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Toward the Development of Plasmonic Biosensors to Realize Point-of-Care Tests for the Detection of Viruses and Bacteria †

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Abstract: Optical fiber biosensors can be used to develop point-of-care tests (POCTs) for detecting viruses and bacteria in several matrices. In particular, the surface plasmon resonance (SPR) and localized SPR phenomena (LSPR) can be excited by exploiting low-cost and small-size optical fiber chips. Generally, SPR or LSPR sensors are realized using several kinds of modified optical fibers (silica, plastic, or specialty) or by exploiting other optical waveguides (e.g., slab, spoon-shaped waveguides, etc.). More specifically, optical fiber sensors can be classified as intrinsic or extrinsic. In the "optical fiber intrinsic sensors", the sensing area is realized in the optical fiber directly, such as in the case of plasmonic platforms based on D-shaped plastic optical fibers (POFs), tapered optical fibers, U-bend POFs, or light-diffusing fibers (LDFs). By contrast, when an optical fiber is used as a mere waveguide allowing for the launch of light to the sensing region and its collection, it is defined as an extrinsic optical fiber sensor, like in the case of the plasmonic sensors realized by Cennamo et al. using POFs combined with spoon-shaped waveguides, 3D-printed platforms, bacterial cellulose waveguides, nanogratings, and InkJet-printed chips. To realize optical biosensor chips for the detection of viruses and bacteria, both intrinsic and extrinsic plasmonic POF sensors can be efficiently combined with receptors specific for membrane proteins, either biological (e.g., antibodies, aptamers, enzymes, etc.) or synthetic (e.g., molecularly imprinted polymers), to build groundbreaking POCTs.

Keywords: optical sensors; biosensor chips; surface plasmon resonance (SPR); plastic optical fibers (POFs); point-of-care tests (POCTs)

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1. Introduction

Immediately after the COVID-19 pandemic highlighted the need for small, inexpensive, and easy-to-use devices useful to detect the virus on site and with the capability of transmitting statistical data over the Internet, POCTs connected to the Internet began to raise significant interest among the medical community [1]. In fact, during a pandemic emergency, these technologies can give a more accurate view of the state of emergency and improve and speed up its management.

Recently, optical biosensors based on surface plasmon resonance (SPR) have been developed for several applications [2,3]. In particular, SPR probes and molecularly imprinted polymer (MIP) receptors were successfully tested [4,5] for several bio/chemical applications, such as for SARS-CoV-2 detection in several matrices [6]. Owing to the method's high sensitivity, the virus can be detected even in diluted samples. The proposed

POCT for SARS-CoV-2 detection reported in [6] can detect the presence of the virus in a few minutes and transmit the outcome to a platform via the Internet, facilitating the generation of automatic statistics useful for pandemic monitoring and management. Since this POCT also allows for the quantitative measures of SARS-CoV-2, it can represent a valid tool for monitoring COVID-19 patients' treatment [6]. In particular, as shown in the outline of Figure 1, an SPR-POF probe [7] coupled with a specific MIP nanolayer [6] has been designed and tested for the recognition of SARS-CoV-2 via its spike protein with the possibility of transmitting the experimental data obtained in real time [8].

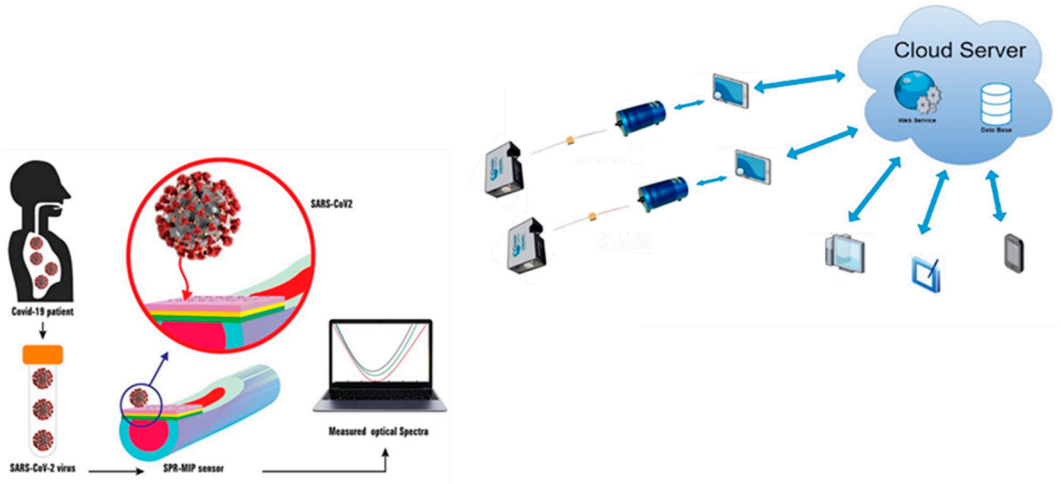


Figure 1. Scheme of the sensor to detect SARS-CoV-2 with the possibility of transmitting and storing the data in a cloud via the Internet [6,8].

Concerning the molecular recognition element (MRE), it is important to mention the possibility of using several specific MIPs (imprinted for different substances) in order to realize a versatile sensor system based on the same optical platform covered with a "programmable" MIP layer, as outlined in Figure 2. So, the potential of the proposed POCT is that it can be quickly updated/developed for a new pandemic emergency or different types of pathogens or viruses of interest. The reprogramming of MIPs is possible because the synthesis process involves copolymerization between appropriate functional monomers and a crosslinking agent in the presence of the target molecule [4,5,9–11].

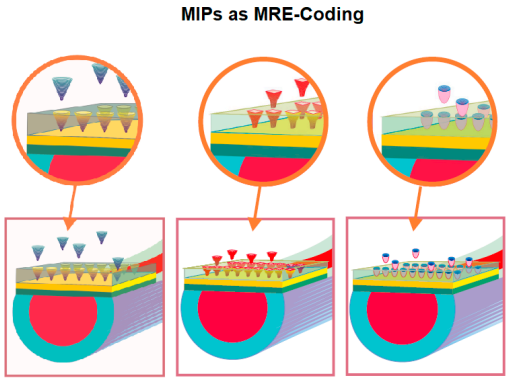
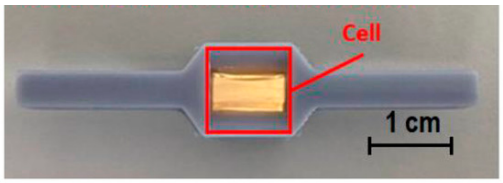


Figure 2. Outline of an SPR-POF platform combined with several MIP layers [6].

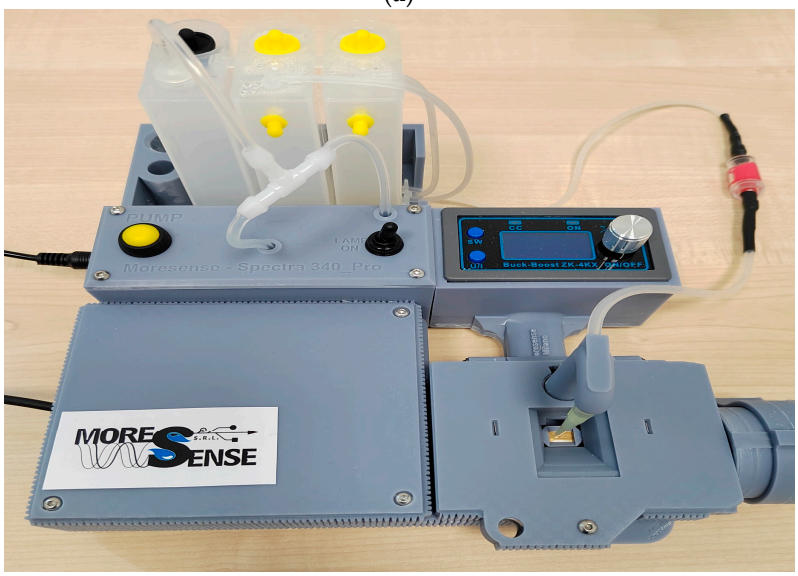
This work involves a mini-review of the capabilities of POF sensors for the detection of viruses and bacteria in POCTs.

2. POCT: SPR-POF-MIP Chips and Experimental Setups

The plasmonic POF-based sensor platforms and the setup used to carry out this POCT were manufactured by Moresense srl (Spectra 340, Moresense srl, Milan, Italy). Figure 3a shows an image of the SPR-POF probe covered by the specific MIP layer, and the POCT device is illustrated in Figure 3b. A developed software tool (Moresense Capture Spectrum Data ver. 2.3) was used to acquire and process the experimental data of the POCT. This tool offers the possibility to connect the POCT to the Internet.



(**a**)



(**b**)

Figure 3. Images of (**a**) the SPR-POF-MIP chip and POCT device (**b**), both manufactured by Moresense srl (Milan, Italy) in collaboration with the University of Campania Luigi Vanvitelly (Naples, Italy).

3. SARS-CoV-2 Detection in UTM

A method for detecting the SARS-CoV-2 spike S1 protein and the SARS-CoV-2 virus has been reported in [6,8], and this was used here to demonstrate the capabilities of the POF-based bio/chemical sensors and the proposed sensing approach.

Nasopharyngeal (NP) swabs positive and negative for COVID-19 were collected to carry out these measurements [6,8]. In particular, the previously positive samples were analyzed with the proposed POCT and in parallel with the RT-PCR technique (gold standard).

Figure 4a reports the experimental results obtained using the SPR-POF-MIP sensor with real SARS-CoV-2-positive and -negative nasopharyngeal (NP) swabs in a UTM (universal transport medium) [6]. Each experimental value is the result of an average of five successive acquisitions, and the error bar shows the standard deviation. Figure 4b shows the SPR spectra of a positive NP swab in UTM diluted with a physiological solution at different dilution factors [6]. In this way, it was possible to show that quantitative measurements of SARS-CoV-2 can be carried out. Using the UTM, shifts in the resonance wavelength were found for dilutions with ratios less than 1:10. The same samples were tested using RT-PCR and were positive only when diluted at a ratio of 1:2 (with a physiological solution).

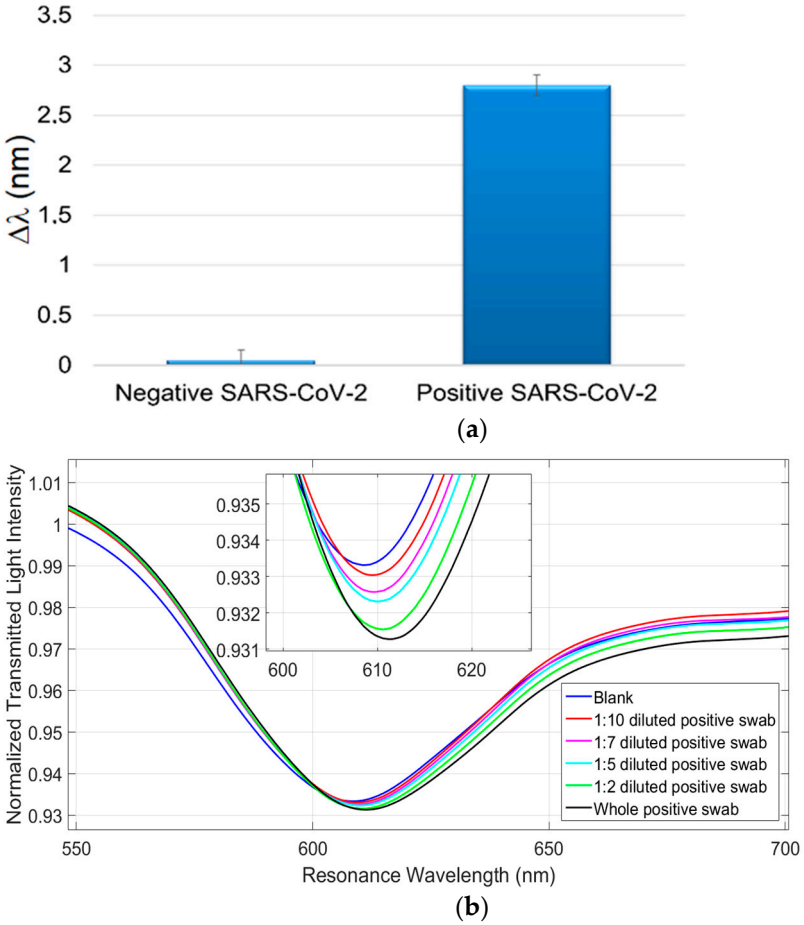


Figure 4. (**a**) Comparison of the positive and negative responses in UTM obtained using the POCT (confirmed with RT-PCR); (**b**) SPR spectra of dilutions of the positive sample in UTM at different ratios (the SARS-CoV-2-positive result was obtained at the 36th RT-PCR cycle). Samples were diluted using a physiological solution.

4. Conclusions

The proposed plasmonic POF-based POCT, aimed at detecting SARS-CoV-2, proved to be highly sensitive in a real scenario. Its operation proved effective in various real matrices, and the measurement system used is cheap, has small dimensions, and is connected to the Internet.

Moreover, it should be noted that what is presented here for SARS-CoV-2 detection is only a proof of concept to demonstrate the efficacy of the proposed POCT. However, it is possible to simply generalize this approach for other viruses or bacteria by reprogramming the MIP.

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