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Nanophotonics: An Emerging and Promising Approach for COVID-19 Diagnostic Technology

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ABSTRACT

The public health crisis initiated by the emergence of the COVID-19 pandemic emphasizes the need for rapid and accurate diagnostic tests to monitor large populations through community mass testing. Many testing techniques have been implemented to prevent disease spread, critical to pandemic control. Polymerase chain reaction (PCR) tests for detecting viral RNA and immunoassay tests for detecting SARS-CoV-2 antibodies are currently used to diagnose COVID-19. PCR tests are time-consuming, with a 24–48 hours turnaround time. Samples undergoing PCR detection must also be sent to a laboratory to be processed by highly specialized workers, preventing a point-of-care diagnosis from being provided. Popular immunoassay tests have drawbacks as well. Enzyme-linked immunosorbent assays (ELISAs) are extremely labor-intensive and expensive, whereas lateral flow assays (LFAs) are primarily used for antigen detection. In this work, we propose a photonic SARS-CoV-2 detection method based on a ring resonator. We calculate the sensor performance using the finite-difference eigenmode (FDE) method. The sensor sensitivity in ring resonator resonance frequency is 29 nm/RIU, with an intrinsic detection level (iLOD) of 6.89×10^{-5} RIU. We envision ring resonator-based lab-on-chip devices being widely used for applications such as early diagnosis, with the added benefit of being ultra-compact and easily handled by non-specialists.

Introduction

The global pandemic that resulted from the outbreak of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has proved the necessity of a viable diagnostic test that can be used to conduct mass population testing as a method of infection control [1]. Responsible for taking over 57 million lives and infecting millions more, the COVID-19 pandemic has initiated a newfound sense of urgency as even fully recovered patients remain anxious regarding the long-term medical consequences of the virus [2]. The need for rapid, accurate, ultrasensitive diagnostic technology has emerged as a major challenge posed to the public health industry [1]. A type of nucleic acid amplification test, PCR (polymerase chain reaction) tests are the current gold standard for diagnosing COVID-19 and have played a pivotal role in managing the spread of the virus thus far [3]. In targeting ribonucleic acid sequences within the virus and amplifying the genomic material, PCR techniques can magnify even minuscule amounts of the virus, making it a highly sensitive test [1]. However, the capabilities of PCR testing are accompanied by several logistical limitations to using this method. PCR tests are routinely analyzed in laboratories, which adds to the heavy turnaround time and renders it impractical for mass population testing [1]. Additionally, the test is dependent on the magnification of nucleic acid targets, meaning that the reaction conditions must be strictly maintained to ensure that the viral material is suitably amplified [3]. Finally, PCR tests are only effective during the specific period the patient releases virus progeny following an infection, typically two days before becoming symptomatic and lasting between seven to ten days after

[3]. Because only an approximated 20 to 40% of patients that receive diagnostic tests display symptoms, PCR tests likely may not identify the presence of the virus [3].

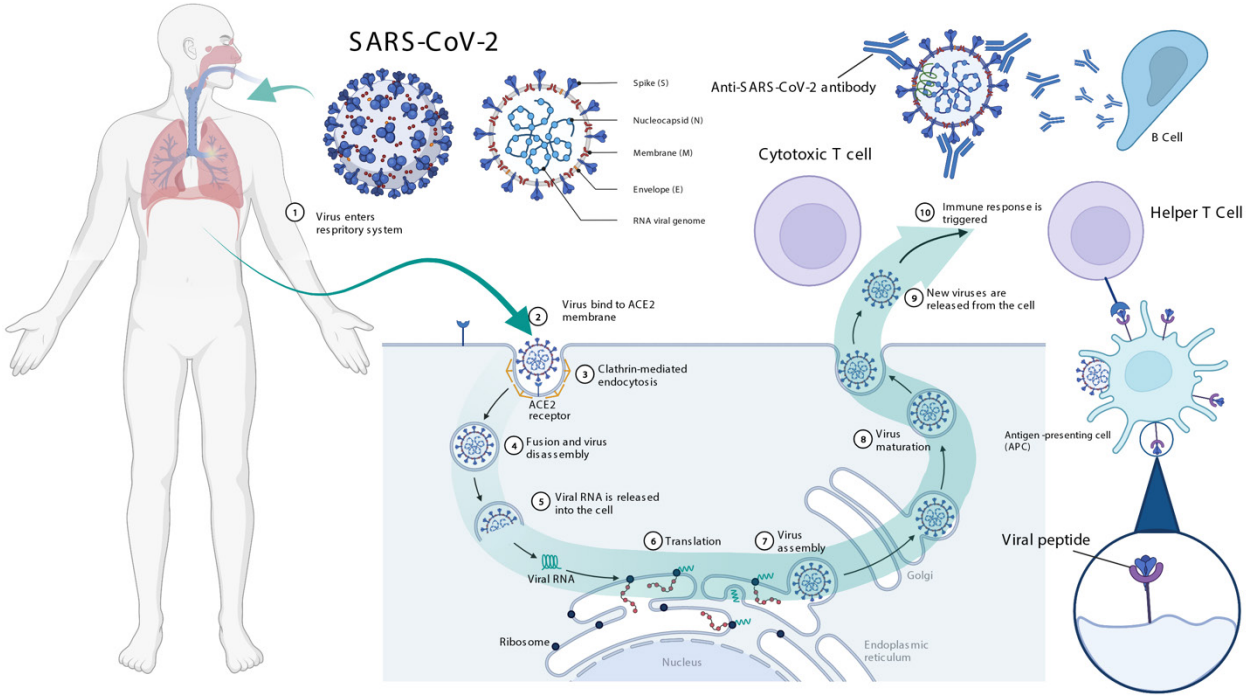

Figure 1. Defining features of SARS-CoV-2. Spike proteins penetrate host cells and coat the outer covering of the SARS-CoV-2 virus. Nucleocapsid proteins encapsulate the viral genome and are the most abundant protein in SARS-CoV-2 molecules. The virus enters the body through the respiratory system and infects host cells. Infected cells begin producing copies of the virus until the immune system recognizes viral proteins and destroys infected cells. Diagram created on BioRender.

Built to overcome such issues with temporal optimization, antibody tests, such as IgM and IgG tests, identify the presence of the body's response to the antigen proteins, namely the nucleocapsid (N) and spike (S) proteins (Figure 1) [4]. However, antibody testing is used to determine whether a patient was previously infected with SARS-CoV-2 rather than identifying active infections. It is a useful test for medical screening rather than population testing [5]. An incorrect interpretation of antibody test results can lead to negligence in taking precautions to prevent the spread of SARS-CoV-2, escalating the infection rate in a population. Furthermore, antibody testing produces inconsistent results compared to the consistency of PCR techniques [3]. Another method of diagnosing COVID-19, antigen testing, can detect viral material in the acute phases of infection using various specimens, including the commonly utilized naso-pharyngeal swab. Antigen testing relies on immunoassays, such as lateral flow rapid diagnostic tests, and is often less sensitive than molecular methods like PCR. These assays require larger amounts of viral material. Additionally, the probability of successfully identifying the virus dramatically decreases after the two weeks of a symptomatic patient's infection [6]. Here, we propose a novel method of diagnosing COVID-19 by using a nanophotonic ring resonator biosensor to identify the immune complex formed by the Sotrovimab antibody, which is an FDA emergency use authorized monoclonal antibody that binds to the SARS-CoV-2 spike protein [7]. Ring resonators are photonic sensors that use recirculating light confined within a microcavity that can detect the changes in surrounding environments. We evaluate the proposed biosensor's performance numerically, exhibiting a quality factor of 762 in water. The bulk refractive index sensitivity of the devices is 29 nm/RIU (for TM polarization), with a detection limit of 6.89×10^{-5}

RIU. A surface functionalization protocol could be used to immobilize the Sotrovimab antibodies designed to capture the target protein (Figure 2). The differences in the light spectrum obtained before and after target binding will be analyzed to determine whether the patient tested positive for SARS-CoV-2 (Figure 2). It is expected that the proposed sensor will be tested experimentally soon to identify the COVID-19 virus in practical settings.

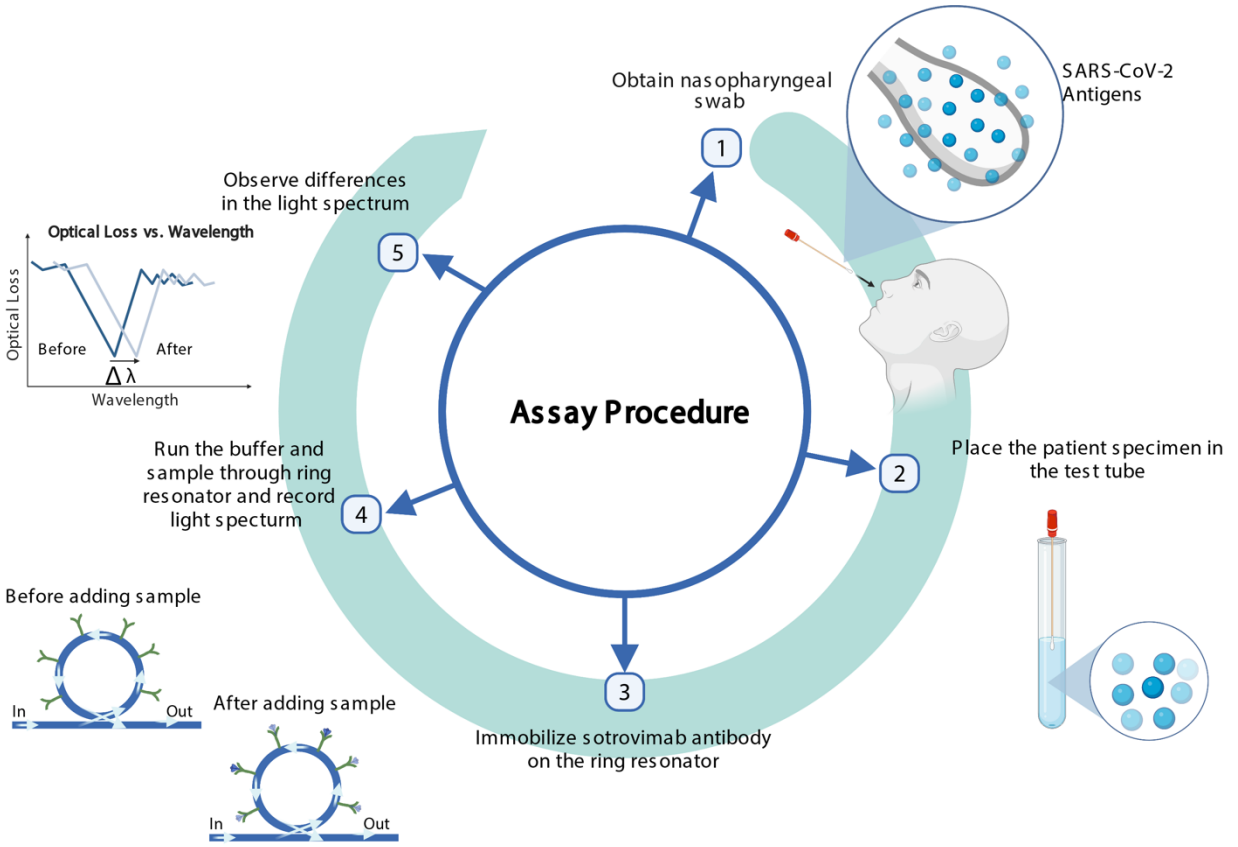

Figure 2. Proposed assay procedure. A 5-step process was designed for rapid, accurate diagnostic testing of SARS-CoV-2. The ring resonator was built to recognize the immune complex composed of the Sotrovimab antibody bound to the SARS-CoV-2 spike protein. Diagram created on BioRender.

Methods

The optical ring resonator, which consists of a straight waveguide and a ring waveguide, is well-known for its ability to deliver rapid results using potentially label-free techniques [8]. After one full rotation, the light of the resonant wavelength is passed through the straight waveguide and propagates through the ring resonator, resulting in constructive interference [9]. When the optical length of the resonator is equal to an integer, the resonance condition is satisfied [10, 11].

Equation 1: Resonance wavelength.

$$\lambda_{res} = L n_{eff}/m$$

where n_{eff} is the refractive index of the mode and λ_{res} is resonance wavelength, and m is an integer. Altering the n_{eff}, in turn, modulates the free-space wavelength of the mode. Therefore, the presence of antigen-antibody complexes, as opposed to pure water alone, will alter the refractive index of the resonating mode. This change will be reflected in the output wavelengths. Since a shift will convey the presence of the bioparticles, thus indicating a positive COVID-19 diagnosis. In our study, all simulations were created and run using Lumerical MODE, the gold standard for simulating optoelectronic devices (Figure 3). After running several rounds of simulations with the proposed device, results were taken from the various monitors. We analyzed a broad range of n_{eff} corresponding to a series of scenarios from the pristine ring resonator to the ring resonator coated with SARS-CoV-2 protein layers.

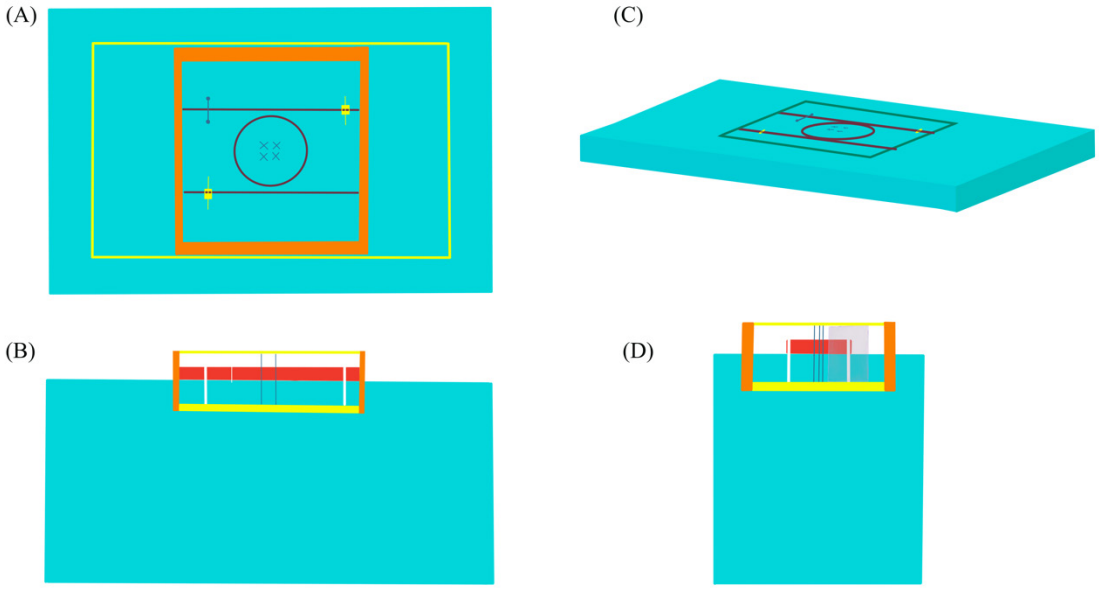

Figure 3. Ring resonator design. The ring resonator was designed and tested on Lumerical MODE, using the Finite-Difference Eigenmode (FDE) solver.

Results and Discussion

Photonic ring resonators have allowed the development of sophisticated and reliable biosensors capable of detecting ultra-low molecule concentrations. A minute difference in the refractive index can be detected by analyzing the shift of the resonance wavelength. To demonstrate this, we employ the finite-difference eigenmode (FDE) solver, which computes the spatial profile and frequency dependence of modes by solving Maxwell's equations on the device's cross-sectional mesh. We perform the simulations using the refractive indices 1.33, 1.39, 1.51, 1.57, and 1.63. We analyze the simulation data to determine the wavelength shift of a single resonant peak (Figure 4A). After running the simulation and increasing the mesh size for a more accurate result, we compare the result to the target curve generated by a refractive index set to water (Figure 4). The resonant peak displacement values are plotted against the refractive index change relative to distilled water in Figure 4B.

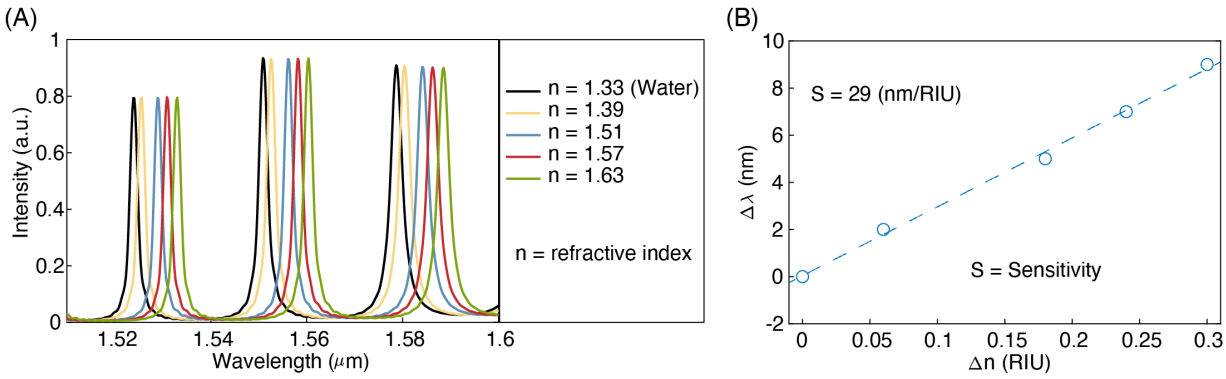

Figure 4. (A) The simulation results with distilled water and increasing refractive index values. After testing on Lumerical MODE, the results revealed that the device is capable of ultrasensitive detection of SARS-CoV-2. (B) The resonant wavelength shift is plotted against the corresponding change in refractive index with respect to distilled water.

Sensor performance is evaluated using three main factors: sensitivity, quality factor, and limit of detection [12]. These metrics indicate how effective the ring resonator is at sensing the COVID-19 spike protein. First, refractive index bulk sensitivity (S) depends on the extent of overlap of the evanescent field with the sample to be analyzed. In terms of sensitivity, improving the sensor performance requires distinguishing between waveguide sensitivity and ring resonator sensitivity. Waveguide sensitivity considers how changes in the cladding refractive index affect the effective refractive index and measures the interactions of guided light with the surrounding medium. Waveguide sensitivity can be given by the following equation:

Equation 2: Waveguide sensitivity.

$$S_{wg} = \frac{\Delta n_{eff}}{\Delta n_{cladd}}$$

where Δn_{eff} represents the change in the effective refractive index, and Δn_{cladd} stands for the change in the refractive index of the cladding solution. Unlike waveguide sensitivity, the ring resonator sensitivity depends on more than just the geometry of the waveguide and also takes into account the resonance wavelength shift. The following equation can give the ring resonator sensitivity:

Equation 3: Ring resonator sensitivity.

$$S_{rr} = \frac{\Delta \lambda}{\Delta n_{eff}}$$

where $\Delta \lambda$ is the full-width half maximum of the corresponding resonance in nanometers [12]. Taking both equations into account, the overall sensitivity of the photonic device can be defined by:

Equation 4: Overall refractive index sensitivity.

$$S = \frac{\Delta \lambda_{res}}{\Delta n_{cladd}}$$

The slope of the linear fit in Figure 4B determines the sensor's overall sensitivity to the refractive index, which is 29 nm/RIU. Second, the quality factor (Q) is the measure of photon lifetime in the waveguide ring resonators. The Q value is dimensionless and considers the intrinsic losses through processes including radiation, absorption, and scattering as well as coupling losses [13]. The quality factor of an optical ring resonator can be quantitatively described using the following formula:

Equation 5: Quality factor.

$$Q = \frac{\lambda res}{\Delta\lambda}$$

where λres is resonant wavelength and $\Delta\lambda$ is the full-width half maximum of the corresponding resonance (nm). This means that Q measures the sharpness of resonance relative to the central wavelength. A higher value of Q means that the minimal detectable wavelength shift is greater, reducing the spectral noise of the sensor and therefore enhancing the sensing performance. Our calculated quality factor was 762 in water. Finally, a system's limit of detection is the maximum refractive index change needed for the output signal to have a detectable shift. However, this value depends on external factors that vary with experimental setup, so we calculated intrinsic limit of detection (iLOD) instead [12]. iLOD depends only on the intrinsic resonator properties like resonant wavelength, sensitivity, and quality factor. The equation is as follows:

Equation 6: Intrinsic level of detection.

$$iLOD = \frac{\lambda res}{QS}$$

where Q is quality factor, and S is overall refractive index sensitivity. Our calculated iLOD is 6.89 $\times 10^{-5}$ RIU.

Conclusion and Future Studies

We proposed a nanophotonic-based biosensor for detecting SARS-CoV-2. Recent research has confirmed the potential of using nanophotonic biosensors in clinical settings, particularly for improving diagnostic and laboratory testing performance and proficiency. These sensors can detect biomarkers on a nanometer scale while maintaining the high sensitivity levels that other tests currently provide. Because of their adaptability in detecting a wide range of target analytes, such as antibodies in serum, DNA and RNA fragments, and entire virus proteins, nanophotonic biosensors show promise in the diagnosis of respiratory viruses (such as SARS-CoV-2). However, before full-scale commercialization of nanophotonic biosensors can begin, much more research must be conducted, including extensive clinical testing and the development of smaller and more affordable equipment, which is expected to soon replace the current laboratory prototypes. The COVID-19 pandemic has only recently urged a push toward research in this field by demonstrating the shortcomings of current diagnostic techniques, but the newly gained momentum is expected to last until the successful introduction of nanophotonic biosensors to the market [9].

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