# Ultrahigh-sensitivity label-free single mode-tapered multimode-single mode fiber U-shaped biosensor for Staphylococcus aureus detection

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**Abstract** The rapid detection of Staphylococcus aureus (*S. aureus*), particularly in the case of very low levels of *S. aureus*, is very important in food safety and medical diagnostics. In this paper, a fast (<20 mins), label-free biosensor using a U-shaped single mode- tapered multimode- single mode (STMS) fiber structure is presented. The average wavelength shift of the sensor (modified with the IgG from porcine serum with a concentration 200 μg/mL) is as high as 1.552 nm when it is immersed into an *S. aureus* sample with a concentration of 4 cells/mL. By further diluting the *S. aureus* to 0.4 cells/mL for a sample volume of 1.5 mL, it is found that a dip wavelength shift of 0.348 nm is observed on occasion which confirms that the biosensor can detect a single colony (cell) of *S. aureus*. Results for the detection of *S. aureus* in milk and lettuce samples are also presented and are compared with the wavelength shift results in phosphate buffered saline (PBS), and it is found that the variation in the average wavelength shift is -21% for *S. aureus* concentrations from 4 to $4\times10^3$ cells/mL.

**Keywords:** Staphylococcus aureus (*S. aureus*); Fiber biosensor; Food safety.

# 1. Introduction

*S. aureus* is a common foodborne pathogenic bacterium that is very common in the natural environment. *S. aureus* is a genus of gram-positive cocci, which can cause purulent inflammation, such as pus infections and pericarditis [1,2]. The traditional isolation and identification method involves inoculation into the broth under sterile conditions for pre-enrichment but this usually takes several days, which greatly limits the application of such traditional methods [3]. Therefore, the development of a biosensor with a simple structure, ultra-high sensitivity, and rapid response of *S. aureus* is important as a means to shorten the detection period for food-borne pathogens and thus preventing food poisoning events caused by *S. aureus*.

In recent years, many rapid detection technologies have been developed, such as an enzyme linked immunosorbent assay [4,5], polymerase chain reaction [6,7], lateral flow assay methods [8], solid phase micro-extraction [9], electrochemical methods [10-13], the use of carbon nanotubes and aptamer based potentiometric methods [14]. However, these methods usually have several significant shortcomings, such as relatively poor limit of detection (LoD), high cost and complex structures, and long detection time. Optical biosensors have developed rapidly in recent years due to the simplicity of their structures and their ability to deliver high sensitivity and short response times. Depending on sensing principle employed, there are a range of different types of fiber biosensors, including fiber gratings [15,16], surface enhanced Raman spectroscopy [17], colorimetric sensors [18], fluorescence spectroscopy [19,20], localized surface plasmon resonance (LSPR) sensors [21], tapered optical fibers [22,23], biolayer interferometry technology [24], impedance spectroscopy [25]. Guo *et al* developed a bacteria-imprinted polydimethylsiloxane film based fluorescence sensor to detect *S. aureus* within 135

min, for which a LoD of 11.12 CFU/mL was obtained [26]. Chen *et al* proposed a tapered singlemode-no core-singlemode fiber coupler for *S. aureus* detection, achieving a LoD as low as 3.1 CFU/mL [27].

In this work, a short section of multimode optical fiber is fusion spliced to two single mode fibers to form a well-known single mode-multimode-single mode (SMS) fiber interferometer structure [28]. The established technique of tapering the centre multimode section of the SMS structure to form an STMS structure is used to improve the refractive index (RI) sensitivity, typically by a factor of ten or more [29]. Bending the tapered fiber into a U-shape is also used to further improve the RI sensitivity [22]. In this paper, the fabrication and performance of a U-shaped STMS fiber structure is investigated for use as a biosensor for the detection of *S. aureus* in both phosphate buffered saline (PBS) and food samples. It is demonstrated that the proposed sensor has the advantage of both fast detection (<20 min) and a low LoD (0.4 cells/mL). The sensor has strong potential for use in the field of food safety, where there is an important need to detect low concentrations of foodborne pathogens in food quickly and cheaply.

## 2. STMS sensor structure and experimental setup

Fig. 1 (a) to (d) illustrates the fabrication processes and the experimental setup of the U-shaped STMS fiber structure. (The detailed content can be found in the supporting document 1).

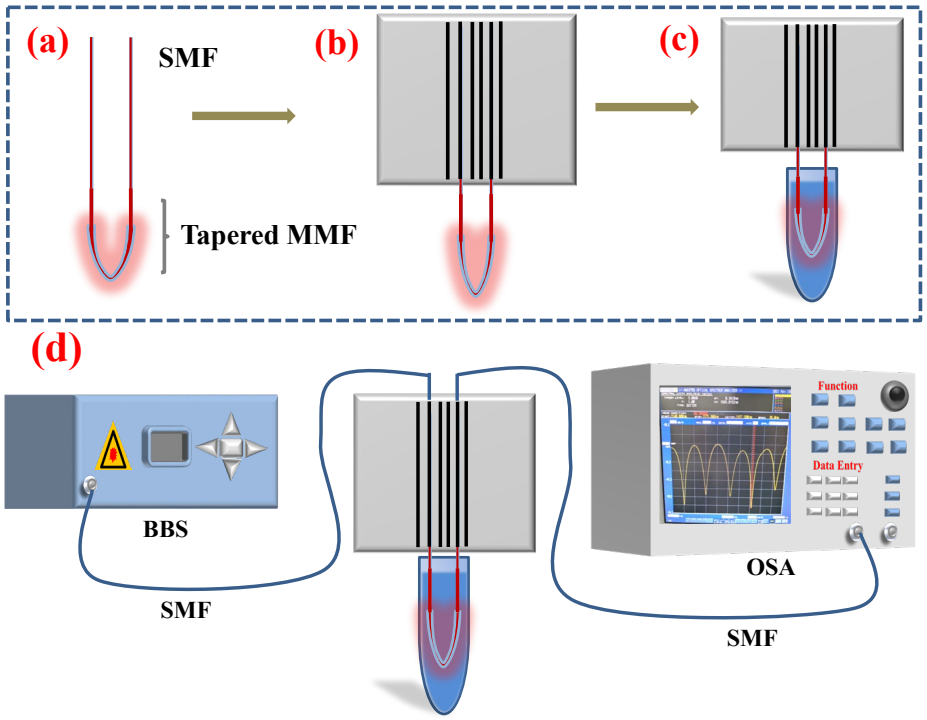


Fig. 1. (a)-(c) The fabrication processes of the U-shaped STMS fiber structure, (d) the experimental setup used for *S. aureus* detection.

# 3. Results and discussion

## 3.1. *U-shaped STMS fiber for RI measurement*

Prior to functionalization, the proposed U-shaped STMS fiber biosensor's RI sensitivity was initially evaluated experimentally over three RI ranges of 1.3333 to 1.3355, 1.351 to 1.3554 and 1.3722 to 1.3772, corresponding to high RI sensitivities of 2110.506 nm/RIU (RI unit), 2823.716 nm/RIU and 4040.368 nm/RIU, respectively. (The detailed content can be found in the supporting document 2.1).

## 3.2. *Functionalization of the U-shaped STMS fiber biosensor*

In order to allow the fabricated U-shaped STMS fiber sensor to specifically detect *S. aureus* [30, 31], the IgG antibodies from porcine serum were immobilized on the fiber surface. (The detailed steps are described in the supporting document 2.2).

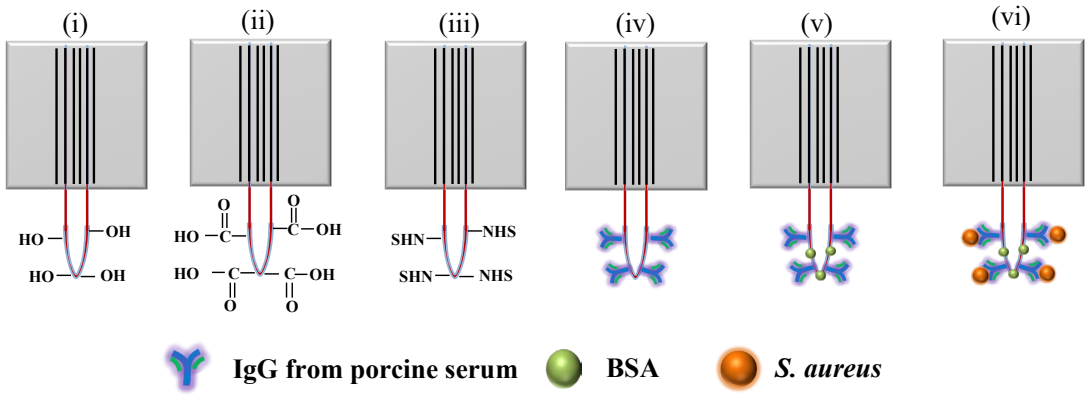


Fig. 2. The schematic diagram of functionalization process: (i) KOH treatment, (ii) silane treatment,(iii) EDC/NHSS treatment, (iv) immobilization of the IgG from porcine serum, (v) BSA to block unbind session, and (vi) specific binding with *S. aureus*.

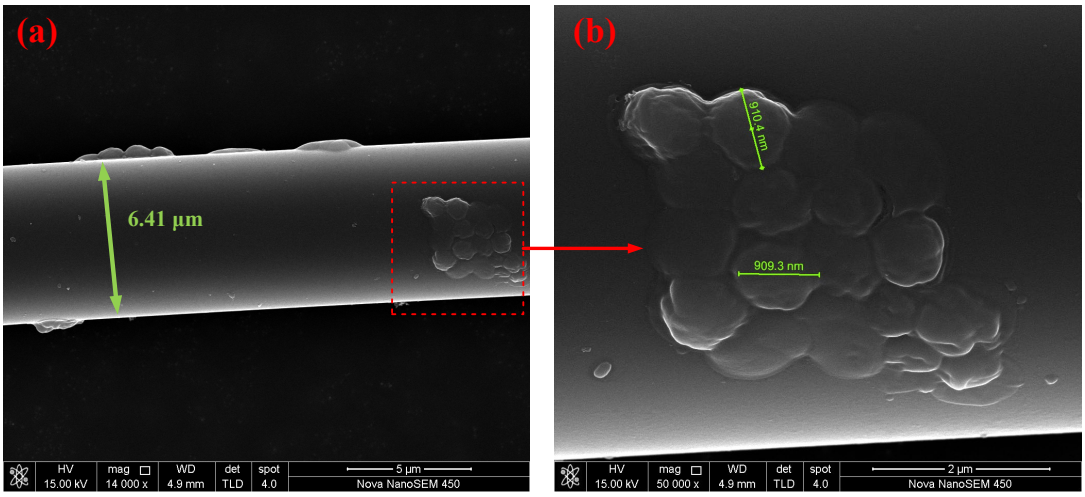


Fig. 3. SEM pictures at (a) the captured *S. aureus* on the surface of the taper waist region, and (b) magnified SEM image of *S. aureus* and the marked size of *S. aureus*.

After the functionalization process is completed, the fiber sensor is ready to specifically capture *S. aureus*. Fig. 3(a) shows the scanning electron microscope (SEM) image of the functionalized taper waist region with a diameter of 6.41 µm. Fig. 3(b) shows the zoom in of *S. aureus* bacteria bound to the fiber biosensor surface. The SEM image shows that functionalized fiber surface can successfully capture *S. aureus*.

3.3. *Detection of S. aureus*

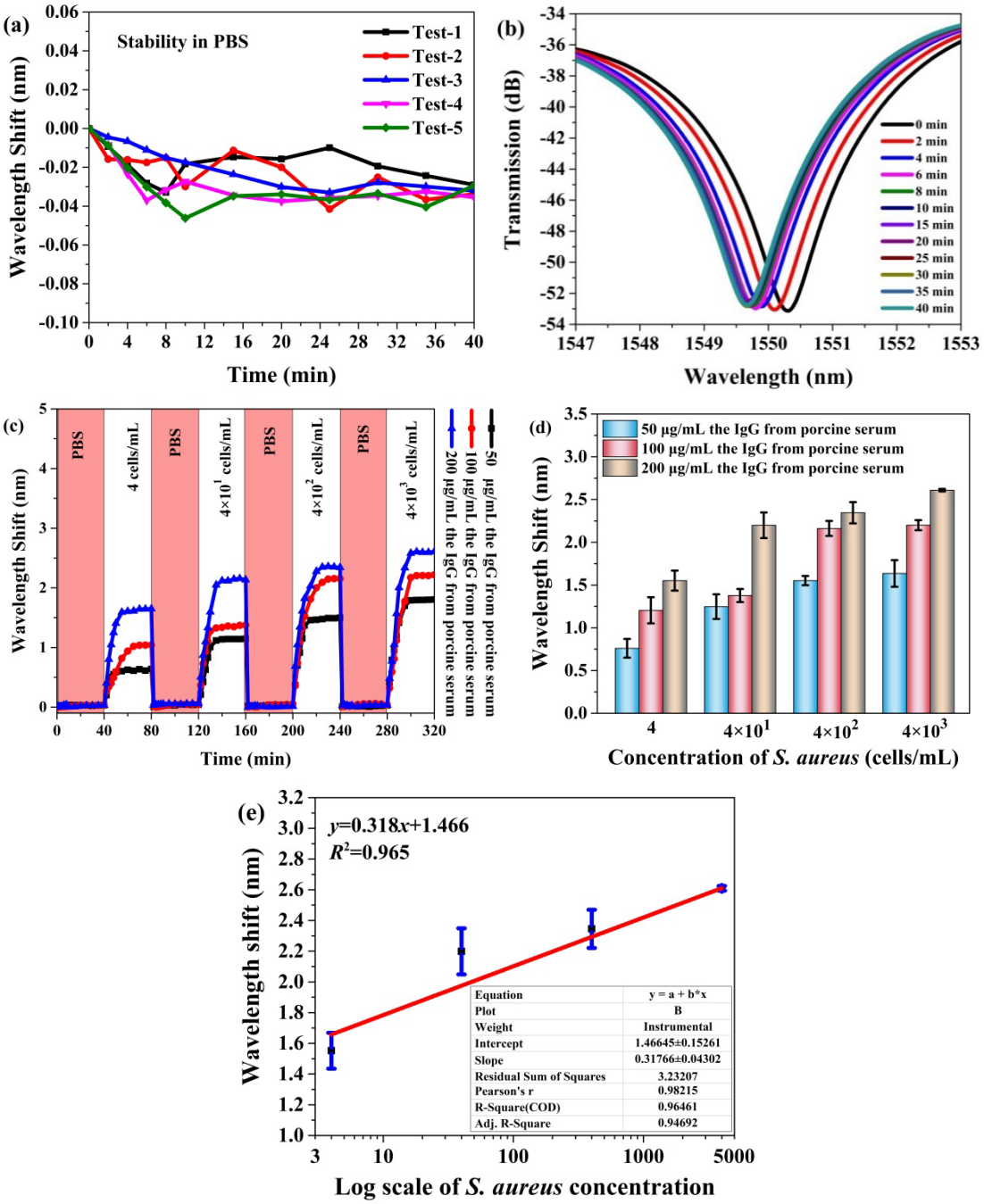


Fig. 4. (a) The stability of the U-shaped STMS fiber biosensor in PBS within 40 minutes, (b) the spectrum responses of a modified U-shaped STMS fiber biosensor (50 μg /mL IgG from porcine serum) with an *S. aureus* sample (4 cells/mL), (c) the comparison of three concentrations (50 μg /mL, 100 μg /mL, and 200 μg/mL), (d) the fiber biosensor's repeatability results, and (e) a plot of the wavelength shift vs. log scale of *S. aureus* concentration (modified with 200 μg /mL IgG from porcine serum).

After the functionalization of the U-shaped STMS fiber biosensor, the spectral stability of the sensor with time was investigated in the absence of *S. aureus,* as a precursor to further tests. Fig. 4 (a) shows that for five separate stability tests over 40 minutes, the wavelength deviations of the five separate U-shaped STMS fiber biosensors all with the same structural parameters, are -0.029, -0.0338, -0.0325, -0.0354, and -0.0294 nm (average value: -0.032 nm), respectively, which confirms that the U-shaped STMS fiber biosensors show excellent spectral stability in the presence of PBS.

At this point *S. aureus* was introduced. The measured detection dynamic range for *S. aureus* is from $4\times10^{0}$ cells/mL to at least $4\times10^{3}$ cells/mL. In the experiment, all the U-shaped STMS fiber biosensors were fabricated and functionalized under the same conditions and each biosensor is only used once for the detection of *S. aureus*. The test concentrations of *S. aureus* ranged from 4 cells/mL to $4\times10^{3}$ and the immobilized concentrations of the IgG from porcine serum cells/mL ranged from 50 μg/mL to 200 μg/mL. When the concentrations of the IgG from porcine serum and *S. aureus* are 50 μg/mL and 4 cells/mL, the spectral responses of the biosensor are shown in Fig. 4(b). As seen in Fig. 4(b), the dip wavelength undergoes a consistent blue-shift with time with the magnitude of the shift gradually decreasing per unit of time, until a steady state is reached. In our experiment, the volume of the sample used for testing is 1.5 mL. The measured results of the wavelength shifts when the U-shaped biosensors are immobilized with different concentrations of the IgG from porcine serum (50 μg/mL, 100 μg/mL, and 200 μg/mL) at different concentrations of *S. aureus* solution (4 cells/mL, $4\times10^{1}$ cells/mL, $4\times10^{2}$ cells/mL, and $4\times10^{3}$ cells/mL) are shown in Fig. 4(c). For the case where the IgG from porcine serum is at the same concentration, an increase in the concentration of *S. aureus* causes the larger dip wavelength shift. This is because for a higher concentration *S. aureus* solution, more *S. aureus* will be captured by the IgG from porcine serum and will bind to the STMS fiber surface.

The largest dip wavelength shift occurs within the first 20 minutes after which the wavelength shift stabilizes and this trend conforms to the reported kinetic response of the immune behavior [32]. A sensor functionalized with higher concentration of IgG shows a larger wavelength shift when the sensor is immersed into *S. aureus* with same concentration. This is because for a given quantity of *S. aureus*, the IgG from porcine serum at a higher concentration means stronger capacity for the fiber to trap *S. aureus*.

The reproducibility of the biosensors was also studied by manufacturing 36 U-shaped STMS fiber biosensors with the same structure parameters. Twelve U-shaped STMS fiber biosensors are modified by IgG from porcine serum using one of three concentrations (50 μg/mL, 100 μg/mL, and 200 μg/mL) Each biosensor is used to detect *S. aureus* only once. The reproducibility test results are summarized in the histogram in Fig. 4(d), which with the aid of range bars, clearly shows that the U-shaped STMS fiber biosensors have good reproducibility. The functionalized fiber biosensors with the IgG from porcine serum at a concentration of 50 μg/mL were used to detect *S. aureus* with different concentrations varying from 4 cells/mL to $4\times10^3$ cells/mL, the average dip wavelength shift increases from 0.760 nm to 1.636 nm. The porcine IgG concentration has an impact on the sensitivity of the fiber biosensor: as it increases from 50 μg/mL to 100 μg/mL and 200 μg/mL, in an *S. aureus* solution with the same concentration (4 cells/mL), the corresponding average wavelength shifts increase from 0.760 to 1.205, and 1.552 nm, respectively. Fig. 4(e) shows a plot of the wavelength shift vs. log scale of *S. aureus* concentration (modified with 200 μg /mL IgG antibody). The LoD of the fiber biosensor was calculated by taking three times the standard deviation ($\sigma$) of the wavelength shift in PBS divided by the slope ($S$) of the plot in Fig. 4(e) [33]. For the proposed U-shaped STMS fiber biosensor, the wavelength shift in PBS is 0.032 nm, and the slope is 0.318, so the calculated LoD value of the

biosensor (LoD=3$\sigma$/$S$) is 0.302 cells/mL.

3.4. *Single colony of S. aureus detection*

In the above results, when the concentrations of the IgG antibody from porcine serum and the *S. aureus* samples are 200 μg/mL and 4 cells/mL, respectively, the average dip wavelength shift of the U-shaped STMS fiber biosensors is 1.552 nm, indicating the potential for ultrahigh sensitivity for *S. aureus* detection. To further investigate the LoD of the developed sensor, the concentration of *S. aureus* was diluted to 0.4 cells/mL, into which the fiber biosensors were immersed. In the experiments, three U-shaped STMS fiber biosensors were used, each was immersed into the 0.4 cells/mL *S. aureus* sample over 5 consecutive times, and then was immersed into the *S. aureus* sample at a concentration of 4 cells/mL for a $6^{th}$ time. The volume of each solution is 1.5 mL. The measured results for the three U-shaped STMS fiber biosensors immersed in this manner is shown in Fig. 5(a). From Fig. 5(a), the first two fiber biosensors showed no response to the 0.4 cells/mL *S. aureus* sample but have significant wavelength shift in *S. aureus* sample with concentration of 4 cells/mL, indicating that both sensors work well. The reason that there is no wavelength shift in 0.4 cells/mL *S. aureus* sample is that the concentration is too low and no *S. aureus* binds to the fiber biosensors. The third fiber biosensor did produce a detectable dip wavelength shift of 0.348 nm when it was immersed into the 0.4 cells/mL *S. aureus* sample for the $3^{rd}$ time. Taking into account the 10 measurements of the two previous sensors this detection represents a successful detection after 13 tries. This is because for the 0.4 cells/mL *S. aureus* sample, the chance of being captured by the IgG antibody immobilized on the fiber biosensor is very low. However once it is captured, the sensor can produce a detectable wavelength shift. Given that the sample volume is 1.5 mL, a concentration of 0.4 cells/mL is indicative of presence a single colony of *S. aureus.* The result confirms that the developed U-shaped STMS fiber biosensor can detect a single

colony of *S. aureus*. Fig. 5(b) shows the spectral responses of the sensor when *S. aureus* was captured by the antibody immobilized on the fiber biosensor, for in 0.4 cells/mL *S. aureus* sample.

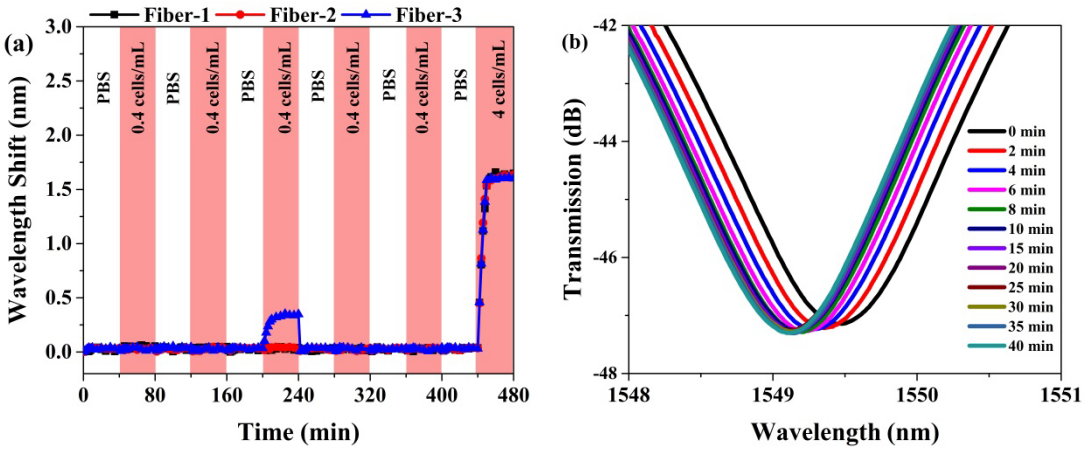


Fig. 5. (a) The detection process of 0.4 cells/mL of *S. aureus* by three fiber biosensors, and (b) the corresponding spectral responses of the fiber biosensor in 0.4 cells/mL of *S. aureus* sample.

### 3.5. *Specificity Test*

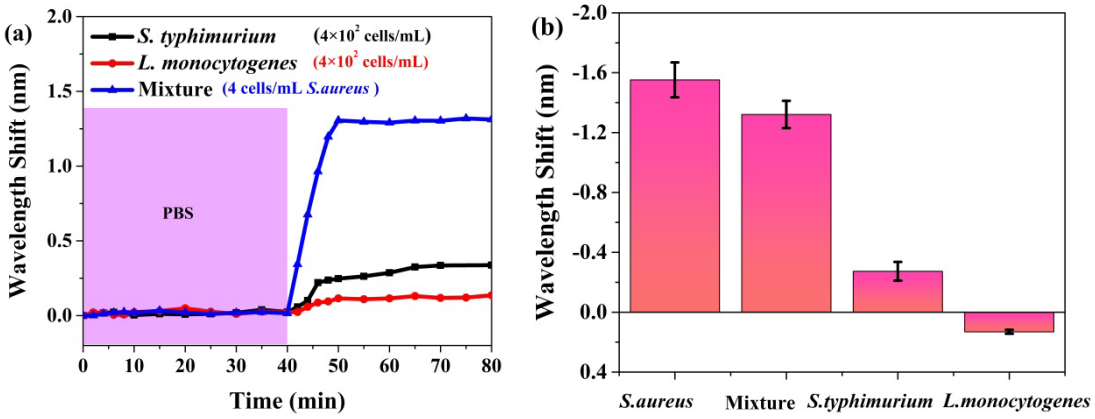


Fig. 6. (a) The specificity test of wavelength shift vs. time in *S. typhimurium*, *L. monocytogenes* and mixture, and (b) the reproducibility tests in different bacterial solutions.

The specificity test of the U-shaped STMS fiber biosensor is investigated by immersing the nine different fiber biosensors made under the same fabrication conditions and antibody functionalization concentration (200 μg/mL) into three different of bacterial sample types *S. typhimurium*, and *L.*

*monocytogenes* and a mixture of *S. typhimurium*, *L. monocytogenes*, and *S. aureus*. In the test, every bacterial type is tested by three individual fiber biosensors. The concentration of both the *S. typhimurium* and the *L. monocytogenes* was $4\times10^2$ cells/mL, and the mixture simples had a *S. aureus* concentration of 4 cells/mL. Fig. 6(a) shows the specificity test result of the wavelength shift vs. time in *S. typhimurium* ($4\times10^2$ cells/mL), *L. monocytogenes* ($4\times10^2$ cells/mL), and mixture (4 cells/mL *S. aureus*). From Fig. 6(a), the dip wavelength shift in a mixture simple is 1.332 nm, which is much larger than that of *S. typhimurium* (0.337 nm) and *L. monocytogenes* (0.136 nm). Fig. 6(b) shows the reproducibility of the specificity tests. It is found from Fig. 6(b) that the dip wavelength experiences redshift for the *L. monocytogenes*, and the *S. typhimurium* samples and the others are still blue-shift. In addition, the wavelength shift in mixture is smaller than that in pure *S. aureus* samples, which may be because the probability of the IgG from porcine serum capturing *S. aureus* is decreased due to the cross impact of the *L. monocytogenes*, and the *S. typhimurium*. The average wavelength shifts of three measurements for the mixture sample, *S. typhimurium*, *L. monocytogenes*, are -1.322, -0.273, and 0.131 nm, respectively, indicating good specificity and reproducibility for the U-shaped STMS fiber biosensor. Table 1 compares the performance between the proposed U-shaped STMS fiber biosensor with other reported results. From table 1, it is clear that the proposed structure has an ultralow LoD of 0.4 cells/mL and reaches the limit level of single colony detection.

**Table 1. Comparison between the proposed fiber biosensor and other reported methods for detecting *S. aureus***

| Refs | Methods | LoD | Response time |
|---|---|---|---|
| 6 | Polymerase chain reaction | $10^2$ CFU/mL | 4 h |

| | | | |
|---|---|---|---|
| 7 | Polymerase chain reaction | $9.5\times10^4$ CFU/mL | 15 min |
| 8 | Lateral flow assay methods | $10^3$ CFU /mL | NA |
| 10 | Electrochemical biosensor | 10 CFU /mL | 108 s |
| 11 | Electrochemical biosensor | 39 CFU/mL | 30 min |
| 12 | Electrochemical biosensor | 3 CFU/mL | 15 min |
| 13 | Electrochemical biosensor | 3 CFU/mL | 30 min |
| 14 | Carbon nanotubes and aptamers based potentiometric method | $8\times10^2$ CFU/mL | 6 min |
| 15 | Long-period fiber grating | 33 CFU/mL | 20 min |
| 16 | Long-period fiber grating | 224 CFU/mL | 30 min |
| 18 | Colorimetric | $1.5\times10^3$ CFU | 40 min |
| 19 | Fluorescence | 290 CFU /mL | 130 min |
| 20 | Fluorescence-enhanced lateral flow biosensor | 540 CFU /mL | 70 min |
| 21 | Localized surface plasmon resonance | $10^3$ CFU/mL | 120 s |
| 24 | Biolayer interferometry technology | 13 CFU/mL | 12 min |
| 25 | Impedance spectroscopy and data processing with information visualization techniques | 2.6 CFU/mL | NA |
| 26 | Fluorescence probes | 11.12 CFU/mL | 135 min |
| 27 | Tapered fiber coupler structure | 3.1 CFU/mL | 20 min |
| This work | U-shaped STMS fiber structure | 0.4 cells/mL | 20 min |

3.6. *Detection of S. aureus in milk sample and lettuce sample*

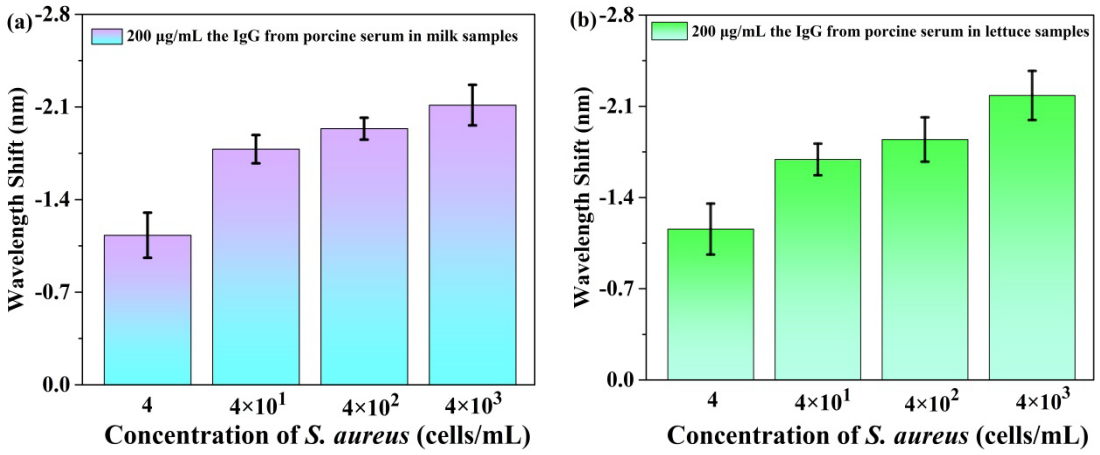


Fig. 7. Wavelength shift of the fiber sensor functionalized with 200 μg/mL IgG from porcine serum for detection of *S. aureus* (a) in milk sample and (b) in lettuce samples.

The prepared pasteurized milk and lettuce samples were first infiltrated with different concentrations of *S. aureus*. Then in order to extract the target *S. aureus*, we used immunomagnetic separation (IMS) technology based on immunomagnetic particles (IMPs) to separate *S. aureus* (The detailed content can be found in the supporting material document 2.3-2.5) [34]. Fig. 7(a) demonstrates the wavelength shifts resulting from the detection of *S. aureus* by the fiber biosensor modified with 200 μg/mL of IgG from porcine serum in milk samples with a volume of 1.5 mL. Twelve fiber biosensors were prepared with the same parameters, and each fiber biosensor was measured only once. Four concentrations of *S. aureus* were used, repeated 3 times with individual fiber biosensors. The measured average wavelength shifts of the fiber biosensors are -1.130, -1.781, -1.936 and -2.114 nm for *S. aureus* at concentrations of 4, $4\times10^1$, $4\times10^2$, and $4\times10^3$ cells/mL, respectively. Compared with the wavelength shift results for *S. aureus* in PBS, the percentage changes in the measured wavelength shift in milk samples were -27%, -19%, -17% and -19%, for the concentrations above respectively. Fig. 7(b) demonstrates the wavelength shifts of the U-shaped STMS fiber biosensor in lettuce samples. The measured

average wavelength shift in lettuce samples are -1.158, -1.692, -1.845 and -2.183 nm, respectively, corresponding to percentage changes of -25%, -23%, -21% and -16%, compared to that of *S. aureus* in PBS, respectively. The summarized results are listed in the Table 2. Table 2 shows less wavelength shift for both milk and lettuce samples, which is because when compared with PBS, the milk and lettuce samples contain matrix interferences, thereby interfering with the binding of a proportion of the *S. aureus* to the fiber surface. In general, while the average change in the wavelength shift in milk samples and lettuce samples is about -21% compared with the results in PBS, the results do confirm the viability and potential of the fiber sensor for the detection of *S. aureus* in food samples.

**Table 2. Wavelength shift in different *S. aureus* sample solution**

| *S. aureus* in different sample solution | 4 cells/mL Wavelength shift (nm) | $4\times10^1$ cells/mL Wavelength shift (nm) | $4\times10^2$ cells/mL Wavelength shift (nm) | $4\times10^3$ cells/mL Wavelength shift (nm) |
|---|---|---|---|---|
| PBS | 1.552±0.12 | 2.199±0.15 | 2.345±0.12 | 2.609±0.02 |
| Milk | 1.130±0.17 | 1.781±0.10 | 1.936±0.08 | 2.114±0.15 |
| Lettuce | 1.158±0.19 | 1.692±0.12 | 1.845±0.17 | 2.183±0.19 |
| Percentage change from PBS | -27% (milk) -25% (lettuce) | -19% (milk) -23% (lettuce) | -17% (milk) -21% (lettuce) | -19% (milk) -16% (lettuce) |

# 4. Conclusion

In conclusion, we have experimentally investigated a U-shaped STMS fiber biosensor with ultrahigh-sensitivity for label-free detection of *S. aureus*. When the concentrations of the IgG from porcine serum and the *S. aureus* samples are 200 μg/mL and 4 cells/mL, respectively, the average dip

wavelength shift can reach 1.552 nm, demonstrating *S. aureus* detection with a concentration as low as 4 cells/mL. Furthermore, the single colony of *S. aureus* detection was studied and verified by diluting the concentration of *S. aureus* to 0.4 cells/mL and using the developed biosensor multiple times of the detection of *S. aureus*. The proposed fiber biosensor also has excellent specificity, demonstrated by immersing the sensor into different types of bacterial samples, including *S. typhimurium*, *L. monocytogenes* and a mixture of *S. typhimurium*, *L. monocytogenes* and *S. aureus*. Finally *S. aureus* contained in milk and in lettuce samples can also be detected by the proposed fiber biosensor, and the average percentage change in the wavelength shifts in milk samples and lettuce samples is -21% compared with the PBS. Compared with traditional biosensors, the fiber biosensor has the advantages of a more compact size, shorter detection time, higher sensitivity, good stability, reproducibility, and specificity. It is expected that the proposed fiber biosensor will have important applications in food testing, biomedicine and other fields.

## CRediT authorship contribution statement

**Shi Qiu**: Formal analysis, Writing-original draft, Investigation. **Yuankui Leng:** Formal analysis, Methodology. **Jinhui Yuan**: Conceptualization, Formal analysis, Writing - original draft, Methodology, Writing - review & editing, Funding acquisition. **Zhichao Zhang:** Formal analysis, Investigation. **Xian Zhou:** Writing - review & editing. **Bin Liu**: Formal analysis, Methodology. **Chao Mei:** Writing - review & editing. **Binbin Yan:** Writing - review & editing. **Kuiru Wang:** Writing - review & editing. **Xinzhu Sang:** Writing-review & editing. **Keping Long:** Writing-review & editing. **Chongxiu Yu:** Writing-review & editing. **Xindao He:** Writing-review & editing. **Gerald Farrell:** Formal analysis, Writing-review & editing. **Qiang Wu**: Conceptualization, Supervision, Formal analysis, Writing-original draft, Methodology, Writing-review & editing, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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