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The SARS-CoV-2 specific IgG antibodies biophotonic sensor

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Abstract

In this paper, we present the design and the principle of operation of the SARS-CoV-2 specific IgG biophotonic sensor, which is based on the single-mode telecommunication fiber. We fabricated the sensor head at the face of the SMF 28 fiber. Due to the process of bio-functionalization, our sensor has the ability to selectively detect the SARS-CoV-2 specific IgG antibodies. The results of preliminary tests allowed us to correctly determine the presence of antibodies in less than 1 minute in 5 µL in a volume sample of concentration of 10 µg/mL, which according to studies, corresponds to the concentration of IgG antibodies in human serum. Additionally, the tested sample can be smaller than 5 µL in volume.

Keywords:

Fiber-optic sensor; IgG; SARS-CoV-2, biophotonics; immunosensor

Abbreviations: (**IgG,** Immunoglobulin G, **IgM**, Immunoglobulin M, **ELISA**, enzyme-linked immunosorbent assay, **ImCH**, immunochromatographic, **PAGE**, polyacrylamide gel electrophoresis, **WGM**, Whispering Gallery Mode, **APTES**, (3-Aminopropyl)triethoxysilane, **OSA**, optical spectrum analyzer, **DMSO,** Dimetyloformamid, **PBS,** Phosphate buffered saline, **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2, **FWHM**, Full Width at Half Maximum)

1 INTRODUCTION

Until now the SARS-CoV-2 antibodies (IgG/IgM) detection has been made by laboratory diagnostic methods [1]. Using these measurement methods is costly – sometimes requires the use of expensive and specialist measurement equipment and also additional elements necessary to take the analysis (e.g., reagents, dedicated trays, method of preparing samples of biological materials), moreover, their proper use is possible only with the qualified personnel [2–5]. The method also takes a lot of time, which influences the preselection process.

Currently, the immunochromatographic (ImCH) test or ELISA test are being used for screening against IgG or IgM antibodies. Those two methods usually require specially modified antigens with gold nanoparticles (immunochromatography) or antibodies labelled by fluorochrome or other molecules (ELISA) [6] allowing for fM concentration detection. The average time of performing the tests in case of ELISA is at least 1 hour, and 20 minutes for immunochromatography. Those timings strictly depend upon sample preparation or IgG/IgM migrating ability on cellulose sheet, which does not allow for shorter times of detection of antibodies from blood [7]. Of course, there are plenty of different methods which allow for IgG detection like PAGE, mass spectrometry. Nowadays, the mass spectrometry techniques are allowing for detection of fM or aM concentration of lower molecular mass compounds (up to 5 kDa), unfortunately, the IgG molecules are one of the biggest molecules in biology (150 kD), thus the most sensitive techniques like mass spectrometry have the limit of detection around 0.01 mg/mL [8]. To overcome this obstacle in mass spectrometry, specific kits for the purification and concentration of antibodies from whole blood are being used [9]. Nevertheless, even this approach is not sufficient for specific SARS-CoV-2 antibody detection [8].

Additionally, the developed methods that are widely used for antibody detection are not sufficient to predict the exact concentration of SARS-CoV-2 antibody in the sample – the

techniques like ELISA or ImCH can give only qualitative information [6]. In whole blood, the average concentration of total IgG is at 10-100 mg/mL level (~ 1nM concentration), thus to detect the anti-SARS-CoV-2 antibodies or other we need the method which will allow for at least fM/aM (~1fg/mL) concentration of antibody detection [10,11].

Although the gold standard for the SARS-CoV-2 antibodies (IgG/IgM) detection has been made by laboratory diagnostic methods [12,13] or electrochemical biosensors [14,15], many research groups work on specific fiber optic sensors [16].

Optic methods are reported as methods used for virus detection: e.g. colorimetry [17], fluorescence [18], Raman scattering [19], chemiluminescence [20,21], plasmon resonance [22], dynamic light scattering [23], plasmonic [24] built with the use of complicated fiber optic structure, there is still a need for fiber optic sensors in that area, especially sensors which use commonly use fiber optic materials and devices.

Fiber optic biosensors can be based on glass [25] or polymer [26] fibers. They can use many measurement mechanisms, which are used to modulate the intensity, phase or spectra of the optical signal. In a sensor, which uses the intensity of the optical signal, the disruption of the correct propagation of light in the fiber can be done like: un-cladding a region of the fiber and coat it with the biolayer sensitive to the virus [27] or antibodies [28]. That configuration can be produced in both kinds of fibres either glass (even single mode fiber) or polymer.

Another example of the disruption of the correct propagation of light in the fiber is by tapering a region of a fiber [29] or by intruding the hole into the structure of fiber [30]. Intensity modulation sensor can be built in the reflection mode and combined with microfluidic system [31]. In the phase modulation sensors, the interferometry is applied. Bian et al. [25] presented fiber optic biointerferometry sensor built from the dedicated fiber optic structure and biolayer which is designed in such a way that specific antibodies attached to the layer. This changes the thickness of the layer what can be detected after 7.5 min of measurement. The sensor uses a fiber optic structure with diameter of 0.68, with no coating around. There are no details about the wavelength of the source which was used. Another example of interferometric antibodies detection sensor is Mach-Zehnder interferometer built from photonic crystal fiber between two single-mode fiber [32] or as a fiber optic multicavity Fabry-Perot interferometer [33].

The example of the spectra modulated sensor are sensors based on fiber optic gratings. Such sensors have been produced as an antibodies detector in both polymer and glass fiber optic configurations [34–36].

In this study, we present a biophotonic sensor with a fiber-optic biofunctionalized measurement head, dedicated to SARS-CoV-2 antibodies detection. The innovation of the presented sensing method mainly lies in:

- Design of a bioactive layer that selectively allows only specific SARS-CoV-2 antibody proteins to be attached in low concentrations [37,38].
- In contrary to many other solutions which used plastic fiber optic [39], our sensor is made of the standard telecommunication optical fiber with a dedicated bioactive layer. This gives us the possibility to elaborate the sensor head of very small dimensions compared to that made by the plastic fiber optic.
- That small sensor head enables to measure of the antibodies' concertation in a drop of the investigated sample [40,41].
- Elaborating the fiber optic biosensors which properly work with the telecommunication wavelength (1550 nm). This is an unusual wavelength for a biophotonic sensor because fiber optic biosensors are dedicated to working in lower wavelengths [23,42,43]
- Elaboration of the effective method of antibodies proteins detection based on the signal transmitted back by standard telecommunication single-mode fiber [44,45].
- Fast detection of the protein of SARS-CoV-2 by the use of the optical method in a drop of sample – with our sensor the detection in 5 μL sample is possible within <1 min 1 [43,46].
- The novelty of the study is the method of optical fiber head preparation for antigen immobilization which does not require the extensive heating of the optical fiber head (we are using dehydrated solvents when chemically modifying the surface) [47,48].
- This sensor can be easily connected to the existing fiber optic telecommunication network due to the use of standard telecommunication elements.

Despite many presented methods of SARS-CoV-2 antibody detection, there is still a demand for the fabrication of sensor, which may demonstrate inferior measurement parameters, compared to laboratory equipment, but which will demonstrate availability for proper measurement, fast response time and low volume of investigated sample. What will make them popular instruments for wide use.

To date, none of the solutions [15] presented in the scientific literature, including electrochemical [49], optical [50], microstructures utilizing Whispering Gallery Mode (WGM) [51], surpass the sensors described in this paper, in terms of fast response time.

2 EXPERIMENTAL SECTION

2.1 Probe immobilization on the surface of the fiber-optic sensor

In this subsection, the process of the immobilization of the surface of the fiber-optic sensor is described. Functionalization of the sensor probe allows it to selectively detect the SARS-CoV-2 specific IgG antibodies specific, the diagram of the process is presented in Figure 1.

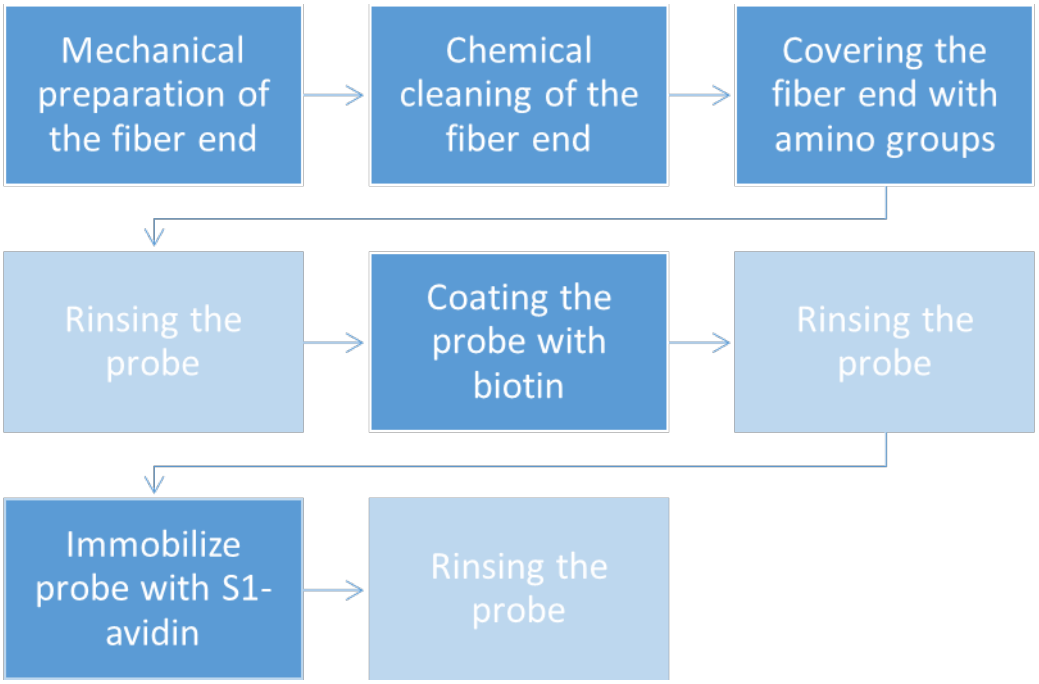


Figure 1. The diagram of the probe preparation.

The molecular sieves (3 Å, Pol-Aura, Poland) were activated in an oven (10h, 350°C) and cooled, then transferred to the 250 mL glass bottle with tight sealing and filled with dimethyl sulfoxide (molecular biology grade, Merck, Germany) or acetone (molecular biology grade, Merck, Germany) (1:1 (v/v)). Finally, it was left for 72 hrs to dehydrate the solvents. The sensor was cleaned extensively by immersing it in H2O2/H2SO4 (WarChem, Poland; ACS reagent, Merck, Germany, respectively) water solution (10%, 50 mM respectively at 60°C) for 30 min. After the cleaning procedure, the optical fiber was immersed in ultrapure water and later in anhydrous acetone solution to remove excess moisture (3 times in different solutions, each incubation lasted 10 min in an anhydrous environment). Cleaned optical fiber was immersed in a freshly prepared 2% 3-Aminopropyltriethoxysilane (99% purity, Merck, Germany) solution in anhydrous acetone for 24 hrs in an anhydrous environment - to cover the optical fiber in amino groups. After 24 hrs the optical fiber was immersed in anhydrous DMSO (3 times, 10 min of incubation) to remove excess APTES solution. Cleaned optical fiber with amino groups on the surface was then immersed in a freshly prepared 10 mM stock solution of NHS-LC-Biotin (95% purity, Merck, Germany) in anhydrous DMSO and left for 24 hrs in an anhydrous

environment. After incubation, the sensor was immersed in the 1xPBS (Phosphate buffered saline tablets; Merck, Germany) solution and rinsed several times to remove unbond biotin and DMSO. To immobilize the probe (S1-avidin), the stock solution (10 mM) of S1 domain of spike protein conjugated with avidin was prepared in 1xPBS and the optical fiber was immersed in the solution for 1 hr, then rinsed with 1xPBS.

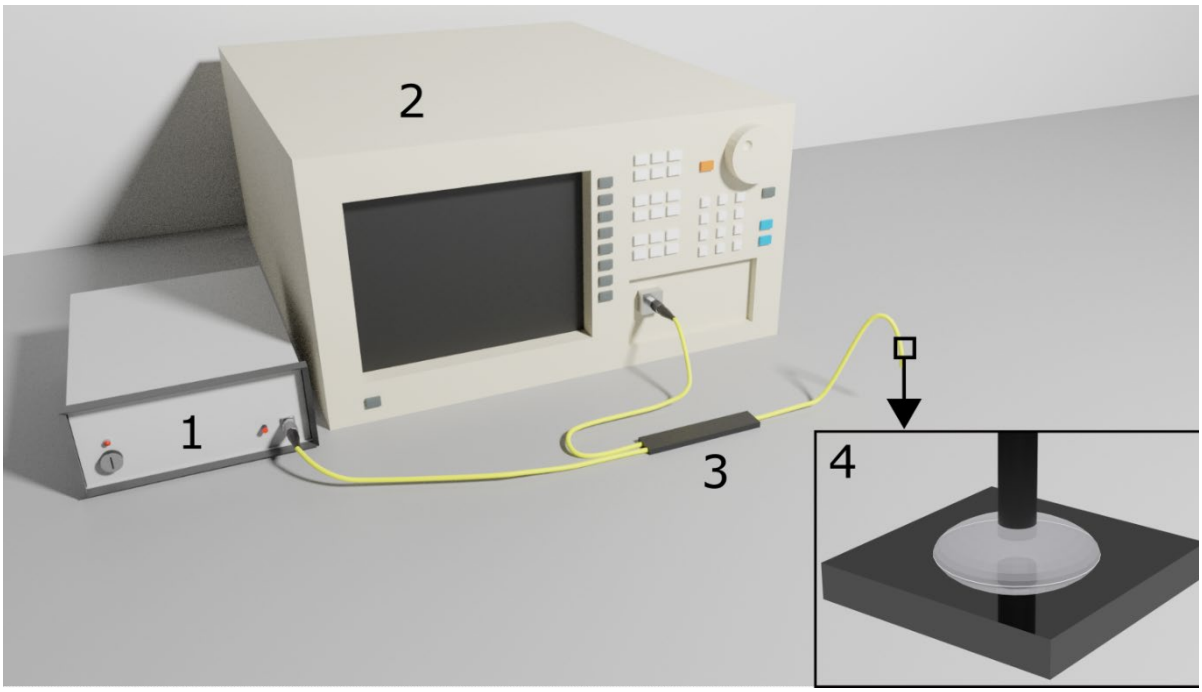
The described bio-active layer was fabricated on the flat end-face of the fiber.

2.2 Measurement methods

The measurements were taken in the measurement setup shown in Figure 2. Prepared samples were measured in the interferometric setup, consisting of a low-coherent broadband light source – superluminescent diode (SLD-1550-13-W, FiberLabs Inc., Fujimino, Japan) with parameters as follows: central wavelength 1550 nm +/- 20nm; output power ≥ 13 mW; spectral bandwidth$_{FWHM}$ ≥ 30 nm [52]), 2:1 50/50% optical coupler (G657A, CELLCO, Kobylanka, Poland) and Optical Spectrum Analyzer (OSA, Ando AQ6319, Yokohama, Japan) and sensor, which is made from single mode fiber (SMF-28, Thorlabs Inc., Newton, NJ, USA) with parameters: a refractive index of core 1.4679 (for 1550 nm) and 0.36% refractive index difference between core and cladding [52]. The end face of the fiber has been coated with the bioactive film which was designed in such a way that only selective protein of SARS-CoV-2 specific IgG antibodies are attached to this layer." (Figure 3).

There were two reasons for using such a 1550 nm wavelength as a light source for the experiment. The most important is that the maximum antibody protein absorption occurs at that wavelength. These phenomena we use to increase the sensitivity of the sensor. The second reason lies in the technical approach because the use of this wavelength gives the possibility to apply commonly used fiber optic elements in the construction of the sensors. Furthermore, these sensors work on the telecommunication wavelength which gives us the possibility to combine the readout with the telecommunication network.

a)



b)

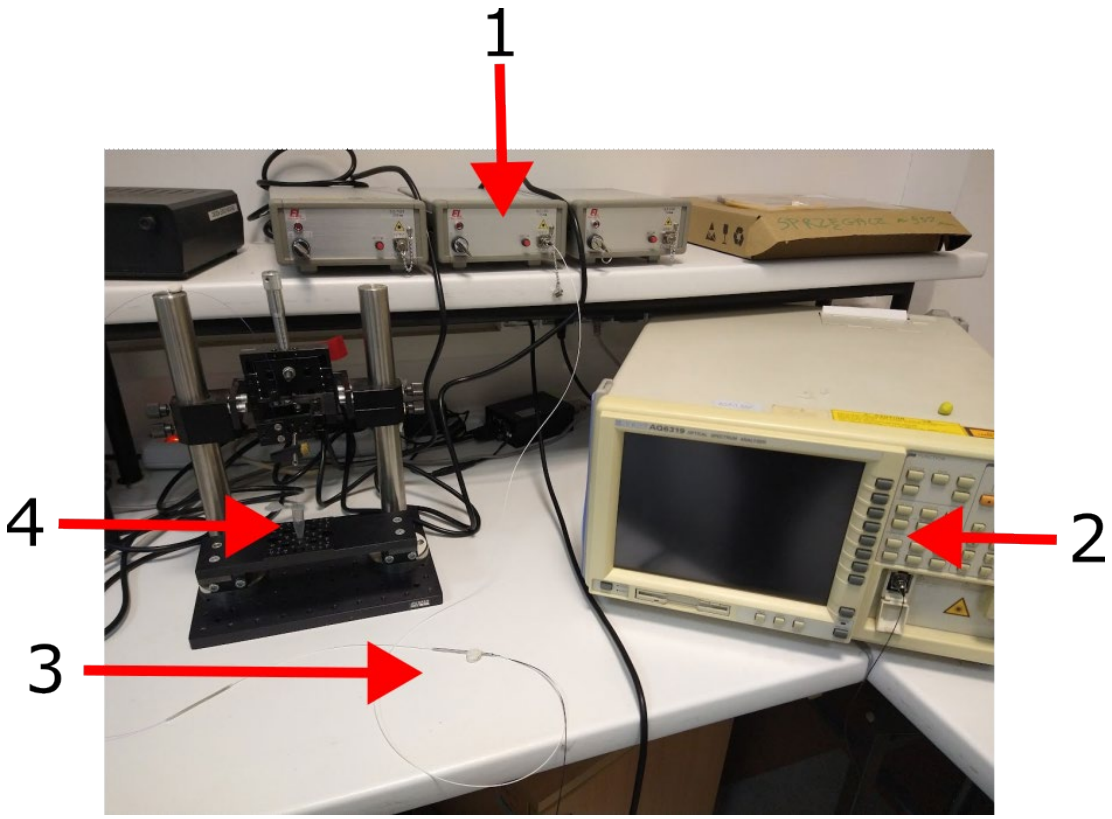


Figure 2. The experimental system, where: 1- light source, 2 – Optical Spectrum Analyzer, 3 – optical coupler, 4 – sensor immersed in the solution. a) schematic of the setup, b) photo of the real-life setup.

In the first series of measurements, the sensor was validated using a measurement setup shown above. The signal generated from the light source with a central wavelength of 1550 nm had been transmitted through an optical coupler to the sensor.

During the measurements, the sensor was immersed in the investigated solution with IgG antibodies. In each setup, the head of the optical sensor was immersed in IgG (10 μg/mL) solution.

The temporal stability of the sensors has been investigated and as a result, the temperature of 25 °C of the sample has been chosen for measurement. The constant temperature of the samples gave the stable measurement condition and limited the impact of temperature changes on the measured signal.

The basis of the measurement method lies in the measurement of intensity changes in the reflected signal from the end face of the fiber which is coated with a dedicated bioactive layer. This layer has been designed in such a way that only the proteins of SARS-CoV-2 specific IgG antibodies can attach to this layer. As the antibodies are attached to the end of the sensor, they absorb in a very effective way the light which is transmitted from the light source to the sensor's head. This affects the intensity changes of the reflected signal measured by the optical spectrum analyzer.

As the antibodies attached to the bioactive layer of the sensor, we were able to observe the changes in optical power during the attachment of the antigen to the surface of the sensor. Similarly, the results during the rinsing of the sensor were recorded. It was possible because we fabricated the fiber optic interferometer (Figure 3), in which mirrors were created by boundaries fiber-optic/bioactive layer and bioactive layer/surrounding medium. Having attached antibodies, we obtained multilayer interferometer, which mirrors consists of fiber-optic/bioactive layer, bioactive layer/antibodies, antibodies/surrounding medium.

Interference originated by the superposition of the reflected waves (Fig. 3). The optical power of a signal reflected on both interfaces as well as its spectrum was observed and recorded using OSA. The operation principle of the sensor is presented in Figure. 3.

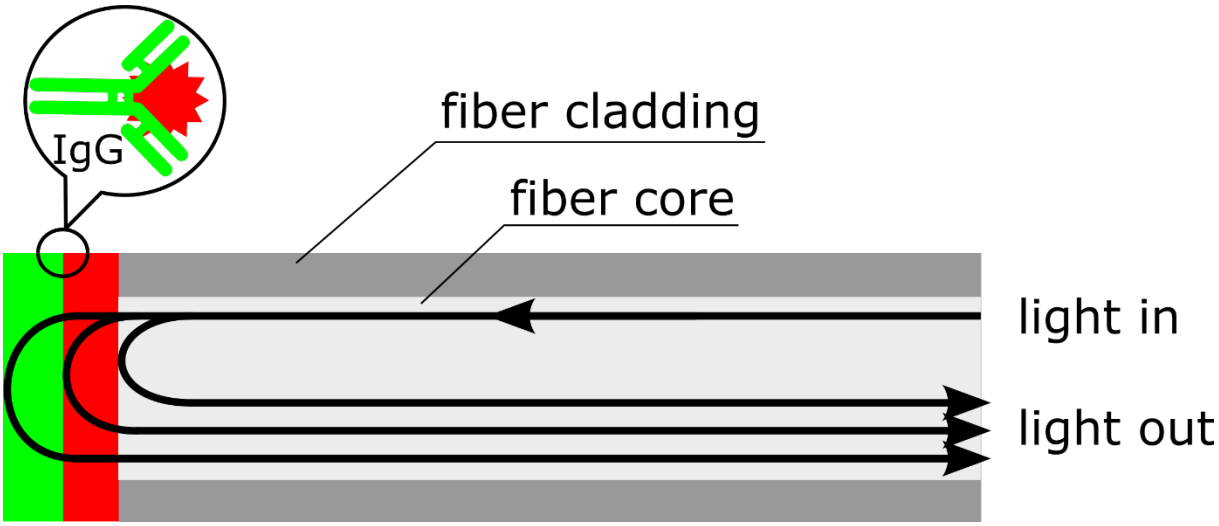


Figure 3. The principle of operation of the sensor for detection of the anti-SARS-CoV-2 IgG.

The measurements were performed with a probe as a reference. Next, the probe was immersed in the pure 1xPBS solution and then transferred to the dilution of anti-S antibody at 10^{-6} g/mL (serial dilutions). The sensor was submerged in the anti-S antibody solution for 5 minutes. At each stage, the optical power of the reflected signal was measured.

3 RESULTS AND DISCUSSION

This section presents the results (time dependence of the optical power at a given concentration of antibody) obtained from the measurements of the time stability. In order to verify the performance of the newly developed sensor, we have investigated the changes in optical power at a wavelength of 1550 nm. This approach allowed us to easily compare our methodology of immobilization of antigen on the surface of the optical fiber with literature data. The signal optical power decreases with increasing antibody concentration. This phenomenon is connected with the ability of protein (antibody, antigen) to absorb the 1550 nm wavelength. The proteins e.g., antibodies and antigens consist of approximately 500 to 1500 amino acids, surrounded by ions of Na+, K+, etc. which have a huge impact on the hydrogen bonding pattern (solvation shells) of water molecules. Thus, when an antibody is attached to the surface of the sensor, the optical power of the signal recorded is lower in comparison to the system without antibodies in solution, which can be observed in Figure 4. The signal response changes of the sensor upon immersion of the optical head in antibody PBS solution or human serum spiked with S1

antibody. The antibody/antigen interaction is known in the literature and immobilization of antigens onto the surface of glass or 96-well ABS plate is regularly being done in laboratories [53]

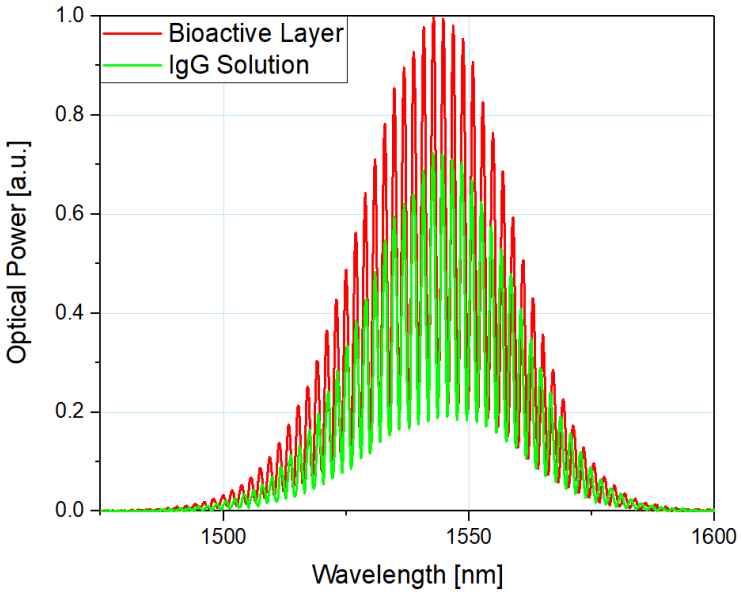


Figure 4. The measured response of the sensor in with bioactive layer and after the immersion in the IgG solution.

The first of the measurements was performed over the period of 5 minutes during the attachment of the IgG (10 µg/mL) to the flat-ended sensor and then during the rising over another 5 minutes. As previously mentioned, the optical power should decrease when the antibodies are being attached to the optical head, due to the interaction with antigen immobilized on the silica surface. As shown in Fig. 5(a), the optical power is decreasing with time suggesting that the antibodies are interacting with immobilized antigens (S1 protein). The characteristic of the plot of binding and unbinding of IgG is like the sigmoidal characteristic. Please note that the time necessary for the equilibration is less than 5 min (faster than the commercially available immunoassays), thus allowing for fast detection of IgG from blood in extremely low concentrations. The graphs of the peak optical power throughout the entire series, presented in Figure 5, were averaged to highlight changes in the reflected signal over time.

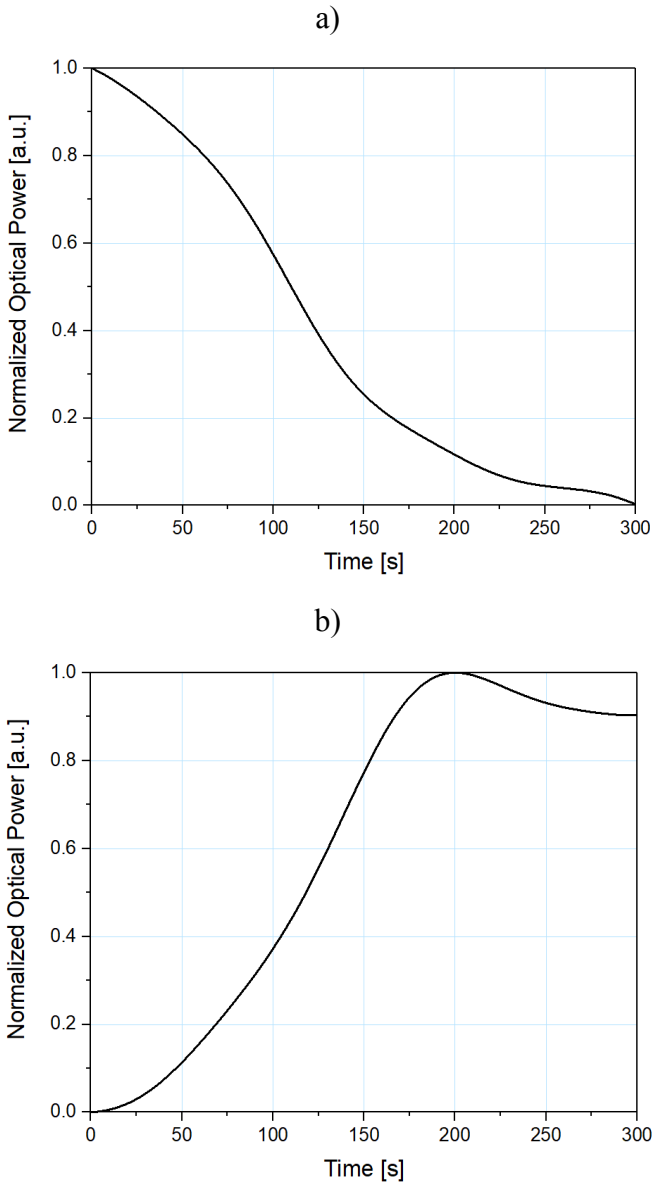


Figure 5. Averaged signal response of the flat-ended sensor over 5 minutes during measurements of the: a) attachment of the antigen to the measuring head causes the decrease of the optical power, b) rinsing of the sensor causes the increase of the optical power.

As can be seen, in Figure 5(a), the peak optical power of the reflected signal decreases, when the antibody is attached to the measuring head of the flat-ended signal. During the attachment process, the layer on the surface of the sensor thickens, therefore causing the change in the optical path difference. The signal decreases until the fully inversed the bioactive layer by antibodies over the sensor surface. Analogically, during rinsing of the sensor, the peak optical power of the reflected signal increases over time until the antibody is no longer attached to the sensor (the concentration decreases).

4 CONCLUSION

In this work, we have presented the results of optical measurements using our newly developed sensor that detects IgG antibodies specific to the SARS-CoV-2 S1 protein. The method of operation of the sensor is based on the measurement of radiation absorption in the range of ~ 1550 nm by the adhering IgG monolayer present in the solution. In order to assure that the sensor selectively detects SASR-CoV-2 specific antibodies, the S1 domain of the SARS-CoV-2 Spike protein was immobilized on the sensor head. This bioactive layer of the fiber-optic sensor head allows an interaction to be established between the antibody and the S1 domain. That kind of interaction and immobilization allows then washing away the interfering background of e.g., serum, blood, or other biological matrices, due to strong interaction of antibody/antigen. Thanks to this methodology, the sensor is able to operate with high sensitivity (1 ug/mL) and in a very short time (< 5 min) to the antibodies specific to the S1 domain appearing in the environment. It is also worth noting that our preliminary studies allowed us to observe concentrations of IgG antibodies as low as it is observed in the serum of people infected with SARS-CoV-2 [50]. As a result, the sensor is very cheap to use and extremely easy to manufacture, including the use of generally available components used in optoelectronics. The volume of the tested sample was smaller than 5 μL in volume. The developed SARS-COV-2 IgG/IgM specific antibodies fiber-optic sensors have significant advantages, as compared to the currently used method:

- very short measurement time (for a single measurement less than 5 minutes),
- lower required amount of the test substance (e.g., blood at the level of fractions less than 1 μL),
- the lack of need for additional preparation of biological samples prior to the measurement,
- immunity to external interferences (electromagnetic, mechanical stress, etc.),
- the possibility of applying for the continuous, real-time inspection,
- potentially, low-cost mass production, due to utilization of standard fiber-optic communication elements.

The elaborated sensors give the possibility to be successfully connected to the telecommunication network, which gives a lot of new possibilities. It can be used in remote places with a lack of a health care system. The screen monitoring of the citizens, done by the design senor, can give the authorities the basic knowledge about the necessity of healthcare in such places in case of the person with increasing levels of the antibody of viral illness. Taking into consideration the latest information about detecting antibodies of SARS-CoV-2 in urine

[54], using such a sensor can be non-invasive and examination easier to perform even in the case of small children and people with disorders

Furthermore, it can be used as a tool for real-time on demand sensor of the patient vaccination response or for the investigation of the organism response during infection.

To summarize, the sensors metrological parameters are presented in Table.1.

Table 1. Parameters of the sensor

The central wavelength	The diameter of sensor head	The measurement time	The sample volume	The preparation of samples	The limit of detection
1550 nm	250 µm	Less than 5 min	Less than 1µL	No	1 µg/mL

AUTHOR CONTRIBUTIONS

Conceptualization M.S, P.W, P.L; Data curation P.L; Formal Analysis M.S, P.W, P.L; Funding acquisition M.S; Investigation M.S, P.W, P.L; Methodology M.S, P.W; Project administration M.S; Resources M.S, P.W, P.L; Supervision M.S; Validation M.S; Visualization P.L; Writing – original draft M.S, P.W, P.L; Writing – review & editing M.S.

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CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are published in open repository of Gdańsk University of Technology: DOI 10.34808/nr3s-nc60.

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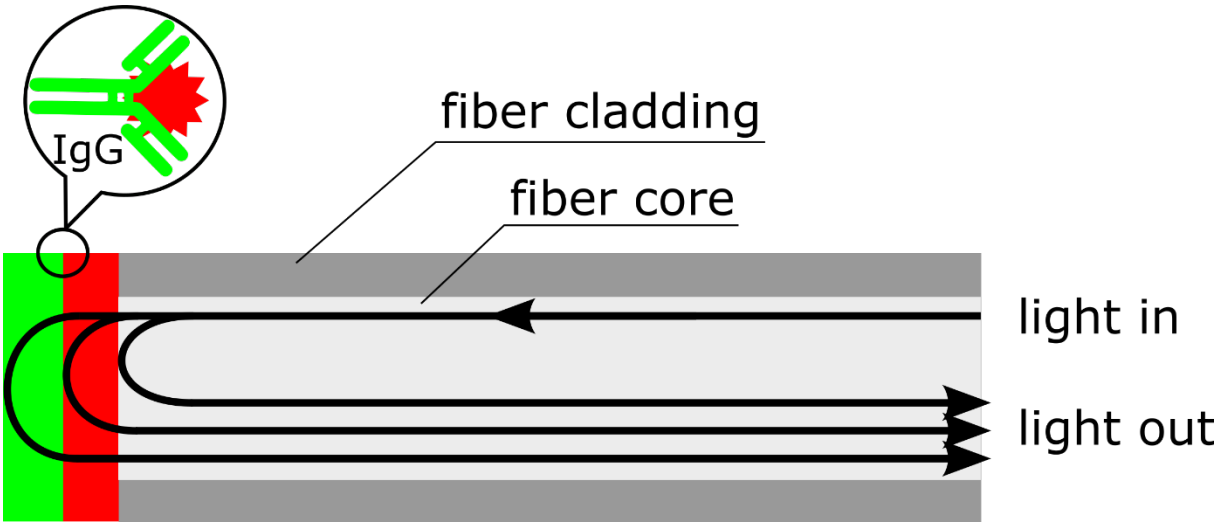

In this paper, the design and the principle of operation of the SARS-CoV-2 specific IgG biophotonic sensor is presented. The sensor head was fabricated at the face of the SMF 28 fiber. Due to the process of bio-functionalization, the sensor has the ability to selectively detect the SARS-CoV-2 specific IgG antibodies. The results of preliminary tests allowed us to correctly determine the presence of antibodies in less than 1 minute in 5 µL in a volume sample of concentration of 10 µg/mL, which corresponds to the concentration of IgG antibodies in human serum.