A Double-Taper Optical Fiber-Based Radiation Wave Other than Evanescent Wave in All-Fiber Immunofluorescence Biosensor for Quantitative Detection of *Escherichia coli* O157:H7

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**Abstract**

Cylindrical or taper-and-cylinder combination optical fiber probe based on evanescent wave has been widely used for immunofluorescence biosensor to detect various analytes. In this study, in contrast to the contradiction between penetration depth and analyte diameter of optical fiber probe-based evanescent wave, we demonstrate that double-taper optical fiber used in a radiation wave-based all-fiber immunofluorescence biosensor (RWAIB) can detect micron-scale analytes using *Escherichia coli* O157:H7 as representative target. Finite-difference time-domain method was used to compare the properties of evanescent wave and radiation wave (RW). Ray-tracing model was formulated to optimize the taper geometry of the probe. Based on a commercial multi-mode fiber, a double-taper probe was fabricated and connected with biosensor through a “ferrule connector” optical fiber connector. The RWAIB configuration was accomplished using commercial multi-mode fibers and fiber-based devices according to the “all-fiber” method. The standard sample tests revealed that the sensitivity of the proposed technique for *E. coli* O157:H7 detection was 10^5 cfu·mL^{-1}. Quantitation could be achieved within the concentration range of 10^3 cfu·mL^{-1} to 10^7 cfu·mL^{-1}. No non-specific recognition to ten kinds of food-borne pathogens was observed. The results demonstrated that based on the double-taper optical fiber RWAIB can be used for the quantitative detection of micron-scale targets, and RW sensing is an alternative for traditional evanescent wave sensing during the fabrication of fiber-optic biosensors.

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**Introduction**

Since the application of fiber optics in sensing technology in the late 1970s [1–2], optical fiber has been established as an ideal substrate for immunofluorescence sensing because of their reliability, small size, and low cost [3]. Immunofluorescence sensing has great potential for rapid and sensitive analysis of various analytes, ranging from molecules to intact cells, and as an effective technique for biodefense, environmental monitoring, food-security control, etc. [4–5]. Most fiber optic biosensors utilize the evanescent wave (EW) field generated by the total internal reflection (TIR) of light restrained within an optical fiber as sensing region. In this sensing region, specifically bound fluorescence-labeled antibodies can be excited to emit light collected as specific signal, whereas the unbound ones outside the sensing region cannot be excited, thereby adding nothing to the noise. Given this natural separation, fiber-optic biosensors have high signal-to-noise ratio [6], and they are used for the detection of various small analytes [7] and microorganisms [8–9].

The development of fiber-optic biosensors has recently received much attention. In hardware design, bulk optical components [10–11], such as biconvex lens and dichroic mirrors are common bases in implementing this type of biosensors. Analyte 2000 [8,12] and RAPTOR [13], two commercial instruments developed using miniaturized and integrated bulk optical components, showed great potential in immunofluorescence sensing, but their optical alignment and precise processing technology remain challenging. Given the rapid development of highly integrated optical components, an “all-fiber” method is used to fabricate more compact fiber-optic biosensors [7] and enables crucial optical alignment no longer necessary. In terms of mechanism of fluorescence sensing, most fiber-optic biosensors utilize EW to generate the excitation field regardless of the continuous development of hardware components. Taper-and-cylinder com-
Combination tapered probes are usually used to generate EW field [7,13] and prepared using a tube-etching technique [14]. To enhance the sensitivity of EW excitation, U-bent optical fiber probes were used [15–16]. However, the fiber probe with definite structure has fixed incident ray angle to stimulate EW and refractive indices of core and cladding and then the characteristics of generated EW cannot be tuned as that of waveguide-based EW [17–20], especially penetration depth (PD). PD provides the inherent advantage of natural separation to EW for fluorescence sensing with high signal-to-noise ratio, but limits its superior when the diameter of the detected target is larger than the PD [6].

Based on the numerical aperture (NA) of fibers, PD of all-fiber biosensors is usually several hundreds of nanometers [21], which hardly exceeds the size of bacteria (1 μm to 3 μm diameter, or larger). Therefore, fluorescein-labeled antibodies bound on bacteria surface but beyond the PD of EW field cannot be detected, resulting in an inevitable loss of sensitivity. Although several simulations have demonstrated that the PD value could be several micrometers in a specially designed fiber probe, a large PD value only exists within ≤5% of the entire probe length, leaving a major portion invalid [22]. This condition might result in poor consistency of quantitation at low concentrations of the detected target. Additionally, EW that penetrates from the probes only accounts for a small part of the entire excitation light power, which leads to a low percentage of utilization of the excitation light [23].

In the present study, finite-difference time-domain (FDTD) method was used to compare the properties of EW and radiation wave (RW). A ray-tracing model was formulated to optimize the taper geometry of the optical fiber probe. Based on a commercial multi-mode fiber, a double-taper optical fiber probe was proposed and fabricated as a low-cost, disposable sensing unit for RW sensing. The sensing unit was connected to the biosensor through a “ferrule connector (FC)” optical fiber connector. Therefore, the consistency and stability of these sensing units for practical tests could be guaranteed by the reliable telecommunication fiber connection technology. Subsequently, a novel RW-based all-fiber immunofluorescence biosensor (RWAIB) was developed to analyze simultaneously the specific signals within and beyond the reach of EW. The configuration of the RWAIB was developed using commercial multi-mode fibers and fiber-based devices according to the “all-fiber” method. The comprehensive performance including quantitation ability, sensitivity, and specificity of RWAIB was estimated using Escherichia coli O157:H7 as the representative micron-scale target/analyte.

Materials and Methods

Reagents

3-Aminopropyl-triethoxysilane (APTES), glutaraldehyde, and bovine serum albumin (BSA) were purchased from Sigma-Aldrich (Gillingham, Dorset, UK). Cyanine 5 (Cy5) and HiTrap Desalting prepacked column were obtained from GE Healthcare (Uppsala, Sweden). Unless otherwise specified, all reagents, which were provided by Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China), were of analytical grade and used without further purification. Deionized water was used throughout the experiment.

Bacterial Culture and Antibody Preparation

E. coli O157:H7, Salmonella cholerasuis, Salmonella enteridis, Salmonella paratyphi A, S. paratyphi B, S. paratyphi C, Salmonella typhi, Salmonella typhimurium, Vibrio parahaemolyticus, Vibrio cholerae O1, and V. cholerae O139 were previously preserved in our laboratory and identified using 16S rRNA sequencing. The bacteria were grown until they reached the exponential phase in Luria-Bertani (LB) media at 37°C. The bacteria were harvested by centrifugation at 6000 rpm (Allegra X-22R, Beckman, Germany) for 10 min at 4°C. The bacterial pellets were washed twice and resuspended with sterile normal saline (0.85% salt solution). Bacterial concentration was determined using plate count and demonstrated as colony forming units (cfu) per milliliter.

A monoclonal antibody (MAb) specific for E. coli O157:H7 was prepared in our laboratory, and its affinity was determined using E. coli O157:H7-coated ELISA. MAb was labeled with Cy5 and

Figure 1. Schematic diagram (A) and prototype (B) of all-fiber biosensor. (A) Twenty percent of the 643 nm excitation light was conducted from the semiconductor laser to the fiber probe through a fiber coupler with FC connectors as the link. Eighty percent of 668 nm fluorescent signal was collected and transmitted back from the fiber probe to the PMT through a fiber coupler, fiber collimator, and high-pass filter. The signal was processed and displayed on the computer screen. (B) The prototype of all-fiber biosensor consisted of an integrated detecting unit and a controlling unit (computer). RW field produced the visible red light around the fiber probe.

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Figure 2. FDTD calculation results of the EW and RW generated by the cylindrical and tapered probes. (A) and (B) are simplified models of the cylindrical and tapered probes; (C), (D), and (E) are the three guided modes of light in the cylindrical probe (A) in increasing order; (F), (H), and (J) are the axial cross-sections (x–z planes) of the cylindrical probe as the light under modes (C), (D), and (E) propagates in the probe separately; (G), (I), (K), and (M) are the axial cross-sections (x–z planes) of the tapered probe as the light under modes (C), (D), and (E) propagates in the probe separately.
and (K) are the axial cross-sections (x–z planes) of the tapered probe as the light under modes (C), (D), and (E) propagates in the probe separately; (L) and (M) are the axial cross-sections (x–z planes) of the cylindrical and tapered probes as the light under all of the modes propagates in the probes simultaneously. Downward arrows (↓) indicate the outlines of the probes.

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purified with HiTrap Desalting prepacked column to separate and clear free Cy5 and antibody molecules, according to the manufacturer’s instruction.

Double-taper Probe Fabrication, Modification and Activation

The double-taper probe designed to generate RW was made from a length of step-index optical fibers (105 μm core/125 μm cladding, Beijing Glass Research Institute, Beijing, China). At the non-sensing end, an FC standard optical fiber connector was fixed to facilitate the alignment of the sensor optical path during the repeated installation-and-uninstallation of the probes. At the sensing end, a double-tapered structure was fabricated using a simple static-and-dynamic etching method with 40% HF as the etchant (experimental details are provided as File S1); this method combined classical static tube etching [24] and dynamic liquid-level-lowering etching [23] and promoted the large-scale preparation of probes with good uniformity. The fabricated double-taper probe was bathed successively in NaOH (1 mol·L\(^{-1}\)) and HCl (1 mol·L\(^{-1}\)) for 10 min, and then dried for future use. The calibrated optical microscopic images show that the diameter of taper 1 of fabricated double-taper probe was etched from 125 μm to ~40 μm within the length of ~270 μm with the F number matching the diameter [21]; the diameter of taper 2 was reduced to 26 μm at distal end within the length of ~2.5 cm.

The double-taper probe was silanized by immersing it in 10% APTES (in isopropyl alcohol) for 2 h. As a result, a monolayer silane film was covalently bonded on the silica surface of the probe with the amino functional groups on top. Subsequently, the silanized probe was functionalized using an amine-reactive homobifunctional cross-linker glutaraldehyde (12.5%, in deionized water) for 2 h. Residual glutaraldehyde was rinsed with phosphate-buffered saline (PBS; 135 mmol·L\(^{-1}\) NaCl, 15 mmol·L\(^{-1}\) sodium phosphate, pH 7.2). The aldehyde group-activated probe was then incubated in MAb solution (0.5 mg·mL\(^{-1}\)) for future use. The fluorescent signal with 668 nm emission wavelength was collected by the fiber probe, and 80% of signal power was sent back to the other input end of the coupler. Fluorescent signal was filtered using a high-pass filter and injected into a photomultiplier tube (PMT-CR131, Beijing Hamamatsu Photon Techniques Inc., Beijing, China) through a fiber collimator. The signal was processed by an electronic system and then displayed on a computer screen. During the entire process of detection, the probe was installed in a 4-mm diameter, 50-mm long poly-propylene sample cell.

Evaluation of RWAIB Performance in Detecting E. coli O157:H7

To determine the sensitivity (detection limit) and quantitation ability of the technique, water samples containing various concentrations (10\(^3\) cfu·mL\(^{-1}\) to 10\(^7\) cfu·mL\(^{-1}\)) of E. coli O157:H7 were used as standard solutions, with each sample detected in triplicate. The samples were separately injected into the sample cell from its inlet and incubated for 10 min at room temperature to achieve the specific capture of bacteria by the antibody-activated probe. After the transfer of the sample from the outlet of the sample cell, the cleaning buffer (0.1% Tween20 in PBS) was injected into the cell, and the nonspecific binding and residual sample in the cell were removed. Subsequently, Cy5-labelled antibodies (25 μg·mL\(^{-1}\)) were injected into the sample cell and incubated for 10 min at room temperature, then transferred out through the tubule. Immediately after another cycle of the cleaning process, the laser was turned on and maintained for 150 s while signal data was monitored, recorded, and displayed. After biosensor analysis, the surface state of probe with adhering bacteria was observed using a scanning electron microscope (S-3400 N, Hitachi, Japan).

Ten kinds of food-borne pathogens, namely, S. enteritidis, S. paratyphi A, S. paratyphi B, S. paratyphi C, S. typhimurium, S. choleraesuis, S. typhi, V. parahaemolyticus, V. cholerae O1, and F. choloreae O139, were tested using the biosensor at 10\(^7\) cfu·mL\(^{-1}\) to estimate the specificity of the technique.

Results and Discussion

EW and RW Sensing Mechanism

Light transmission within optical fiber is based on the principle of TIR. Light beams propagating inside the fiber core with incident angles (\(z\)) greater than the critical incident angle (\(z_c\)) can be guided along the fiber, where \(z_c\) is determined using the refractive indices of the fiber core and cladding \(z_c = sin^{-1}(n_{cl}/n_{co})\).

When TIR occurs, EW exists beyond the reflecting interface, and the electric field intensity of EW decays exponentially with the distance from the interface. The PD of EW generally refers to the distance at which the magnitude of electric field at the surface

Figure 3. Ray tracing model of a tapered probe.
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Table 1. $L_{i}^{a \leq z \leq c}, R_{2i}^{a \leq z \leq a}$ and $L_{i}^{d}$ at different $\beta_{i}$ values.

| $\beta_{i}$ ($^*$) | $L_{i}^{a \leq z \leq c}$ (um) | $R_{2i}^{a \leq z \leq c}$ (um) | $L_{i}^{d}$ (um) |
|-----------------|-----------------|-----------------|---------------|
| 0.05            | 37591           | 19.70           | 60761         |
| 0.1             | 18773           | 19.73           | 30080         |
| 0.5             | 3717            | 20.06           | 6016          |
| 1               | 1834            | 20.49           | 3008          |
| 5               | 318             | 24.68           | 600           |
| 10              | 109             | 33.28           | 298           |

*Half cone angles of taper 1.
**TIR propagating distance alone taper 1 when $z$ is equal to or greater than $z_{c}$.
$\beta$ Complete length of taper 1.

Ray-tracing in the Tapered Probe

The incident angle ($\theta$) is the critical factor that determines the generation of RW of a tapered probe. When $z \leq z_{c}$, the guided wave changes into RW; otherwise, only the EW penetrates outside the probe. To characterize the incident angles $\theta(z)$ in the tapered probe, a ray-tracing model was established (Figure 3).

The core radius of a step index fiber with core and cladding refractive indices of $n_{c}$ and $n_{b}$, respectively, was etched from $R_{1}$ to $R_{2}$ to form taper 1, and then successively etched from $R_{2}$ to $R_{3}$ to form taper 2. The lengths of these two tapers were $L_{1}$ and $L_{2}$ and their half cone angles were $\beta_{1}$ and $\beta_{2}$, respectively. The refractive index of the medium surrounding the tapered probe was $n_{m}$.

For continuous tapered probe (i.e., taper 2 is not considered), a guided ray from clad section at an angle of $\theta_{1}$ with respect to the $z$-axis was launched into taper 1, and reflected at position $z$, where the launch angle is changed into $\theta_{1}(z)$. According to reference [28], $\theta_{1}(z) = \sin^{-1}[R_{1}\sin \theta_{1}/R(z)]$, where $R(z) = R_{1}-z\tan \beta_{1}$. Hence, the incident angle in taper 1, $\theta_{1}(z)$, can be given as.

$$\theta_{1}(z) = 90^\circ - \sin^{-1}\left[\frac{R_{1} \sin \theta_{1}}{R_{1}-z \tan \beta_{1}}\right] - \beta_{1}$$ (1)

As $\theta_{1}(z)$ decreased into less than $\theta_{c}$ after a TIR propagating distance of $L_{i}^{z \leq z_{a}}$, RW started to appear when the core radius was reduced to $R_{2}^{z \leq a}$. Given that $NA = 0.22$, $R_{1} = 52.5\, \mu m$, $n_{c} = 1.456$, $n_{a} = 1.444$, and $n_{m} = 1.333$, the same as the actual parameters used in our sensor, $L_{i}^{z \leq z_{a}}$ for different $\beta_{i}$ values were calculated. Several results are listed in Table 1, in which $L_{i}^{z \leq z_{a}}$ is the complete length of taper 1 at a certain $\beta_{i}$ if taper 2 does not exist.

Table 1 shows that the continuous tapered probe is not suitable for RW sensing because the invalid length $[L_{i}^{z \leq z_{a}}]$ consists of more than 60% of the total length ranging from 3 mm (3008 $\mu$m) to 6 cm (60761 $\mu$m). The taper-and-cylinder combination tapered probe is also unsuitable for RW sensing because $\theta_{1}(z)$ is constant in the cylindrical section, and RW disappears at the start of this
Figure 4. Evaluation of RWAIB for the quantitative detection of E. coli O157:H7. (A) A group of typical signal-time traces at different concentrations of E. coli O157:H7 during a complete test cycle (150 s). (B) Sensitivity for E. coli O157:H7 detection, where $x$ is the concentration of bacteria, and $y$ is the NI. The bar graph revealed a significant difference between positive sample ($10^3$ cfu·mL$^{-1}$ to $10^7$ cfu·mL$^{-1}$) and negative control with the cutoff value determined as mean $+3$ SD of the negative control NIs. The sensitivity was $10^3$ cfu·mL$^{-1}$. (C) Quantitation ability for E. coli O157:H7 detection, where $x$ is the NI, and $y$ is the logarithm of concentration. The correlation and regression analyses revealed an exponent correlation between $x$ and $y$, with $r=0.99$ ($p<0.05$) in the quantitative range of $10^3$ cfu·mL$^{-1}$ to $10^7$ cfu·mL$^{-1}$. (D) The scanning electron microscope images of probes corresponding to negative and positive samples (with concentrations from $10^3$ cfu·mL$^{-1}$ to $10^7$ cfu·mL$^{-1}$) proved the direct proportion between the amount of adhering bacteria and the concentration of sample. (E) Specificity for E. coli O157:H7 detection. A significant difference was observed between the NIs of 10 different kinds of food-borne pathogens at $10^7$ cfu·mL$^{-1}$ (white bars) and the NIs of E. coli O157:H7 samples at $10^3$ and $10^7$ cfu·mL$^{-1}$ (gray bars) with cutoff value as the threshold.

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section after a short-distance propagation. Therefore, double-taper probe is necessary for RW sensing. taper 1 is used to reduce $a_{1}(z)$ that is smaller than $a_{2}$ in a short length to avoid a long invalid length, whereas taper 2 is used to release RW power gradually and continually reduces the $a_{2}(z)$ of the other beams with lower mode order to generate new RW. The double-taper probe used in this paper can generate RW almost from the beginning of taper 2 to the distal end.

Detection Data Analysis
A group of typical signal-time traces at different concentrations of detected target during a complete test cycle (150 s) are shown in Figure 4A. For each trace, signal intensity reached the maximum value immediately after the laser was turned on (0 s), and then gradually decreased back to the baseline because of fluorescence quenching. The integral intensity within the time of a complete test cycle (150 s) was regarded as an effective result for each test. Given that the batch-to-batch variation in the antibody-activated probe production is inevitable, a normalization of intensity was used to obtain comparable results of different tests. The normalized intensity (NI) is expressed as follows:

$$NI_{h} = \frac{I_{h} - I_{blank}}{I_{max} - I_{blank}}$$

where $I_{h}$ is the integral intensity for a certain test, $I_{max}$ is the integral maximum for the concentration of the detected target ($10^{7}$ cfu·mL$^{-1}$ for the detection of E. coli O157:H7), and $I_{blank}$ is the integral intensity for the activated sensing probe in blank solution without any procedure for detection. For a certain batch of activated probe, $I_{max}$ and $I_{blank}$ were definitive.

RWAIB Performance Evaluation for Detection of E. coli O157:H7
E. coli O157:H7 was selected as the representative micron-scale target to evaluate the performance of RWAIB, including the sensitivity (detection limit), quantitation ability (correlation analysis), and specificity of the technique. Water samples with $10^{3}$ to $10^{7}$ cfu·mL$^{-1}$ E. coli O157:H7, as well as a negative control (0 cfu·mL$^{-1}$), were detected using RWAIB. NI against the concentration of the bacterium is shown in Figure 4B, with the integral intensity of $10^{7}$ cfu·mL$^{-1}$ as $I_{max}$. NIs of all positive samples ($10^{3}$ to $10^{7}$ cfu·mL$^{-1}$) were significantly higher than the cutoff threshold (mean±3 SD of NIs corresponding to the negative control), which suggests that the sensitivity of RWAIB is $10^{3}$ cfu·mL$^{-1}$. The regression curve for the quantitative detection of E. coli O157:H7 is shown in Figure 4C. An evident curvilinear correlation (exponent correlation) was found between $y$ (logarithm of concentration) and $x$ (NIs), in which the correlation coefficient ($r$) is equal to 0.99 ($p<0.001$) from $10^{3}$ cfu·mL$^{-1}$ to $10^{7}$ cfu·mL$^{-1}$. Regression analysis can be expressed as follows:

$$y = 6.98 + 2.01 \ln x$$

The scanning electron microscope images of the probes corresponding to negative and positive samples (with concentra-

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