A differential weak measurement system based on Sagnac interferometer for self-referencing biomolecule detection

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Abstract

A differential weak measurement system was presented, exhibiting the self-referencing function for biomolecule real time detection as a label-free optical biosensor. We built a Sagnac interferometer, which limited horizontal (H) and vertical (V) polarization to propagating along the common path but in opposite directions to realize weak measurements with two measuring channels installed in two corners of this Sagnac interferometer. By introducing two half wave plates into the system alternately with the two channels to convert between H and V polarization, we obtained a differential measurement for phase delay, which could quantitatively characterize the refractive index change corresponding to the concentration of samples in the channels. With this system, a real time monitor of molecule concentration in the dialysis process was accomplished, demonstrating the function of self-referencing, which is important for optical label-free molecule detection in a complex biological sample solution.

Keywords: weak measurement, self-referencing, differential measurement, biomolecule detection

(Some figures may appear in colour only in the online journal)

1. Introduction

Weak measurement, which was first proposed by Aharonov, Albert and Vaidman in 1988 [1], has stepped into the public spotlight as a signal amplification technique, due to the principles of weak value amplification (WVA). In weak measurement, the parameter under test induces a perturbation to the measuring system, providing a tiny shift between the two eigenstates, which were always represented with two orthogonal polarization states in an optical system [2]. With appropriate pre- and post-selection, this tiny shift can be amplified and finally read out from the pointer received by a detector. In the concept of WVA, an amplification factor called the weak value was contained in the pointer, defined
as $A_w = \langle \psi_f | A | \psi_i \rangle / \langle \psi_f | \psi_f \rangle$, where $| \psi_i \rangle$ and $| \psi_f \rangle$ were the pre- and post-selection respectively, and $A$ was the observable operator.

In recent years, weak measurement has shown great superiority in numerous high precision measurements, such as phase measurement [2, 3], velocity measurement [4], temperature sensing [5], reflection angle of optic beam [6], photonic spin Hall effect [7], Goos–Hänchen and Imbert–Fedorov shifts [8, 9], optical rotation [10] and detection of a trapped electron [11]. Besides, weak measurement also presents great potential in biomolecule detection by inducing a weak interaction between the system and meter with analytes or biochemical reactions. Recently, the merits of high sensitivity [12], real-time detection [13] have been experimentally demonstrated in biomolecule detection with a weak measurement in the frequency domain, based on the quantitative relation between the central wavelength shift of the output spectra and the phase change of the optical system induced by analytes or biochemical reactions. In addition, weak measurement exhibits a great advantage by realizing phase-sensitive biosensing on a single glass surface with a common path [14], providing great convenience to cooperate with microscopy, as well as some other setups.

Towards a biosensor, self-reference detection is necessary and important [15, 16]. The precision detection of analytes concentration in a complex sample solution may face numerous interferences, including non-specific binding of target molecules, binding of nontarget molecules and background parameter changes [15]. The demand of difference measurement could be met by some traditional optical systems, such as the difference interferometer reported by Lukosz and Stamm [17, 18] and dual-mode surface-plasmon resonance (SPR) sensors [15], which required accurate film thickness control and optimization of the incident angle and wavelength. Hence, it was complicated for the preparation with these methods. Compared with them, weak measurement shows a great advantage with the simple configurations and it can be easily integrated into other systems [14]. In addition, a weak measurement system is practical as a biosensor with the feature of real time detection, as well as label free. However, the self-referencing sensor based on weak measurement has never been accomplished so far. Because of the same propagating direction of the two polarizations, it was difficult to realize a differential measurement result with the phase change caused by analytes in a traditional weak measurement configuration [14], even if referential and measuring channels were set up.

In this work, a differential weak measurement system in a common path based on a modified Sagnac interferometer was proposed, for the first time as we know, to realize self-referencing biological molecule detection in a complex sample. We introduced two half wave plates (HWP) to switch the horizontal ($H$) and vertical ($V$) polarization, resulting in a differential effect between the two channels for the phase change. Thus, with this system, self-reference measurement was realized for biomolecule detection. We experimentally demonstrated the feasibility and practicability of this differential system by monitoring molecule separation in the dialysis process in real time.

2. Methods

The schematic diagram and photograph of the Sagnac interferometer based double-channel weak measurement system is shown in figure 1. The incident light from SLD (IPSDS0803, 5 mW, Inphenix) centered at 830 nm, passing through a Gaussian filter with a bandwidth of 12 nm, was preselected by the first linear polarizer (Thorlabs Inc., LPVIS050-MP2, extinction ratio of 100000:1) with a pointing angle of $\alpha$. Then, the light beam was separated by the PBS (Thorlabs Inc., PBS102, extinction ratio of > 1000:1) with two components according to the polarization, entering into the Sagnac interferometer configuration. The horizontally and vertically polarized light propagated along the clockwise and anticlockwise paths, respectively. SBC (Thorlabs Inc., SBC-IR) was used for continuous phase adjustment. CH1 and CH2 represented two homemade channels that stuck to the surface of the prism, and they provided a detective area where the sample in the channel contacted.
with the prism. The two HWPs were located at an angle of 45° with the vertical direction, resulting in a switch between \( H \) and \( V \) polarization. The two elements were recombined by the PBS, and then post selected by the second linear polarizer, which pointed at an angle of \( \frac{\pi}{2} + \beta \) with the vertical direction, while \( \beta \) was a tiny angle. Finally, the light was received by a spectograph. The total internal reflection, which happened on the interface of the prism contacting with flow channel, was utilized to introduce optical phase difference between \( H \) and \( V \) polarization. This phase difference could quantitatively connect the refractive index corresponding to the concentration of analytes to the phase difference of the two orthogonal polarizations. Thus, the analytes concentration could be detected through the central wavelength shift of output spectra due to the principle of weak value amplification.

3. Results and discussions

Depending on the weak measurement procedures shown in figure 1, we could definitely express the states of the system. According to the angle of the preselected polarizer, the preselection could be expressed as \( |\psi_i\rangle = \cos(\theta) |H\rangle + \sin(\theta) |V\rangle \). After passing through the Sagnac configuration, the optical path of the two polarizations would be changed. For \( H \) polarization, the total internal reflection in prism1 would induce a phase delay of \( \varphi_{1H} \). After being switched into \( V \) polarization by the HWP, another phase delay \( \varphi_{2V} \) would be added. Thus, the total phase delay of \( H \) polarization in the clockwise path was \( \varphi_{1H} = \varphi_{1H} + \varphi_{2V} \). Similarly, we could obtain the total phase delay of \( V \) polarization in the anticlockwise path as \( \varphi_{2V} = \varphi_{2H} + \varphi_{1V} \). Hence, the total phase difference between \( H \) and \( V \) polarization could be expressed as \( \varphi = \varphi_V - \varphi_H = \varphi_{2H} + \varphi_{1V} - (\varphi_{1H} + \varphi_{2V}) = (\varphi_{1V} - \varphi_{1H}) - (\varphi_{2V} - \varphi_{2H}) = \varphi_1 - \varphi_2 \). Then, according to the angle of \( P_2 \), the postselection could also be expressed as \( |\Psi_f\rangle = - \sin(\alpha + \beta) e^{i\varphi/2} |H\rangle + \cos(\alpha + \beta) e^{i\varphi/2} |V\rangle \). In addition, the observable operator was \( A = (|V\rangle \langle V| - |H\rangle \langle H|)/2 \). Thus, the weak value could be obtained

\[
A_w = \frac{\langle \psi_f | A | \psi_i \rangle}{\langle \psi_f | \psi_i \rangle} = \frac{1}{2} \sin(\alpha + \beta) \cos \alpha e^{i\varphi/2} + \sin \alpha \cos(\alpha + \beta) e^{-i\varphi/2} - \sin(\alpha + \beta) \cos \alpha e^{-i\varphi/2} + \sin \alpha \cos(\alpha + \beta) e^{i\varphi/2}.
\]

In equation (1), we define \( \gamma = \frac{\sin(\alpha + \beta) \cos \alpha}{\sin \alpha \cos(\alpha + \beta)} \), so the weak value could be simplified as

\[
A_w = \frac{1}{2} \times \frac{\gamma e^{i\varphi} + 1}{-\gamma e^{i\varphi} + 1} \left( \frac{\gamma e^{i\varphi} + 1}{-\gamma e^{i\varphi} + 1} \right)\sin \varphi.
\]

Also, the imaginary part was \( \text{Im} A_w = \frac{\gamma \sin \varphi}{\gamma^2 + 1 - 2\gamma \cos \varphi} \).

Depending on the relationship between the momentum and the imaginary part of the weak value [12], we could finally achieve the quantitative expression of central wavelength shift with respect to phase change.

![Figure 2](image)

**Figure 2.** The phase response curve of central wavelength shift. Squares represent experimental data and the solid line is theoretical expectation.

\[
\delta \lambda = - \frac{2k(\Delta \lambda)^2}{\lambda_0} \text{Im} A_w = - \frac{2k(\Delta \lambda)^2 \gamma \sin \varphi}{\lambda_0(\gamma^2 + 1 - 2\gamma \cos \varphi)}.
\]

To realize the principle of weak measurement in this scheme, we acquired the phase response curve of the central wavelength shift by adjusting the optical phase between \( H \) and \( V \) polarization continuously with the SBC. The result was shown in figure 2.

Shown in the inset of figure 1(a), the initial spectrum had a Gaussian shape, while the output spectra were reshaped because of the central wavelength shift, which was induced by the phase difference between the two polarizations propagating in reverse paths. Also, this phase difference was brought in by the SBC and the total internal reflection in the prisms. In this section, to demonstrate the feasibility of weak measurement in this system, the phase difference was only induced by the SBS. Figure 2 displayed the result of the central wavelength shift by adjusting the SBC for an increasing phase from 0.5 to 5 rad, while the phase of 0.5 rad was the initial phase difference of the system. As shown in figure 2, the experimental data agreed well with the theoretical expectation with equation (3). The error bar was obtained by repeating the measurements four times. Obviously, the value of the central wavelength shift enhanced then saturated with respect to the phase change. The phase response rate, which corresponds to the slope of the phase response curve, progressively grew smaller with the increasing phase. As shown in figure 2, the phase range from 0.56 to 1.1 rad was the linear interval, which was also the dynamic range for our measurement. Hence, the internal with a high slope from 0.56 to 1.1 rad was chosen as the working points for the detection in this work.

In equation (3), the phase \( \varphi = \varphi_1 - \varphi_2 \) contains the phase difference introduced by the refractive index difference of the measured media in the two channels. Depending on Fresnel's equation, there is a quantitative relationship between the phase difference and the refractive index, given as below.
In equation (4), $\phi'$ is the phase difference between $H$ and $V$ polarization reflecting on the interface of the prism, which contacts with the material to be examined. $i_1$ is the incidence angle, and $n$ is the refractive index of the material. In equation (3), $\phi_1$ is the phase difference induced by CH1, while $\phi_2$ is brought in by CH2. That is, the phase difference between the two polarization components revealed in equation (3) actually refers to the difference of the phase induced by the sample flowing in the two channels, resulting in a differential measurement. Hence, the refractive index of the material passing through the two channels can be detected. Usually, the refractive index is relative to the concentration of the sample, which can also be determined. As for glucose solution, the relationship between the refractive index and concentration can be expressed as $\phi_1 = \cos i_1 \sqrt{\sin^2 i_1 - n^2}$. Thus, the LOD could be calculated to be $0.03 \text{ g l}^{-1}$, corresponding to a LOD of $4.545 \times 10^{-6}$ RIU for refractive index.

This differential measurement provides a self-referential condition, which is absolutely vital to applications in real time monitoring of the molecule separation and depuration; for instance, the technology of dialysis. As far as we know, a non-marking real time monitor for the evaluation of dialysis efficiency and sufficiency is scarce and expectant. Existing molecular real time monitoring technology, such as ion mobility spectrometry (IMS) and cavity ring-down spectroscopy (CRDS), needed a marker [22], or the accuracy of the technologies via monitoring the Kt/V was limited due to various interferences [23]. In this work, a simple dialysis application, which aimed to separate the micromolecule from the mixture with macromolecule, was investigated with our proposed differential weak measurement system with the function of self-reference.

The mixture solution containing 100 g l$^{-1}$ of glucose and 50 g l$^{-1}$ of albumin Bovine V (BSA, purchased from Scientan) was prepared before the experiment. A dialysis tube (bought from shuyuan, SP131336-1m) with a molecular weight cut-off (MWC) of 20 000 was utilized for molecule separation. As shown in figure 4(a), the mixture firstly flowed through CH2, entered the dialysis tube to a separate glucose molecule, and then passed through CH1. To achieve an adequate dialysis, a peristaltic pump, which was not displayed here, was used to provide a repeated cyclic sample flow through the dialysis tube and CH1. The mixture flowing through CH2 was taken as a calibration, while the concentration of the sample in CH1 changed with the dialysis performed. The dialysis process was monitored via the central wavelength shift of the output signal. Thus, the efficiency of the separation could be monitored in real time, shown as figure 4(b).

With the separation of the glucose molecule, the concentration of the solution would be changed and then the concentration difference of the samples in the two channels was brought in. Since the concentration difference corresponding to the

\[
\tan \frac{\phi'}{2} = \frac{\cos i_1 \sqrt{\sin^2 i_1 - n^2}}{\sin^2 i_1}
\]
phase difference could be determined by the central wavelength shift of output spectra, the real time change of the concentration could be monitored. In this simple dialysis system, a dialysis tube was combined with the two hoses connecting with CH1 and CH2, respectively. Then, the dialysis tube was submerged into a cup of PBS (phosphoric buffer solution), providing the condition for the dialysis. While the mixture of BSA and glucose flowed into the tube from CH2, the glucose molecule passed through the tube to the PBS. Hence, the concentration of glucose in the mixture decreased, which led to the concentration difference corresponding to the phase difference, induced by the sample in CH1 and CH2. On the basis of the principle of weak measurement as described above, the increasing phase difference could induce an increasing central wavelength shift as figure 2. For a sufficient dialysis, the mixture out of CH1 was imported into the tube cyclically. As the dialysis went on, the concentration difference between CH1 and CH2 increased, and the growth rate diminished with the reduction of dialysis efficiency. The curve of the central wavelength shift corresponding to the glucose concentration change with respect to the time (figure 4(b)) presented an overall trend, which first increased and gradually reached a saturation state. However, since the glucose molecule was dialyzed into PBS from the side of the tube, and the diameter was greater than that of the hoses, the mixture in the tube may be uneven. The concentration of the analytes closed to the side might be bigger than that in the center because the molecular weight of glucose was smaller than that of BSA, and the concentration of the mixture out of the tube to CH1 may be unstable. Thus, some dips and peaks would appear in the curve. The peaks revealed a higher concentration of the mixture in CH1 coming from the side of the tube through a higher efficiency of dialysis, while the dips revealed a lower concentration of the mixture from the center of the tube. With the dialysis process, the glucose molecule went into the PBS solution though the side of dialysis tube, and the BSA molecule went into CH1. With this difference measurement system, the shift of the central wavelength quantitatively corresponded to the concentration difference between the analytes in CH1 and that in CH2. It means that the central wavelength was quantitatively related to the concentration of glucose, which went out of the dialysis tube. Hence, according to the concentration response curve in figure 3(a) for CH1, the glucose concentration corresponding to the central wavelength shift could be calculated, shown in the right vertical scale in figure 4(b). Thus, the application of this differential weak measurement system in the dialysis was accomplished for the real time monitoring of molecule separation for the first time.

Besides the advantage of self-reference, the common path system also has the feature of stability. An experiment of 1 h at the zero point in figure 3 was performed to demonstrate the stability. In this section, the two channels were filled with pure water. Continuously collecting the central wavelength of the output spectra, shown in figure 5, we could discuss the stability by calculating the standard deviation of the data. Qualitatively, the stability of the system can be revealed by the standard deviation of experimental data collected in a period of time. In this case, the standard deviation was calculated to be 0.0178 nm with the data in 1 h in figure 5. Compared to the result of the Mach–Zehnder interferometer based weak measurement system in our previous work [12], the standard deviation in 1 h of this common path design was smaller than that in 20 s in the uncommon system in the same working point, exhibiting a superiority of stability.
4. Conclusion

A self-referencing differential weak measurement system based on a modified Sagnac interferometer with two measuring channels was presented in this work. The design of two-channel measuring system based on a Sagnac interferometer with the join of two HWPs, which were used to switch $H$ and $V$ polarizations to each other, resulted in a differential measurement. The concentration of the sample in the channels could be evaluated by the central wavelength shift of the output spectra. We experimentally demonstrated the feasibility of this differential weak measurement with the concentration detection of glucose solution in each channel. In addition, the study of a dialysis system for molecule separation in real time was performed, exhibiting the application of this system with the function of self-reference. Moreover, compared with previous un-common path system, this common path design had a higher stability. In addition, since the phase difference between the $H$ and $V$ polarization was induced by the analytes that touched the interface of the prism with total internal reflection, the test light did not actually pass through the analytes. Hence, the opacity of liquid could not have any effect on the measurement. It also exhibits a high convenience, as well as a wide range of applications for this weak measurement based biosensor. In conclusion, this differential weak measurement scheme not only enriched the types of optical label-free biosensors, but also met the requirement about self-reference.

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