Tapered plastic optical fiber sensor for dengue non-structural protein 1 (Ns1) detection

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A simple fiber optic sensor is proposed and demonstrated for detection of different concentration of dengue non-structural protein 1 (NS1) using a tapered plastic optical fiber (POF). The working mechanism of the device is based on intensity modulation technique where the transmitted light intensity variation is measured when the probe is immersed into dengue NS1 antigen and antibody solution with various concentrations. The dengue NS1 antigen and antibody of various concentrations ($1x10^{-2}$, $1x10^{-3}$, $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, $1x10^{-7}$, $1x10^{-8}$ mg/mL) were prepared by serial dilution of a stock concentration of 1mg/ml with phosphate buffer saline solution. The tapered POF is fabricated through a chemical etching method by using acetone and deionized water to achieve a waist diameter and length of 0.45 mm and 25 mm, respectively. For detection of dengue NS1 antigen, as the solution concentration varies from $1x10^{-8}$ mg/mL to $1x10^{-2}$ mg/mL, the output voltage of the sensor reduces linearly from 1.21 mV to 1.17 mV with a slope sensitivity of 0.004 mV/ (mg/mL) and a linearity of 92.61%. As for detection of dengue NS1 antibody, the tapered POF based sensor produces a sensitivity of 0.84 mV/ (mg/mL) with a linearity of 98.61%.

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1. Introduction

Dengue fever is a flu-like viral disease, which is commonly found throughout the tropical and sub-tropical regions around the world. Today, it is a lethal disease that affects 50 to 100 million peoples per year [1]. The disease is caused by four distinct but related dengue viruses that are known as DENV-1, DENV2, DENV 3, and DENV-4. By recovering from one virus strain, gives lifelong immunity to that strain but not to the other three. Further infection by different virus strains can lead to dengue haemorrhagic fever (DHF). About 2.5% of DHF cases are fatal. With intensive theraphy, the rate can be reduced to 1% but if it is untreated the rate can reach as high as 20% [1-2]. Dengue virus is transmitted by the female *Aedes Aegyptus* mosquitoes [1]. Currently, there is no vaccine available for the virus and thus an appropriate early treatment is very important to save life.

Recently, non-structural 1 (NS1) antigen has gained a lot of interest as a new biomarker for early diagnosis of dengue infection. It forms in the host cell after infection and acts as the antigen to stimulate antibody production [3]. This means that NS1 antigen can be detected before the formation of antibodies [4, 5]. NS1 antigen is detectable in blood from the first day after the onset of fever up to day 9 post-infection [6]. Thus, it is appropriate to say that detection of dengue NS1 antigen represents a new approach to diagnose the dengue infection.

On the other hand, tapered optical fibers have also received much attention in recent years especially for sensing applications. By tapering a fiber, more evanescent wave field can be made to travel outside the core region. Thus, the travelling wave characteristics are more sensitive to the physical ambience of its surrounding. However, the focus of most literatures is on the feasibility of silica-based tapered fiber optic sensors [7-8], leaving the plastic-based tapered optical fiber much to be explored. The main advantages of plastic optic fibers (POFs) as compared to silica fibers are easier to handle, higher mechanical strength, better disposability, and easier mass production. In addition, POF based sensors do not required sophisticated materials and can be operated at room temperature and varying pressure conditions [9-10].

In this paper, a new fiber-optic NS1 detection system is proposed and demonsrated using a tapered multimode POF as a probe. The sensor is based on intensity modulation technique where dengue NS1 detection is carried out for various concentrations of dengue NS1 antigen and antibody. The proposed sensor measures the output voltages of the detector that is influenced by the interaction of the evanescent wave produced in the tapered cladding and the solution which forms its surrounding. This method offers simplicity and reliability.

2. Experimental arrangement

At first, a tapered POF (TPOF) was prepared using a chemical etching technique. The untapered POF has an overall cladding diameter of 1 mm, a numerical aperture of 0.51, and an acceptance angle of 61^{O}. The refractive indexes of the core and cladding are 1.492 and 1.402, respectively. To taper the fiber, acetone was applied to the POF using a cotton bud and neutralized with deionized water. The acetone reacted with the POF surface and formed milky white foam which was then removed by the sand paper. This process was repeated until the tapered fiber had a stripped region waist diameter of about 0.45 mm. The total length of the tapered region in the POF was measured to be around 25 mm. Finally, the tapered POF was cleansed using deionized water.

Fig. 1 illustrates the schematic diagram for proposed sensor system to detect different concentrations of dengue NS1 antibody and antigen. The setup consists of a He-Ne light source, an external mechanical chopper, a TPOF probe, a highly sensitive silicon photo-detector (818 SL, Newport), a lock-in amplifier (SR-510, Stanford Research System) and a computer. The input and output ports of the microfiber were connected to He-Ne light source and photo-detector, respectively. The light source operates at a wavelength of 633 nm with an average output power of 5.0 mW. The silicon photo-detector is placed at the other end of the fiber to convert the received optical signal into an electrical signal. Then, the converted electrical signal is fed into lock-in amplifier. The light source is set at the modulation frequency of 113 Hz before being launched into the TPOF. The modulated light source is used in conjunction with the lock-in amplifier to reduce the dc drift and interference of ambient stray light. The lock-in amplifier output voltage of the transmitted light is directed recorded by a computer automatically using Delphi software through a serial port RS232. The tapered section was placed on the channel holder which was fabricated by using a simple computer numerical controlled (CNC) lathe machine.

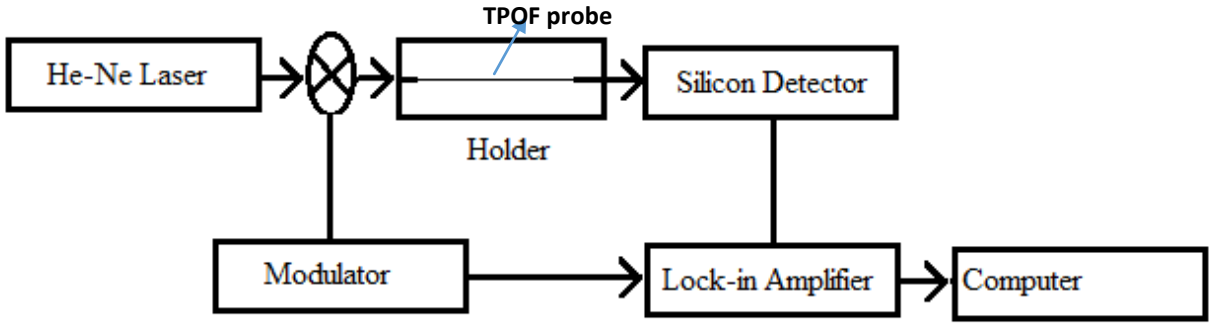

Fig. 1. Experimental setup for Dengue NS1 antibody and antigen detection by using TPOF.

Recombinant dengue NS1 protein was used in this study as an antigen with a stock concentration of 1mg/ml and purity of >90%. This protein consists of full length recombinant protein of dengue virus serotype 3 to be detected by mouse monoclonal antibody against dengue 3 NS1 protein. The antibody concentration cannot be determined since it is not purified. Thus, it was used based on the manufacture's recommendation. The phosphate buffered saline (PBS, 10 mM) solution with pH 7.4 was prepared as diluents for the antibody and antigen. For this study, lower concentrations (1×10^{-2}, 1×10^{-3}, 1×10^{-4}, 1×10^{-5}, 1×10^{-6}, 1×10^{-7}, 1×10^{-8} mg/ml) of antibody and antigen were prepared by serial dilution. After the detection of antibody and antigen using TPOF, the antibody and antigen of the same concentration were mixed together by pour the antigen into antibody solution in the holder. The mixing reaction were observed and analyzed. During the experiment, the errors caused by temperature are taken to be negligible and the temperature is kept constant at 25^{0}C.

3. Results and discussion

Fig. 2 shows the variation of output voltage against the concentration of dengue NS1 antibody and antigen. As shown in the figure, the output voltage from the photo-detector which is proportional the transmitted light from the TPOF, linearly decreases as the concentration of both solution increases. As the concentration increases, the light absorption by the sample also increases. Thus, less light is collected by the detector. It is observed that the light absorption is higher in NS1 antibody compared to that of antigen. For detection of Dengue NS1 antigen, the TPOF has a sensitivity of 0.004 mV/(mg/mL) with a slope of linearity of 92.61%. Meanwhile for detection of dengue NS1 antibody, the TPOF has a sensitivity of 0.84 mV/(mg/mL) with a slope of linearity of 98.61%. The adjusted R-square value or the coefficient of the determination is the measure of the goodness of fit. The considerably high values of the adjusted R-square allow the prediction of unknown antibody/antigen concentration by the model.

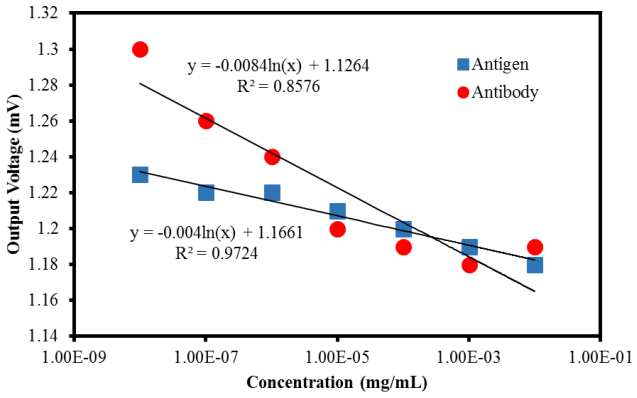

Fig. 2. Output voltage against dengue NS1 antibody and antigen concentration using TPOF.

Fig. 3 shows the output voltage variation against time during the mixing reaction at the antibody and antigen concentration of 1×10^{-2} mg/mL. As shown in the Fig. 3, the output voltage from the photo-detector increases abruptly from 1.13 mV to 1.26 mV when the antigen is mixing with the antibody in the channel holder. This is due to the chemical reaction between the antibody and antigen, which changes the absorption of the light. The output voltage difference before and after the mixing the solution is measured and the value is plotted against the concentration of solution.

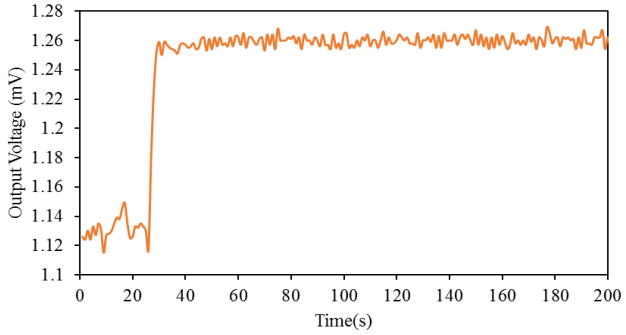

Fig. 3. The change of the transmitted light when the antigen is mixing with the antibody in the channel holder.

Fig. 4 shows the output voltage difference, which was obtained from the photo-detector when mixing dengue NS1 antigen and antibody at various solution concentrations. It is shown that the difference of the output voltage which corresponds to the amount of the transmitted light, linearly increases as the concentration of the solution increases. As the concentration increases, the chemical reaction between antigen and antibody is also increased and forms a bigger molecule. This increases the transmission of light through the sensor probe, which is translated in a larger voltage at the photo-detector. For the case of mixing of the dengue NS1 antigen and antibody, the TPOF sensor curve has a sensitivity of 0.0059 mV/(mg/mL) with a slope of linearity of 95.24%. The performance characteristic of the proposed TPOF sensor is summarized in Table 1. Throughout the experiment, a fix quantity of solution was placed in the holder. The corresponding output voltage was measured by a lock-in amplifier which provides accurate measurements even though the signal is small compared to the thousand times larger noise sources. In adition, a well-regulated power supply was used for the red He-Ne laser and this minimizes the fluctuation of source intensity.

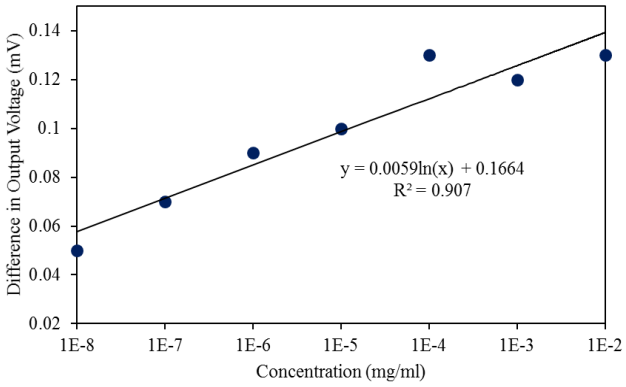

Fig. 4. The changes of the output voltage when mixing dengue NS1 antigen and antibody.

Table 1. Performance dengue NS1 antibody and antigen sensor.

Parameter	Antibody	Antigen	Mixing
Sensitivity (mV/(mg/dL))	0.084	0.004	0.0059
Linear Range (mg/dL)	1×10^{-2}-1×10^{-8}	1×10^{-2}-1×10^{-8}	1×10^{-2}-1×10^{-8}
Linearity (%)	98.61	92.61	95.24

4. Conclusion

A simple TPOF sensor was proposed and demonstrated for dengue NS1 detection. The dengue NS1 antigen and antibody with various concentrations were prepared by serial dilution using PBS solution. The TPOF was fabricated through a chemical etching method by using deionized water and acetone to achieve a waist diameter and length of 0.45 mm and 25 mm, respectively. It is observed that the output voltage of the sensor decreases with the increase of the concentration of the dengue NS1 antigen and antibody from 1×10^{-8} mg/mL to

1×10^{-2} mg/mL. For detection of dengue NS1 antigen, the TSOF produces a sensitivity of of 0.004 mV/ (mg/mL) with a linearity of 92.61%. Meanwhile for detection of dengue NS1 antibody, the TSOF produces a sensitivity of 0.84 mV/ (mg/mL) and a linearity of 98.61%. These results indicate that the sensor could potentially be used for dengue detection with further improvement.

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