractive index of the solutions to be detected on the prism surface (6), the refractive index of the tested solutions can be secured by the measurement of the spectrum shift.

3. Experimental Results

To test the resolution of the system, some lab work was performed. Firstly, on the surface of the prism, the sodium chloride solution which was diluted was injected to the cell, altering the initial phase. Then, noise in high frequency related to shot noise was reduced because of the usage of an FFT filter which makes the spectrum smoother. The change of the sodium chloride solution concentration would make a frequency shift so that a real-time signal could be obtained by establishing a LabVIEW program. Since the number of photons collected by CCD is proportional to probability of a different wavelength, the expectation of the spectrum could be calculated then the shifts could be finally obtained.

Initially, the central wavelength of the Gaussian 830nm. Then it is different from the original Gaussian shape due to the longitudinal movement of the interaction. The concentration for the solutions of sodium chloride is $1.47 \times 10^{-3} \text{C}$ [18], where $C$ presents the percentage of the mass. Figure 2 shows that the shift caused by 1.8% sodium chloride solution is 4.35nm in comparison with deionized water. The sensitivity secured by $\delta \lambda / \delta n$ is 1644nm/RIU. And the stability of the measurement obtained by calculating the standard deviation was 0.0097 nm. Therefore, the defined resolution is calculated as $1.2 \times 10^{-6}$ RIU.

Figure 2. Experiment results of the solutions of diluted sodium chloride.

(a), original spectrum collected by CCD. (c), linear fitting of the shifts of spectrum.

In recent years, the determination of tumor markers attracts much attention which for tumors diagnosis. Taken Carcinoembryonic antigen (CEA), we for the investigation of weak measurement biosensing. A flow channel is developed for the process detection about identification of CEA. The solution of analyte was pumped, with a speed of 100μL/min, into the channel. The refractive index of the solution remains unchanged by using the flow setting. The analyte solution is acquired by a recognition spot to increase the refraction index. The reaction process is related to a phase difference, expressed by equation (6).
Silica dioxide is well known for surface functionalization for biomolecule detection. We employed dopamine to modify the surface considering its variety of bonding capabilities. A thin film was made on the surface of prism when the dopamine was pumped to the channel, which could be employed to modify the surface of many materials. The concentration of dopamine solution is 2 mg/mL under the conditions of pH 8.5, and buffered to 10 mM tris.

The detection of CEA process is displayed in figure 3. A thin polydopamine film was formed continuously on the substrate surface with the dopamine solution injected into the channel. Then, the remaining dopamine was washed out by the PBS solution. Then, an anti-CEA solution with a concentration of 50 μg/mL was buffered to 10 mM PBS under the same conditions of pH with the speed of 100 μg/mL. Then, the remaining anti-CEA was washed out by the PBS solution. The protein-free blocking buffer was employed to avoid the non-specific connecting spots, avoiding adsorption of the non-specific condition. Finally, the solution of CEA (50 μg/mL) was injected with the speed of 100 μg/mL under condition of pH 7.4. The CEA solution was buffered to the 10 mM PBS under the same condition of pH.

Figure 4 gives a good explanation of detection process. The substance refractive index was changed by a thin surface adhesion film formed by self-polymerized Dopamine. The alter of refractive index would induce the phase difference when the light transmitted. So, as shown in equation (1), the wavelength shift reflected the alter of optical phase. Figure 4 depicts that the adsorption dynamic curves, the adsorption time was shown on x-axis. Meanwhile, the real-time wavelength shift was represented by y-axis in comparison with initial central wavelength. A quick shift was made by a PBS (pH7.4) solution after dopamine film was deposited on the surface, since there is difference between PBS and DPA in terms of body refractive index and there is no sodium chloride in DPA buffered by tris. To capture CEA, a ligands layer on the film of dopamine was formed by Anti-CEA. A quicker central wavelength shift
resulted from different protein-free blocking buffer was made by protein-free blocking buffer in comparison with PBS solution. At the same time, the gap of anti-CEA was filled by buffer mentioned above. The wavelength shift of 0.45nm was caused by the infusion of CEA antigen. Hence, from Figure 4 a good demonstration of our weak measurement system that the CEA molecule recognition could be detected.

In our optical system, we can realize the label-free biomolecule detection with the simple setup. We can also realize the determination in real-time of reaction of tumor markers, which matters much for cancer diagnosis. In short, the results confirmed the feasibility of the biosensor based on the optical weak measurement, which matters much in drug analysis.

4. Summary

We developed a biosensor based on optical weak measurement. This system is robust and simple owing to its common-path structure. In this system, there is quantitative relationship between wavelength shift and the phase difference. The phase difference was caused by TIR generated on the surface of the prism. So we can secure the parameter which generates the phase difference by analyzing the wavelength shift. It is anticipated that this biosensor could be easily employed with microscopy because there is no surface coating with the transparent substrate. Meanwhile, this biosensor could also be developed for multi-channel biomedical detection.

5. Acknowledgement

This research was made possible with the financial support from National Science Foundation of China (NSFC) (61875102, 61675113, 61527808), Science and Technology Research Program of Shenzhen City(JCYJ20170412170255060,JCYJ20160324163759208,JCYJ20170412171856582,JCYJ20170816161836562, JCYJ20170817111912585). Oversea cooperation foundation, Graduate School at Shenzhen, Tsinghua University (HW2018007)

6. References

[1] S. Patskovsky, I.-H. Song, M. Meunier and A. V. Kabashin. Silicon based total internal reflection bio and chemical sensing with spectral phase detection. Opt. Express, 17(2009) pp 20847-52.
[2] Y. Guo, J. Y. Ye, C. Divin, B. Huang, T. P. Thomas, J. J. R. Baker and T. B. Norris. Real-Time Biomolecular Binding Detection Using a Sensitive Photonic Crystal Biosensor. Analytical Chemistry, 82 (2010) pp 5211-18.
[3] X. Guo. Surface plasmon resonance based biosensor technique: A review. Journal of Biophotonics. 5(2012) pp 483-501.
[4] R. M. A. Azzam. Phase shifts that accompany total internal reflection at a dielectric–dielectric interface. J. Opt. Soc. Am. A. 21(2004) pp 1559-63.
[5] M. Piliarik and J. í. Homola. Surface plasmon resonance (SPR) sensors: approaching their limits. Opt. Express 17 (2009) pp 16505-17.
[6] S. Patskovsky, M. Vallieres, M. Maisonneuve, I.-H. Song, M. Meunier and A. V. Kabashin. Designing efficient zero calibration point for phase-sensitive surface plasmon resonance biosensing. Opt. Express 17(2009) pp 2255-63.
[7] N. Brunner and C. Simon. Measuring Small Longitudinal Phase Shifts: Weak Measurements or Standard Interferometry. Phys. Rev. Lett. 105(2010) 010405.
[8] Y. Aharonov, D. Z. Albert and L. Vaidman. How the result of a measurement of a component of the spin of a spin-1/2 particle can turn out to be 100. Phys. Rev. Lett. 60(1988) pp 1351-54.
[9] N. W. M. Ritchie, J. G. Story and R. G. Hulet. Realization of a measurement of a weak value. 66 (1991) pp 1107-10.
[10] A. M. Steinberg, P. G. Kwiat. And R. Y. Chiao. Measurement of the single-photon tunneling time. Phys. Rev. Lett. 71 (1993) pp 708-11.
[11] G. I. Viza, J. Martinez-Rincon, G. A. Howland, H. Frostig, I. Shomroni, B. Dayan. And J. C. Howell. Weak-values technique for velocity measurements. Opt. Lett. 38 (2013) pp 2949-52.
[12] P. B. Dixon, D. J. Starling, A. N. Jordan and J. C. Howell. Ultrasensitive beam deflection measurement via interferometric weak value amplification. Phys. Rev. Lett. 102(2009) 173601.

[13] G. Jayaswal, G. Mistura and M. Merano. Weak measurement of the Goos-Hänchen shift. Opt. Lett. 38(2013) pp 1232-34.

[14] L. Luo, X. D. Qiu, L. G. Xie, X. Liu, Z. X. Li, Z. Y. Zhang and J. L. Du. Precision improvement of surface plasmon resonance sensors based on weak-value amplification. Opt. Express 25(2017) pp 21107-14.

[15] B. D. L. Bernardo, S. Azevedo and A. Rosas. Ultrasmall polarization rotation measurements via weak value amplification. Phys. Lett. A 378 (2014) pp 2029-33.

[16] L. J. Salazar-Serrano, D. Janner, N. Brunner, V. Pruneri and J. P. Torres. Measurement of sub-pulse-width temporal delays via spectral interference induced by weak value amplification. Phys. Rev A. 89(2014) 012126.

[17] L. J. Salazar-Serrano, D. Barrera, W. Amaya, S. Sales, V. Pruneri, J. Capmany and J. P. Torres. Enhancement of the sensitivity of a temperature sensor based on fiber Bragg gratings via weak value amplification. Opt. Lett. 40 (2015) pp 3962-65.

[18] W. Lu and W. M. Worek. Two-wavelength interferometric technique for measuring the refractive index of salt-water solutions. Applied Optics. 32 (1993) pp 3992-4002.