



Optical biosensor based on weak measurement for ultra-sensitive detection of calreticulin in human serum

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Abstract: A novel real-time optical phase sensing method based on the Mach-Zehnder interference principle has been proposed for the detection of calreticulin (CRT) levels in human serum samples. In this approach, anti-CRT antibodies are utilized to capture CRT molecules in serum, leading to a phase shift in both the measuring and reference arms of the system. By employing the concept of weak amplification within the framework of weak measurements, it becomes feasible to continuously monitor the response of CRT in real-time, allowing for the precise determination of serum CRT content at the picomolar level. Our achievement may pave the way in establishing CRT as a diagnostic biomarker for a wide range of medical applications, including rheumatoid arthritis.

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1. Introduction

Calreticulin (CRT) is one of the main calcium-binding proteins in the endoplasmic reticulum and sarcoplasmic reticulum, present in all cells of higher organisms except for red blood cells, with a relative molecular weight of approximately 48.7 kDa [1]. It can be found in the cytoplasm of cells or expressed on the cell surface, serum, and extracellular matrix. The gene composition and amino acid sequence of CRT display a high degree of conservation and play a role in regulating various physiological functions of cells [2]. According to the site of action of CRT, its main functions can be broadly categorized into major domains: intracellular and extracellular. Within the intracellular realm, CRT fulfills critical roles as a molecular chaperone, ensuring proper protein folding, maintaining cellular Ca^{2+} homeostasis, and the regulation of cell apoptosis. While in the extracellular domain, CRT participates in cell adhesion processes, contributes to immune system regulation, and is implicated in the pathogenesis of autoimmune diseases. Furthermore, it also plays an important role in promoting angiogenesis and facilitating tissue damage repair. The multifaceted nature of CRT's functions underscores its importance as a central player in cellular physiology and pathology [3]. It has revealed that calreticulin regulates the protein expression in heart development [4–7]. Furthermore, calreticulin is associated with a range of medical conditions, including neurodegenerative diseases [8,9], cancer [10–15], autoimmune diseases [16–19], and wound healing [20–22]. Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial tissue proliferation, neovascularization, and infiltration of various cells and cytokines [18]. In recent years, multiple studies have found the presence of anti-CRT antibodies in the serum of rheumatoid arthritis patients [19]. CRT may be involved in the

pathological mechanism of RA [22,23], and the level of CRT in the serum of patients with RA is significantly increased [24]. It was speculated that CRT is associated with synovial inflammatory response and pannus formation in RA [25]. Therefore, the examination of CRT expression in the serum, synovial fluid, and synovial tissue of individuals afflicted with rheumatoid arthritis has great significance in the pursuit of elucidating the potential of CRT as a diagnostic tool for RA.

Immunological methods include enzyme-linked immunosorbent assay (ELISA) [24,26], Western blot [27], immunohistochemistry [27], etc. Technique utilizes antibodies against calreticulin and is suitable for detecting the presence of calreticulin, as well as quantitatively analyze the total amount and distribution of calreticulin. However, there are several limitations, such as low detection accuracy with the results being significantly impacted by various factors, the need for labeling, and the operational complexity over the entire process. Biochemical methods include chromatographic techniques (e.g. high-performance liquid chromatography, gel electrophoresis) [28], spectral techniques (e.g. ultraviolet visible spectrophotometry, fluorescence spectrophotometry) [29], etc. These methods extract proteins from cells, separating and purifying calreticulin using chromatographic techniques, and finally measuring them through biochemical means, are suitable for separating, purifying, and identifying calreticulin, as well as determining their molecular weight and amino acid sequence. However, they need the utilization of costly equipment and laborious experimental procedures. Furthermore, its applications are limited to the characterization of proteins. Cell biology methods include immunofluorescence labeling technology [30], green fluorescent protein (GFP) labeling technology [31], fluorescence resonance energy transfer (FRET) technology [29,32], utilizes the localization and distribution of CRT within cells, which can be measured by observing cell morphology and immunofluorescence labeling. However, they are mainly used in protein localization for high resolution imaging.

Traditional interferometric optical systems can meet the needs of measuring specific proteins, for example, Ng et al [33]. used a spectral phase interferometer based on surface plasmon resonance (SPR) to detect aBSA with a limit of detection (LOD) of 0.5 ng/ml (3.3 pM). Lu et al [34]. used optical microfiber interferometric biosensor to detect a LOD of 1.32 fM for DNA-t. However, these sensors usually demand either a relatively complex optical system or involve necessary procedures for labeling and coupling. Here, we use a structurally simple weak measurement method for protein detection, and it can be easily integrated into other systems [35]. In our weak measurements, the protein concentrations changes can cause disturbances to the system, resulting in a slight shift between two eigenstates, which are represented by two orthogonal polarization states in the optical system. By appropriate pre selection and post selection, this small longitudinal phase shift can be amplified and ultimately read out in the pointer received by the detector [36]. Moreover, frequency domain weak measurement is achieved using Gaussian spectrum, which theoretically has higher accuracy than time-domain weak measurement and interferometric measurement [36]. Compared with traditional interferometric methods, our weak measurement systems have advantages such as high sensitivity, no need for labeling, simple operation, simple system structure, low cost and real-time monitoring [37,38].

In our study, we applied a novel weak measurement system utilizing a Mach-Zehnder interferometer for real-time monitoring and quantification of serum calreticulin without labeling. By introducing an optical phase differential element into the system, we can obtain the concentration of CRT in the serum of patients with rheumatoid arthritis by analyzing weak measurement signals. This innovative approach enables the precise quantification of serum CRT concentrations at the pico-molar level, and thereby advancing the field of concentration analysis in RA. Inspired by current fiber optic sensors characterized by a compact structure, a straightforward manufacturing process, and cost-effectiveness [39–41], as well as other biosensors featuring miniaturization, stretch ability, and portability for wearable applications on the human body [42–45], we will further optimize our device to make it more lightweight and easier to operate, highly integrated into various detection systems, to promote research in biomedical molecular detection.

2. Methods and materials

2.1. Weak measurement system based on Mach-Zehnder interferometer

A weak measurement system utilizing the Mach-Zehnder interferometer configuration is illustrated in Fig. 1.

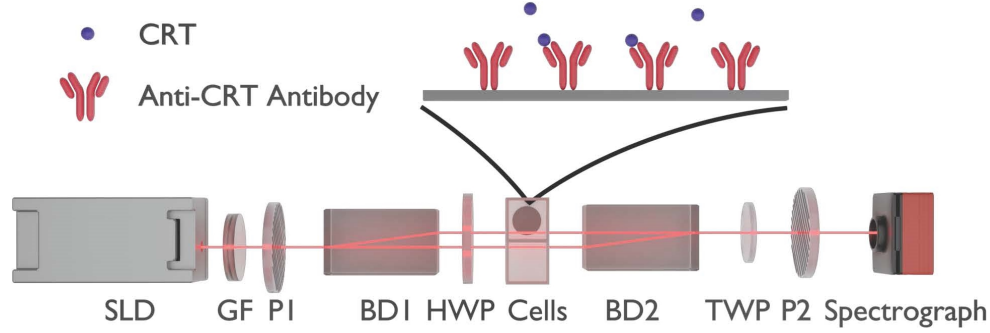


Fig. 1. Weak measurement system with Mach-Zehnder interferometer structure. SLD, super luminescent diode. GF, Gaussian filter. P1 and P2, polarimeters. BD1 and BD2, birefringent crystal beam splitters. HWP, half wave plate. TWP, tunable wave plate. The black lines on P1 and P2 represent the transmission axis of the polarizer.

In this system, the light source is a super luminescent diode (SLD, 15 mW), with a central wavelength of 830 nm and a spectral bandwidth of 20 nm. The light emitted by the light source passes through a Gaussian filter (GF) with a bandwidth of 12 nm. The Gaussian filter is used to correct the Gaussian peak of the spectral profile, which is necessary for weak measurement in the frequency domain. After the beam passes through the polarizer P1 (MFOPT Technology Co., Ltd, MFP10-800/1150, extinction ratio of 10000:1), it is prepared as a pre-selected state, which can be expressed in the form of $|\psi_i\rangle = \frac{\sqrt{2}}{2}|H\rangle - \frac{\sqrt{2}}{2}|V\rangle$. Followed is a birefringent crystal beam splitter (BD1, Thorlabs Inc., 4.0 mm Beam Separation), in where the polarized light is then divided into two beams with polarization directions perpendicular to each other and travelling in the same direction, namely horizontally polarized light $|H\rangle$ and vertically polarized light $|V\rangle$. Afterwards, the polarization direction of the light is adjusted through a half wave plate (HWP, WPH05M-830). Upon exiting the half wave plate, a cuvette with a central divider is introduced, enabling one side of the cuvette to transmit horizontally polarized light while the other side transmits vertically polarized light. We choose one of these two paths as measuring arm and the other as reference arm. The light from both arms is then coupled through a second inverted birefringent crystal beam splitter (BD2). A tunable wave plate (TWP, ALPHALAS GmbH, PO-TWP-MP-25-UV, retardation adjustable from 0 to λ) is then used to adjust the phase difference between the two optical paths to ensure that they are within the measurement range. Subsequently, polarizer P2 is engaged to post select a state. The post selected state could be expressed as $|\psi_f\rangle = -\cos(\alpha + \beta)|H\rangle + \sin(\alpha + \beta)\exp[i(\varphi + \pi/2 + x)]|V\rangle$, where x was the initial phase difference, and φ was the added phase difference between the two paths. Finally, the output light is directed toward the spectrometer for spectral analysis, facilitated by the LabVIEW program.

Both polarizers, P1 and P2, have their transmission axes positioned at angles of $\pi/4$ and $-\pi/4$, respectively, relative to the vertical direction. The weak value of A could be expressed as,

$$A_w = \frac{\langle\phi|A|\psi\rangle}{\langle\phi|\psi\rangle} = \frac{\cos\alpha\sin(\alpha+\beta)e^{-i(\varphi+\frac{\pi}{2}+x)}}{-\sin\alpha\cos(\alpha+\beta)+\cos\alpha\sin(\alpha+\beta)e^{-i(\varphi+\frac{\pi}{2}+x)}} \quad (1)$$

We defined $\gamma = \cos \alpha \sin(\alpha + \beta) / \sin \alpha \cos(\alpha + \beta)$. So, we can find that the imaginary part of the weak value was

$$\text{Im}A_w = \frac{\gamma e^{-i(\varphi + \frac{\pi}{2} + x)}}{-1 + \gamma e^{-i(\varphi + \frac{\pi}{2} + x)}} \approx i \frac{\gamma \sin(\varphi + \frac{\pi}{2} + x)}{1 + \gamma^2 - 2\gamma \cos(\varphi + \frac{\pi}{2} + x)} \quad (2)$$

So when we analyze the momentum formula $\delta P = 2k(\Delta P)^2 \text{Im}A_w$, where $k = 2\pi/P_0$, we can get the shift of wavelength as follows:[46]:

$$\delta\lambda = -\frac{4\pi(\Delta\lambda)^2}{\lambda_0} \text{Im}A_w = -\frac{4\pi(\Delta\lambda)^2 \gamma \sin(\varphi + \frac{\pi}{2} + x)}{\lambda_0(1 + \gamma^2 - 2\gamma \cos(\varphi + \frac{\pi}{2} + x))} \quad (3)$$

Where A_w is a weak value related to the pre and post selection states, α is the azimuth of pre-selected polarization, while β is the angle from post-selected polarimeter to the orientation perpendicular to the pre-selected polarimeter, λ_0 and $\Delta\lambda$ are the wavelength and bandwidth of the light source, and x is the initial phase difference. This equation enables the determination of optical phase through spectral analysis, with optical phase being linked to parameters such as transmission length and refractive index.

A solid-phase carrier coated with anti CRT antibodies can adsorb CRT present in human serum. It is in the shape of a microtiter plate, made of polystyrene, and the protein is encapsulated with the plate (i.e., the bottom of the microtiter plate) by adsorption through hydrophobic bonding. After the serum injections into the sample cell, which was previously placed in the micropore, the anti-CRT antibodies immobilized at the bottom of the micropore bind to the CRT molecules present in the serum. As a result, the concentration of CRT on the measuring arm decreases continuously until all CRT molecules in the serum are captured. The effective refractive index of a solution is determined by the concentration of its constituent molecules. Therefore, the refractive index of the sample changes, causing an optical path difference between the two arms, resulting in a phase difference. We fit the center wavelength shift to the phase difference between two arms, observing the center wavelength of the output spectrum periodically changes with different sensitivities as the phase difference increases. The displacement of the center wavelength is recorded in LabView software, corresponding to specific phase changes between the two arms, effectively measuring changes in calcium reticulin levels within the sample. Consequently, we can deduce the concentration of the tested solution through spectral analysis, with the aid of the amplified weak value (A_w) enhancing measurement accuracy.

2.2. Materials

In our experiments, phosphate buffer solution (PBS) was purchased from Hangzhou Haotian Biotechnology Co., Ltd., and RA patient serum was provided by Shaoxing Second Hospital. The human calreticulin (CRT) enzyme-linked immunosorbent assay kit was purchased from Hangzhou Sodium Magnesium Technology Co., Ltd.

3. Experiment and results

3.1. Detection sensitivity, resolution, and detection range of the system

In order to explore the range of CRT detection within the system, we meticulously configure the system to operate within specified parameters. Tunable paddles are employed to finely adjust the phase difference between the two optical paths. As the phase difference increases, the central wavelength of the output spectrum periodically shifts with different sensitivities, which can be represented by the slope of the curve. As shown in Fig. 2, when the phase difference spans from 2.0 to 2.4 rad, the central wavelength rapidly decreases from the highest point in a linear relationship. The region between the two peaks, where the central wavelength exhibited rapid

fluctuations in response to phase variation is the bimodal area for weak measurements. By linearly fitting this region (highlighted in red within the figure), it was found that $R^2 > 0.999$ (central wavelength range: 830.9394–836.0130 nm). Therefore, this region can be considered as the working range of a weak measurement system.

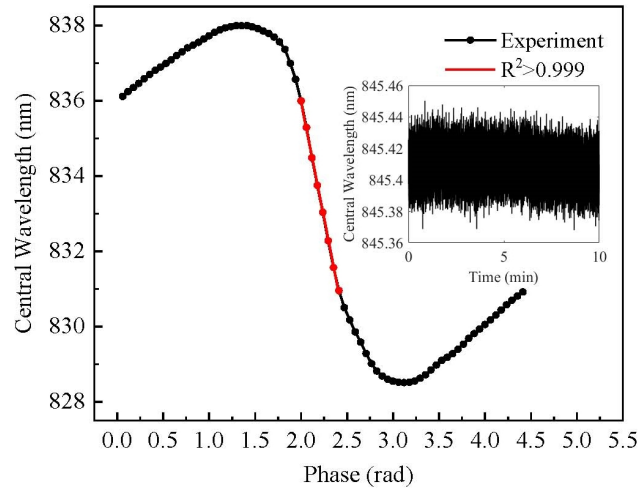


Fig. 2. The relationship between central wavelength and phase difference. The points in the figure represent the spectral center wavelengths corresponding to different phases obtained by adjusting the phase difference through the tunable waveplates in the sensor, and the red line represents the fitting curve. The illustration shows the fluctuation of the central wavelength within 10 minutes without any operation on the system.

The weak measurement system exhibits the same sensitivity in the same linear range. Consequently, fluctuations at any point in the central wavelength range of 830.9394 nm to 836.0130 nm are used to characterize the stability of the system. The illustration in Fig. 2 shows the fluctuation of the central wavelength in the blank experimental system, with a standard deviation of $\sigma_s = 9.7 \times 10^{-3}$ nm. According to the formula $\sigma = 3\sigma_s/(\delta\lambda/\delta n)$ [47], the system detects CRT with a resolution of 1.76×10^{-3} ng/ml (3.6×10^{-2} pM), which was about 2 orders of magnitude higher than surface plasmon resonance (SPR) sensor which is among the best reported in literature [33].

3.2. CRT calibration curve

A cuvette with a size of 12.5×22.5×45 mm separated by glass in the middle to form two identical and connected sample cells was used, each with a size of 10×10×40 mm, which can reduce environmental disturbances compared to using two separate cuvettes. Each of these sample cells received a precise addition of 2 mL of PBS solution as a solvent, and the liquid level is controlled to ensure that light can pass through the solution. After the system has stabilized, we dropped 20 μ L of CRT standard solution diluted with PBS to a concentration of 5 ng/mL into the sample cell of measuring arm. As graphically depicted in the inset of Fig. 3, the addition of CRT to the measuring sample cell increased the refractive index of the solution, also increased the phase difference between the two sample cells, resulting in a sudden positive shift in the central wavelength of the output spectrum. Depending on Eq. (1), the central wavelength of the light shifts along with the change in concentration. Once the solution was thoroughly homogenized, the central wavelength of the system gradually converged to a stabilized state. By repeating the above steps, a gradient curve could be obtained which represented the response of the system to different concentrations of CRT. After completing the above steps, we rinsed the sample cells

with deionized water, and repeated the above experiment for 5 times. We plotted a function of the center wavelength shift and CRT standard concentration, calculated the error bar of the center wavelength shift, as shown in Fig. 3.

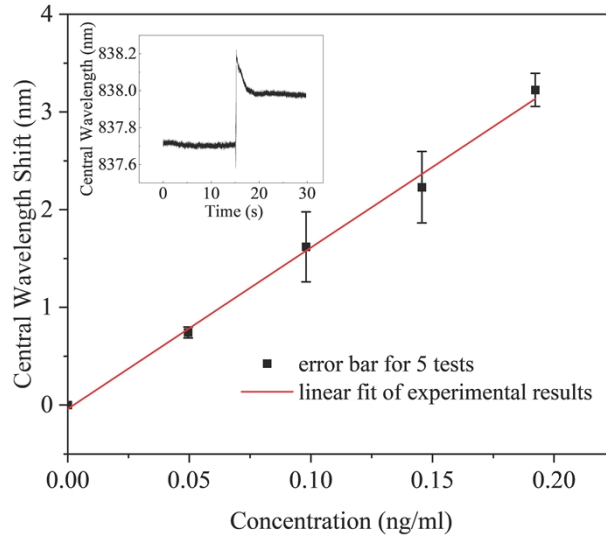


Fig. 3. CRT standard calibration curve. The illustration shows the deviation of the center wavelength before and after dropping a CRT standard.

The sensitivity of this system in CRT detection is quantified as $\delta\lambda/\delta n = 16.5067 \text{ nm}/(\text{ng/ml})$, and detection range from 0 to 0.3 ng/ml. From the amassed data, we derived the calibration curve equation for CRT, which assumes the form of $\Delta\lambda = 16.50672C - 0.03897$. Here, the unit of $\Delta\lambda$ and C was nm and ng/ml. This calibration curve stands as a foundational tool for the precise measurement of CRT concentration in our subsequent experiments.

3.3. Calcium reticulum protein concentration detection

2 mL of PBS solution was added to each of the two sample cells. A micropore coated with anti-CRT antibodies had been pre-added to the measuring sample cell to capture CRT. After the system was adjusted to the working range and the system had been stabilized, 50 μL of patient serum diluted 100-fold in PBS was added to the measuring arm. Within a short period of time, the central wavelength fluctuated violently due to the uneven local refractive index of the solution. Additionally, due to the increase in the overall refractive index, the central wavelength increased compared to the initial value, after the homogeneous diffusion of the serum. At the same time, due to the binding of CRT in the solution with anti-CRT antibodies on the micropore, the concentration of CRT continued to decrease until it was completely captured, and the central wavelength was stabilized. This binding reaction took 1-2 hours. By replacing the patient serum and repeating the above experiment, the central wavelength shift $\delta\lambda_1$ from before serum addition to the end of CRT response of different patient serum samples can be obtained. Figure 4 shows real-time monitoring images of serum CRT capture from 8 patients.

It can be seen from the Fig. 4, there was a sharp rise in the central wavelength shift due to the perturbation caused by the addition of serum, followed by a decrease in the central wavelength shift due to the decrease of CRT in the solution. The center wavelength shift ($\delta\lambda$) after serum addition (i.e. the difference in central wavelength between the highest concentration of CRT in the solution at the beginning of serum addition and the end of CRT response) was positively correlated with the total content of CRT in solution. However, while the serum has not yet spread

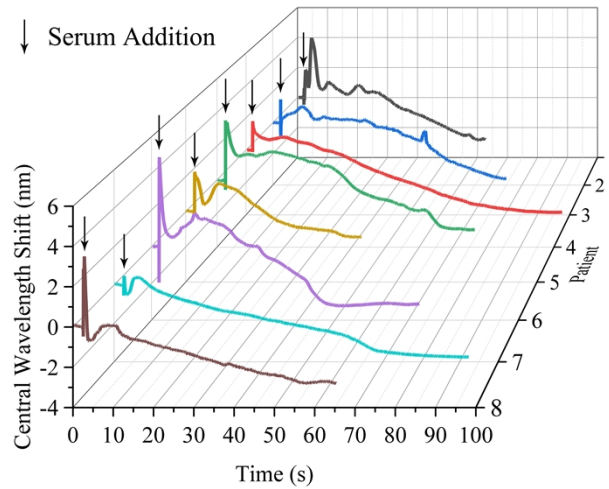


Fig. 4. Real time monitoring of serum CRT capture.

evenly, CRT is adsorbed by anti CRT antibodies on the micropore, resulting in a continuous decrease in CRT concentration and the inability to obtain the center wavelength at the highest CRT concentration. Therefore, a reference experiment was introduced as follows.

2 mL of PBS solution was added to two sample cells and adjusted the system to a linear range. When the system had been stable, we added 50ul of patient serum diluted 100-fold with PBS to the measuring cell. The difference lies in the fact that reference experiment did not pre-added micropore. The center wavelength tended to be stabilized after the serum spread evenly and the central wavelength shift before and after the addition of serum can be obtained. The sample cell was rinsed with PBS and the experiment was repeated. The average central wavelength shift of multiple experiments was $\delta\lambda_2$. By replacing the patient serum and repeating the above experiment, $\delta\lambda_2$ of different patient serum samples can be obtained.

Therefore, the central wavelength shift caused by CRT concentration reduction is $\delta\lambda$, which satisfies the relation $\delta\lambda = |\delta\lambda_1 - \delta\lambda_2| = |\delta\lambda_1| + |\delta\lambda_2|$ where $\delta\lambda_1$ is positive and $\delta\lambda_2$ is negative due to our system. The histogram of our results is shown in Fig. 5.

The CRT content within the serum samples measured by our weak measurement methods, and the results of ELISA assay on the same samples, are cataloged in Table 1.

Table 1. Comparison of CRT concentration measurement results in patient serum^a

Patient ID	Weak measurement method(ng/ml)	ELISA method (ng/ml)
1	28.681	30.8
2	33.077	33.4
3	32.778	33.3
4	31.015	30.5
5	28.998	27.3
6	25.364	25.1
7	26.239	28.4
8	22.962	22.4

^aNote: The correlation coefficient $r > 0.9$

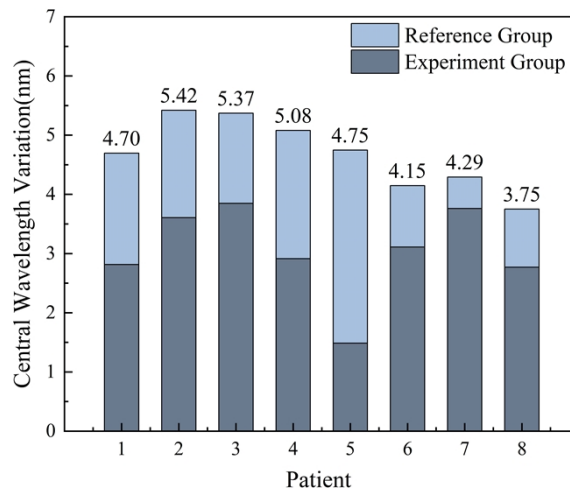


Fig. 5. Center wavelength shift of patient serum diluent.

The outcomes underscore that the measurement of CRT content in serum from RA patients via our weak measurement approach closely parallels the results obtained through the conventional ELISA method. Additionally, there are notable variances in CRT expression levels among different patients.

The sensitivity of the system in this study for the detection of CRT obtained in this experiment is 16.5067 nm/(ng/ml), with a detection range of 0 – 0.3 ng/ml and a resolution of 1.76×10^{-3} ng/ml (3.6×10^{-2} pM). This study lays a robust experimental foundation for the utility of serum CRT content detection in clinical applications, encompassing disease severity assessment, diagnosis, and therapeutic interventions.

4. Discussion

In this study, we have successfully established a weak measurement system employing the Mach-Zehnder interferometer configuration to quantitatively assess the content of CRT in patient serum. By manipulating the phase difference between two orthogonal polarizations, weak value amplification is achieved, thereby achieving an exceptionally high level of precision in the detection of biological sample concentrations. This precision is manifested through the analysis of the central wavelength shift within the spectrum, enabling us to ascertain variations in molecular concentrations within the test solution, all in real-time. This method was employed to calibrate the concentration of the CRT standard, resulting in a sensitivity of 16.5067 nm/(ng/ml) for detecting CRT. It demonstrates the precise advantage of weak measurements in biomedical molecular detection. Our weak measurement method provides a new tool for real-time monitoring or precise detection of CRT levels in serum, which may promote the study of CRT as a diagnostic marker for diseases such as rheumatoid arthritis.

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Data availability. Data underlying the results presented in this paper are not publicly available at this time but maybe obtained from the authors upon reasonable request.

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