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Highly sensitive biosensing through Silicon Photonics: Ring resonators for early detection of viral infections

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Department of Electrical and Information Engineering
ELECTRICAL AND INFORMATION ENGINEERING

Ph.D. Program

SSD: IINF-01/A–Electronics

Final Dissertation

Highly sensitive biosensing through Silicon Photonics: Ring Resonators for early detection of viral infections

by

Annabella la Grasta

Supervisors:

Prof. Vittorio M.N. Passaro

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Al Magnifico Rettore
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**BIOSENSING ALTAMENTE SENSIBILE ATTRAVERSO LA FOTONICA DEL SILICIO: RISONATORI AD ANELLO
PER IL RILEVAMENTO PRECOCE DELLE INFEZIONI VIRALI.**

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Abstract

The doctoral thesis investigates the significant advancements in ring resonator-based devices for biosensing applications, with a particular focus on silicon and silicon nitride platforms. The research is organized in four chapters, each examining the potential and efficacy of this technology, thereby providing valuable insights into its practical applications within the biosensing domain.

The first chapter offers a comprehensive overview of biosensors, highlighting the working principle of ring resonators. It emphasizes the critical importance of functionalization techniques that enhance the sensitivity and specificity of these devices, supported by case studies of established companies such as SiPhox and Genalyte, which have successfully commercialized ring resonator-based biosensing technologies.

The second chapter focuses on the fabrication and characterization of ring resonators developed using Silicon-on-Insulator (SOI) technology at SiPhotonIC in Copenhagen, Denmark. Four distinct configurations—namely, single ring, slotted ring, panda ring, and ring with “S” junction—are explored, with performance evaluated through bulk sensitivity experiments measured in terms of figure-of-merit. The findings reveal that the slotted ring configuration exhibits superior sensitivity, which is crucial for future biosensing applications.

In the third chapter, the focus shifts to silicon nitride ring resonators fabricated at the Nanophotonic Technology Center (NTC), Polytechnic University of Valencia, Spain. This chapter examines two configurations of ring resonators obtained with strip and slot waveguides, employing bulk sensitivity measurements with progressively concentrated ethanol solutions, alongside surface sensitivity experiments involving the BSA-antiBSA pair. Preliminary results suggest the ring resonator with slot waveguides as the well-suited for subsequent applications in viral detection.

The fourth chapter summarizes the practical implementation of the most promising resonator configuration for the detection of viruses, specifically SARS-CoV-2. It compares the detection capabilities of its spike protein through two functionalization methods: *in-situ* and with the employment of a microprinter. The experimental results yield estimations of the limit-of-detection, affirming the potential of the developed

platform in addressing critical public health challenges. These results not only highlight the efficacy of the ring resonator design in achieving high sensitivity but also demonstrate its applicability in rapid diagnostics, which is particularly vital in the context of global health crises.

In conclusion, the thesis establishes a foundational understanding of ring resonators as powerful biosensing tools on silicon and silicon nitride platforms. The comparative analyses across various configurations, combined with practical testing for viral detection, affirm the versatility and effectiveness of these devices in real-world applications. The insights gained from this research lay the groundwork for future innovations in biosensing technology, potentially leading to the development of more sensitive, specific, and rapid diagnostic tools. Further exploration is justified to optimize fabrication processes and functionalization strategies, as well as to expand applications beyond viral detection to encompass a broader range of biomarkers, significantly enhancing the impact of ring resonators in clinical and environmental monitoring.

CHAPTER 1

Optical Ring Resonator-based Biosensors: principle, uses, and comparison with competitive methods

Fundamentals of Biosensors

A biosensor is a device that, according to the International Union of Pure and Applied Chemistry (IUPAC) definition, generates signals that are proportional to the concentration of an analyte in the reaction, thereby measuring biological or chemical reactions [1]. Disease monitoring, drug discovery, and the detection of contaminants, disease-causing microorganisms, and disease markers in physiological fluids (blood, urine, saliva, perspiration) are among the applications in which biosensors are employed [2].

The components of a typical biosensor are provided below [3]:

- The biological material to be detected is referred to as the **analyte**.
- A **bioreceptor** is a molecule that is capable of recognising the analyte with high precision. Bioreceptors include enzymes, cells, aptamers, deoxyribonucleic acid (DNA), and antibodies. “Bio-recognition” is the term used to describe the process of signal generation (in the form of light, heat, pH, charge or mass change, etc.), that occurs when the bioreceptor interacts with the analyte.
- A **transducer** is an element that converts one form of energy into another. In a biosensor, the transducer's function is to convert the bio-recognition event into a measurable signal. “Signalisation” is the term used to describe this process of energy conversion. Optical or electrical signals are typically generated by the majority of transducers, and their intensity is generally proportional to the number of interactions between analytes and bioreceptors.
- The **electronics** of a biosensor is responsible for processing the transduced signal and preparing it for display. It is composed of an intricate electronic circuitry that performs signal conditioning, including the amplification and the conversion of signals from analogue to digital format. Next, the biosensor's display instrument quantifies the processed signals.

- **Display**, which is a user-interpretation system that generates numbers or curves that are comprehensible to the user, such as the liquid crystal display of a computer or a direct printer. This component is frequently produced through the integration of hardware and software, which generates biosensor results in an easy-to-use way. Depending on the end user's needs, the display can output a numeric, graphic, tabular, or image signal.

To develop a highly effective and capable biosensor system, certain static and dynamic requirements are necessary [3][4]. Based on these specifications, the performance of the biosensors can be optimized for commercial uses [5][6].

- (a) **Selectivity**: ability to accurately identify and measure the target analyte without being influenced by other non-target substances that might be present in the sample. A highly selective biosensor can minimize the occurrence of false positives, which are erroneous indications that the target analyte is present when it is not.
- (b) **Sensitivity**: ability to dependably and measurably identify the minimum amount of analyte in a minimum number of steps and in low concentrations.
- (c) **Linearity**: attribute that shows the accuracy of the measured response (for a set of measurements with different concentrations of the analyte) to a straight line, mathematically represented as $y = mc$, where c is the concentration of the analyte, y is the output signal, and m the sensitivity of the biosensor.
- (d) **Response time**: time required by the biosensor to obtain the output signal after being exposed to a change in the analyte concentration; this is often quoted as T_{90} , which is the time required for the signal to reach 90% of its final value.
- (e) **Reproducibility**: ability to produce identical responses upon repeated measurement of the same sample. It is characterized by the precision and the accuracy of the transducer. In particular, precision is the ability to provide alike results every time a sample is measured, and accuracy indicates the capability to provide a mean value close to the true value when a sample is measured more than once.

- (f) **Stability:** degree of susceptibility to environmental disturbances inside and outside the biosensing system. The factors that affect stability are the affinity of the bioreceptor, namely is the degree to which the analyte binds to the bioreceptor, and the degradation of the bioreceptor over a period of time.

A biosensor can be classified as piezoelectric, calorimetric, thermoelectric, pyroelectric, magnetic, electronic, optical, or electrochemical, depending on the transducer used [7][8]. In particular, optical biosensors have provided a significant advantage in the fields of biotechnology, environmental studies, disease diagnosis, and medical applications [9][10].

Optical Biosensors

One of the primary benefits of optical biosensors is their high sensitivity and specificity. These sensors can detect minute changes in the refractive index, allowing for the identification of very low concentrations of analytes. This capability is further enhanced by functionalizing the sensor surface with specific bioreceptors, which ensures that the sensor is highly selective for the target biomolecules. The rapid response time of optical biosensors is another significant advantage. They provide real-time monitoring, which is crucial for dynamic biological processes and clinical diagnostics where timely results are essential.

A key feature of many optical biosensors is their ability to perform label-free detection. Unlike traditional methods that require fluorescent or colorimetric labels, optical biosensors can operate without these markers, simplifying the detection process and reducing costs. Additionally, the miniaturization and portability of optical biosensors make them suitable for on-site and point-of-care testing. Compact and portable designs allow for convenient and efficient monitoring outside of traditional laboratory settings.

Optical biosensors also excel in multiplexing capabilities, where multiple analytes can be detected simultaneously. This enhances the efficiency of assays and allows for comprehensive analysis within a single test.

Based on the design aspects and the transducers, optical biosensors can be classified in different ways [9].

An optical fiber biosensor consists of a fiber acting as sensing element, where the biosensing element is immobilized on the core to react with the analyte. Ring resonators (RRs) consist of one or more closed loop waveguides where the light traveling through the ring gets coupled to it at specific wavelengths; any binding event on the resonator's surface changes the refractive index, causing a detectable shift in the resonant wavelength. Interferometric biosensors rely on the interference experienced by two light beams traveling along similar paths, such as the reference and the sensing arms; the biomolecular binding in the sensing arm causes phase shifts that alter the interference pattern upon recombination. Mach–Zehnder Interferometers, Sagnac-interferometers, bimodal waveguide (BiMW) and Fabry–Perot interferometers are some of the most widely used optical interferometer biosensors. Photonic Crystal (PhC) devices consist of one or more spatially arranged dielectric materials, which are repeated periodically with a period in the range of the photon wavelength. PhC devices can be categorized as one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) depending on the number of directions with a periodic repetition. Fluorescence/luminescence biosensors are characterized by the presence of photodiodes or photomultipliers to detect light from a fluorescence/luminescence process. In particular, fluorescence biosensors rely on the emission of light caused by the excitation of a substance, namely the fluorophore, which can be correlated to the presence and concentration of a target analyte. Unlike fluorescence, luminescence biosensors do not require an external light source for excitation, but detect light emitted as a result of a chemical (chemiluminescence) or biological (bioluminescence) reaction. Surface Plasmon Resonance (SPR) biosensors use the phenomenon arising from light and free electron interaction in a metal-dielectric interface. Under certain conditions, the surface electron oscillation resonates with the incident electromagnetic field and, as a result, photon loses a significant amount of its energy. This energy transfer takes place at a specific resonance wavelength of light, and the momentum of surface plasmon and the photon also must match. The coupling between the incident light and plasmons is highly sensitive to the refractive index immediate to the metal surface. A change in this refractive index in return shifts the resonant angle of the light, the resonant wavelength or other characteristics of the incident light.

Ring Resonator Technology

Recent developments in optical biosensors based on integrated photonic devices are reviewed with a special emphasis on ring resonator (RR) technology [11][12]. In general, these devices consist of an optical silicon-based waveguide on top of a buried oxide substrate, which is looped back on itself and uses the principle of resonance to selectively filter light at specific wavelengths. A ring resonator as a stand-alone device only becomes useful when there is a coupling to the outside world. The most common coupling mechanism is the **codirectional evanescent coupling** between the ring and an adjacent bus waveguide. In such a condition, the ring is on resonance when the phase ϕ is a multiple of 2π , or when the wavelength of the light fits a whole number of times inside the optical length of the ring [13][14]:

$$\lambda_{res} = \frac{n_{eff}L}{m}, \quad m = 1, 2, 3, .. \quad (1.1)$$

where n_{eff} is the effective index, L is the length of the round trip, and m is the order of the resonant mode.

All-pass Ring Resonator

In its simplest form a ring resonator can be built by feeding one output of a directional coupler back into its input, obtaining the so-called all-pass filter (APF) or notch filter configuration (see Fig. 1.1). The term ring resonator is typically used to indicate any looped resonator, but in the narrow sense it is a circular ring. When the shape is elongated with a straight section along one direction (typically along the coupling section), the term racetrack resonator is also used [15][16][17].

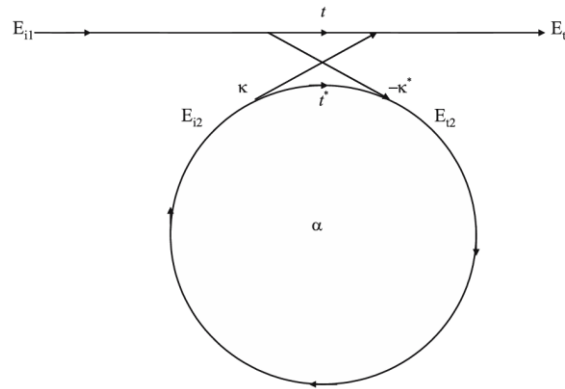


Figure 1.1: Model of an all-pass ring resonator

The basic relations between the incident and transmitted fields (E_{i1} and E_{t1}), and the circulating fields in the ring (E_{i2} and E_{t2}) can be derived by considering the following unitary matrix:

$$\begin{pmatrix} E_{t1} \\ E_{t2} \end{pmatrix} = \begin{pmatrix} t & k \\ -k^* & t^* \end{pmatrix} \begin{pmatrix} E_{i1} \\ E_{i2} \end{pmatrix} \quad (1.2)$$

which can be solved as follows:

$$\begin{aligned} E_{t1} &= tE_{i1} + kE_{i2} \\ E_{t2} &= -k^*E_{i1} + t^*E_{i2} \end{aligned} \quad (1.3)$$

where t and k are the self- and cross-coupling coefficients respectively, and they are assumed to satisfy the relation $tt^* + kk^* = 1$ or $|t|^2 + |k|^2 = 1$, since the $*$ denotes the conjugated complex value of t and k .

To further simplify the model, E_{i1} is chosen to be equal to 1. Then, the round trip in the ring is given by:

$$E_{i2} = ae^{j\theta} E_{t2} \quad (1.4)$$

where a is the loss coefficient of the ring (zero loss: $a = 1$) and $\theta = \omega L/c$, being $L = 2\pi r$ the circumference of the ring, with r the radius measured from the centre of the ring to the centre of the waveguide, $c = c_0/n_{eff}$ the phase velocity of the ring mode, and $\omega = kc_0$ the fixed angular velocity; c_0 refers to the vacuum speed of light. The vacuum wavenumber k is related to the wavelength λ through the relation $k = 2\pi/\lambda$; using this parameter, it is possible to easily introduce the effective refractive index, n_{eff} , within the ring coupling relations by:

$$\beta = k \cdot n_{eff} = \frac{2\pi n_{eff}}{\lambda} \quad (1.5)$$

where β is the propagation constant of the circulating mode. This leads to:

$$\theta = \frac{\omega L}{c} = \frac{kc_0 L}{c} = \frac{kc n_{eff} 2\pi r}{c} = k n_{eff} 2\pi r = \frac{2\pi n_{eff} \cdot 2\pi r}{\lambda} = 4\pi^2 n_{eff} \cdot \frac{r}{\lambda} \quad (1.6)$$

Considering Eq. (1.3) and Eq. (1.4), it is possible to obtain:

$$E_{t1} = t + k e^{j\theta} E_{t2} \quad (1.7)$$

$$\begin{aligned} E_{t2} &= -k^* + t^* a e^{j\theta} E_{t2} \rightarrow E_{t2} - t^* a e^{j\theta} E_{t2} = -k^* \\ \rightarrow E_{t2} (1 - t^* a e^{j\theta}) &= -k^* \rightarrow E_{t2} = -\frac{k^*}{1 - a t^* e^{j\theta}} \end{aligned} \quad (1.8)$$

Substituting Eq. (1.8) in Eq. (1.7), E_{t1} becomes:

$$\begin{aligned} E_{t1} &= t + k a e^{j\theta} \left(-\frac{k^*}{1 - a t^* e^{j\theta}} \right) \\ &= \frac{t(1 - a t^* e^{j\theta}) - k k^* a e^{j\theta}}{1 - a t^* e^{j\theta}} = \frac{t - a t t^* e^{j\theta} - a k k^* e^{j\theta}}{1 - a t^* e^{j\theta}} \\ &= \frac{t - a e^{j\theta} (t t^* + k k^*)}{1 - a t^* e^{j\theta}} = \frac{e^{j\theta}}{e^{j\theta}} \cdot \frac{\left(-a + \frac{t}{e^{j\theta}} \right)}{\left(-a t^* + \frac{1}{e^{j\theta}} \right)} \\ \rightarrow E_{t1} &= \frac{-a + \frac{t}{e^{j\theta}}}{-a t^* + \frac{1}{e^{j\theta}}} \end{aligned} \quad (1.9)$$

Substituting Eq. (1.8) in Eq. (1.4):

$$\begin{aligned} E_{i2} &= a e^{j\theta} \left(-\frac{k^*}{1 - a t^* e^{j\theta}} \right) = \frac{\frac{1}{e^{j\theta}}}{\frac{1}{e^{j\theta}}} \cdot \frac{-a k^* e^{j\theta}}{1 - a t^* e^{j\theta}} = -\frac{a k^*}{\frac{1}{e^{j\theta}} - a t^*} \\ \rightarrow E_{i2} &= -\frac{a k^*}{e^{-j\theta} - a t^*} \end{aligned} \quad (1.10)$$

Assuming $t = |t|e^{-j\varphi}$ and $t^* = |t|e^{j\varphi}$, it is possible to derive the expression of the transmission power, P_{t1} , in the output waveguide:

$$P_{t1} = \left| \frac{-a + |t|e^{-j(\theta+\varphi)}}{-a|t|e^{j\varphi} + e^{-j\theta}} \right|^2 = \left| \frac{-a + |t| \cos(\theta + \varphi) - j|t| \sin(\theta + \varphi)}{-a|t| \cos(\varphi) - ja|t| \sin(\varphi) + \cos(\theta) - j \sin(\theta)} \right|^2$$

$$\begin{aligned}
&= \frac{a^2|t|^2 \cos^2(\theta + \varphi) - 2a|t| \cos(\theta + \varphi) + |t|^2 \sin^2(\theta + \varphi)}{a^2|t|^2 \cos^2(\varphi) + \cos^2(\theta) - 2a|t| \cos(\varphi) \cos(\theta) + a^2|t|^2 \sin^2(\varphi) + \sin^2(\theta) + 2a|t| \sin(\varphi) \sin(\theta)} \\
&\rightarrow P_{t1} = \frac{a^2 + |t|^2 - 2a|t| \cos(\theta + \varphi)}{a + a^2|t|^2 - 2a|t| \cos(\theta + \varphi)} \quad (1.11)
\end{aligned}$$

where $|t|$ represents the coupling losses and φ the phase of the coupler.

Similarly, following the same calculations, it is possible to obtain the circulating power, P_{i2} , in the ring:

$$P_{i2} = |E_{i2}|^2 = \frac{a^2(1 - |t|^2)}{1 + a^2|t|^2 - 2a|t| \cos(\theta + \varphi)} \quad (1.12)$$

Eq. (1.11) and Eq. (1.12) can be generalized by using the resonance condition, remembering that this requires that the total phase shift is a multiple of 2π . Since on resonance $(\theta + \varphi) = 2\pi m$, the following is achieved:

$$P_{t1} = |E_{t1}|^2 = \frac{(\alpha - |t|)^2}{(1 - \alpha|t|)^2} \quad (1.13)$$

$$P_{i2} = |E_{i2}|^2 = \frac{\alpha^2(1 - |t|^2)}{(1 - \alpha|t|)^2} \quad (1.14)$$

In using the above equations, it is possible to get a good idea of the behaviour of an all-pass filter, shown in Fig.1.2.

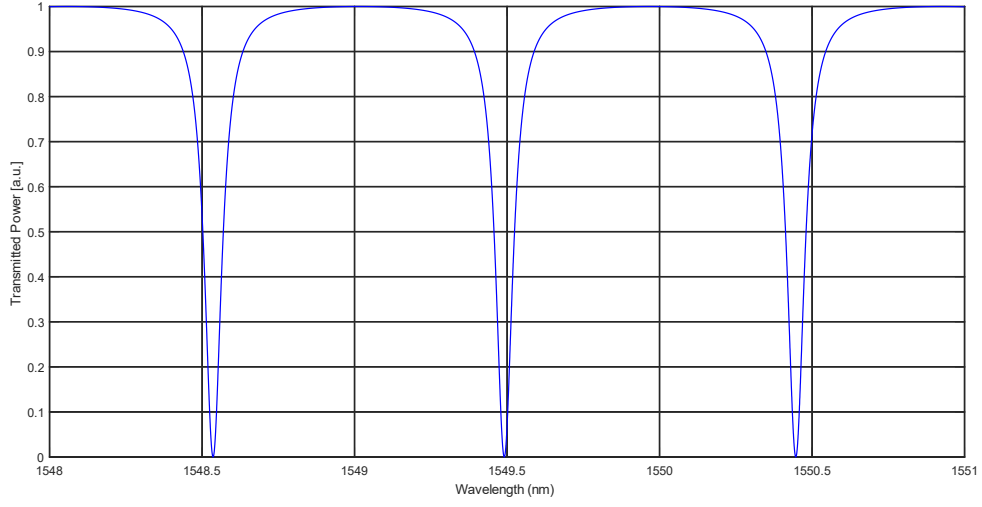


Figure 1.2: *Transmission diagram of the all-pass filter*

A special case happens when $a = |t|$ in Eq. (1.13), that is when the internal losses are equal to the coupling losses, causing that the transmitted power is equal to zero. This is known in literature as **critical coupling**, which is due to destructive interference.

Add-drop Ring Resonator

In the add-drop ring resonator, the incident field is partly transmitted to the drop port and partly transmitted to the throughput port.

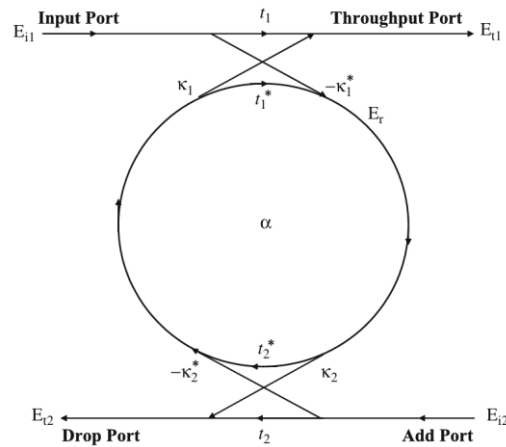


Figure 1.3: *Model of an add-drop ring resonator*

The ring resonator simulation model is updated according to Fig. 1.3; the throughput mode amplitude in the first waveguide is given by:

$$E_{t1} = \frac{t_1 - t_2^* a e^{j\theta}}{1 - t_1^* t_2^* a e^{j\theta}} \quad (1.15)$$

As shown in the schematic, the mode amplitude in the ring must pass the second coupler to become the new dropped mode amplitude, E_{t2} . The dropped mode amplitude in the second waveguide is then given by:

$$E_{t2} = \frac{-\kappa_1^* \kappa_2 \sqrt{a} e^{j\theta/2}}{1 - t_1^* t_2^* a e^{j\theta}} \quad (1.16)$$

At resonance, the output power from the drop port is derived as follows:

$$P_{t2-Resonance} = |E_{t2-Resonance}|^2 = \frac{(1 - |t_1|^2) \cdot (1 - |t_2|^2) \cdot a}{(1 - a|t_1 t_2|)^2} \quad (1.17)$$

The throughput port mode amplitude E_{t1} in Eq. (1.15) will be zero at resonance for identical symmetrical couplers ($t_1 = t_2$) if $a = 1$, which indicates that the wavelength on resonance is fully extracted by the resonator. The value of $a = 1$ can only be achieved by the implementation of gain incorporated in the ring resonator to compensate the waveguide losses.

A possibility of achieving minimum intensity ($P_{t1} = 0$) at resonance of the output transmission at the throughput port is to adjust the coupling parameters t_1, t_2 to the loss coefficient a , which is:

$$a = \left| \frac{t_1}{t_2} \right| \quad (1.18)$$

If the ring is lossless ($a = 1$), then the couplers must be symmetric in order to achieve minimum intensity. The transmission of a lossless add-drop ring resonator is shown in the figure above (Fig. 1.4):

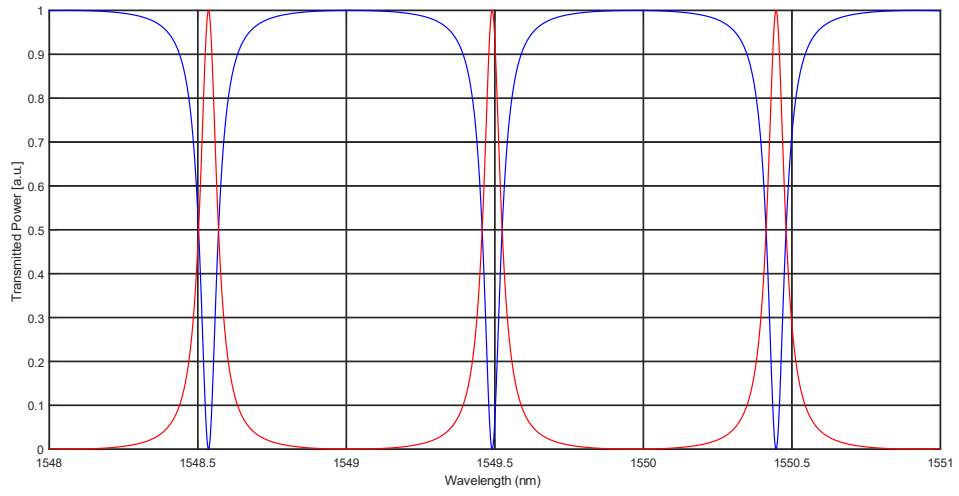


Figure 1.4: *Transmission diagram of the add-drop filter*

Serially Coupled and Parallel Coupled Ring Resonators

The basic configurations previously described are the building block of complex systems such as serially coupled configuration and parallel coupled configuration (see Fig. 1.5).

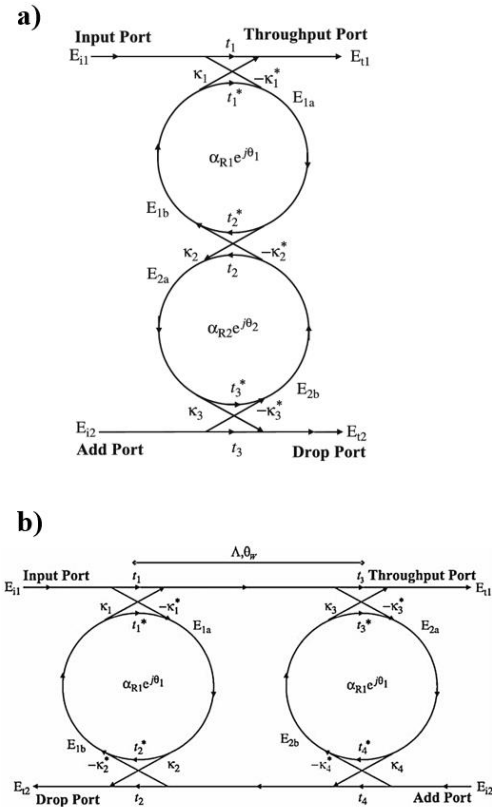


Figure 1.5: *a) serially coupled configuration and b) parallel coupled configuration.*

In the serially coupled configuration, each ring resonator is coupled to one another so that the signal is dropped from the input port to the drop port, passing sequentially through each resonator (Fig. 1.5a). This configuration is characterized by sequential power transfer and, consequently, all resonators must be precisely resonant at a common wavelength. The resulting resonant line shape in the series configuration is therefore physically determined by the separation between the ring resonators. In this case, the FSR of the double ring resonators coupled in series with two different radii is expressed as:

$$FSR = m_1 FSR_1 = m_2 FSR_2 \quad (1.19)$$

which leads to

$$FSR = (|m_2 - m_1|) \left(\frac{FSR_1 FSR_2}{|FSR_1 - FSR_2|} \right) \quad (1.20)$$

where m_1 and m_2 are coprime numbers. As a consequence, the FSR is significantly larger than the FSR of a single ring resonator. Therefore, it is also called extended FSR and the underlying effect is called **Vernier effect**. The Vernier effect causes the transmission peaks of the ring resonators within the overall obtained FSR to be suppressed, which results in the larger FSR than would be achieved for a single ring resonator. A figure-of-merit that is used to estimate the performance of a Vernier-based ring resonator is the Vernier gain:

$$G = \frac{FSR_1}{|FSR_1 - FSR_2|} \quad (1.21)$$

Silicon photonic sensors based on the Vernier effect have shown an enhanced sensitivity compared to single ring resonators [18]. However, it should be noticed that the design of Vernier-based ring resonators is challenging because the position of the resonances drastically depends on the fabrication tolerances [19].

In the parallel-coupled configuration, instead, all resonators are coupled to both the input and drop port waveguides, without the requirement that must be coupled directly to one another (Fig. 1.5b). An optical signal in the parallel configuration passes through all ring resonators simultaneously. The resonators are indirectly coupled to each other by the

optical path lengths along the input and output waveguides that interconnect the ring resonators, and these lengths determine the resonant line shapes. The overall FSR can be increased by adjusting the length of the waveguide joining the two ring resonators. It is worth mentioning that the parallel configuration can be treated as a grating. In this case, constructive interference of the reflected waves from each ring resonator is obtained by choosing the length Λ to be equal to an odd multiple of a quarter wavelength:

$$\Lambda = (2m + 1) \left(\frac{\lambda_0}{4n_{w_{eff}}} \right) \quad (1.22)$$

where λ_0 is the central wavelength of the passband and $n_{w_{eff}}$ is the effective refractive index of the input waveguide. If the length Λ is chosen such that the FSR of the ring resonators and the FSR of the “grating” obey the following condition $FSR = N_{ring}FSR_{ring} = M_{grating}FSR_{grating}$, the distance between the resonators can be calculated as:

$$\Lambda = \frac{M_{grating}n_{eff}}{N_{ring}n_{w_{eff}}} \pi r \quad (1.23)$$

The parallel configuration has less restrictive requirements because it is not mandatory that each RR resonances have to be precisely identical. In case of nonaligned resonant frequencies, multiple peaks, or ripple in the line shape occur.

Metrics for Ring Resonators

Ring resonator filters can be described by certain figures-of-merit which are also generally used to describe optical filters [20]. An important parameter is represented by the distance between resonance peaks, which is called the **free spectral range (FSR)**. A simple approximation can be obtained for the FSR by using the propagation constant from Eq. (1.5), neglecting the wavelength dependency of the effective refractive index:

$$\frac{\partial \beta}{\partial \lambda} = -\frac{\beta}{\lambda} + k \frac{\partial n_{eff}}{\partial \lambda} \approx -\frac{\beta}{\lambda} \quad (1.24)$$

This leads to the FSR , which is the difference between the vacuum wavelengths corresponding to two resonant conditions:

$$FSR = -\frac{2\pi}{L} \left(\frac{\partial \beta}{\partial \lambda} \right)^{-1} \approx \frac{\lambda^2}{n_{eff} L} \quad (1.25)$$

Note that Eq. (1.25) is for the resonant condition next to a resonance found for the used propagation constant. If the wavelength dependence of the effective index cannot be neglected, it can be incorporated in the following way to obtain a modified version of Eq. (1.24):

$$\frac{\partial \beta}{\partial \lambda} = -\frac{k}{\lambda} n_g \quad (1.26)$$

where n_g is the group refractive index, which is defined as:

$$n_g = n_{eff} - \lambda \frac{\partial n_{eff}}{\partial \lambda} \quad (1.27)$$

The group refractive index can be used instead of the effective index whenever appropriate avoiding the approximation and obtaining more accurate values. The modified FSR is then given by:

$$FSR = \Delta \lambda = \frac{\lambda^2}{n_g L} \quad (1.28)$$

The next parameter of importance is the resonance width which is defined as the **full width at half maximum (FWHM)** or 3-dB bandwidth $2\delta\lambda$ of the resonance line shape. Using Eq. (1.16) and Eq. (1.17) for the drop port:

$$\left| \frac{-\kappa_1^* \kappa_2 \alpha_{1/2} e^{j\theta_{1/2}}}{1 - t_1^* t_2^* \alpha e^{j\theta}} \right|^2 = \frac{1}{2} \frac{|\kappa_1|^2 |\kappa_2|^2 \alpha}{(1 - \alpha |t_1 t_2|)^2} \quad (1.29)$$

and assuming that the coupling coefficients are real, lossless, and without a phase term, Eq. (1.29) can be written as:

$$\frac{(\kappa_1 \kappa_2 \alpha_{1/2})^2}{1 - 2t_1 t_2 \alpha \cos(\theta) + (t_1 t_2 \alpha)^2} = \frac{1 (\kappa_1 \kappa_2 \alpha_{1/2})^2}{2 (1 - t_1 t_2 \alpha)^2} \quad (1.30)$$

Then,

$$2(1 - t_1 t_2 \alpha)^2 = 1 - 2t_1 t_2 \alpha \cos(\theta) + (t_1 t_2 \alpha)^2 \quad (1.31)$$

For small values of θ , using the real part of the series expansion of the Euler formula:

$$\cos(\theta) = 1 - \frac{\theta^2}{2} \quad (1.32)$$

Therefore:

$$\theta^2 = \frac{(1 - t_1 t_2 \alpha)^2}{t_1 t_2 \alpha} \quad (1.33)$$

This equation can further be simplified if the loss in the ring is negligible, and the coupling is symmetric ($t = t_1 = t_2$) to:

$$\theta = \sqrt{\frac{(1 - t^2)^2}{t^2}} = \frac{1 - t^2}{t} \quad (1.34)$$

Using Eq. (1.6) and Eq. (1.24) to translate into the wavelength domain:

$$2\delta\lambda = \frac{\lambda^2}{\pi L n_{eff}} \frac{1 - t^2}{t} \quad (1.35)$$

The expression which is commonly used can be obtained by assuming weak coupling and $\lambda \gg \delta\lambda$:

$$FWHM = 2\delta\lambda = \frac{\kappa^2 \lambda^2}{\pi L n_{eff}} \quad (1.36)$$

Another parameter which can now be directly calculated is the **finesse** (**F**) defined as the ratio of the *FSR* and the *FWHM*, and if $\kappa \ll 1$, it can be written as:

$$F = \frac{FSR}{FWHM} = \frac{\Delta\lambda}{2\delta\lambda} = \pi \frac{t}{1-t^2} \approx \frac{\pi}{\kappa^2} \quad (1.37)$$

A parameter which is closely related to the finesse is the **quality factor** or **Q-factor** of a resonator, which is a measure of the sharpness of the resonance. It is defined as the ratio of the operation wavelength and the resonance width:

$$Q - factor = \frac{\lambda_{res}}{FWHM} = \pi \frac{n_{eff}L}{\lambda} \frac{t}{1-t^2} = \frac{n_{eff}L}{\lambda} F \quad (1.38)$$

The quality factor can also be regarded as the stored energy divided by the power lost per optical cycle.

Optimization of Ring Resonators for Biosensing

From a practical perspective, it is advantageous to differentiate between waveguide sensitivity and ring resonator sensitivity, since the total sensor performance may be enhanced by considering both factors.

Waveguide Sensitivity

In contrast to more traditional free-space optical sensors, and as it has been already introduced, integrated photonic sensors based on ring resonator technology use light that is confined inside an optical waveguide.

In general, three waveguide structures have been the subject of extensive research over the past two decades. The strip waveguide is the most prevalent variety, and it is typically distinguished by a rectangular shape with a height of 220 nm and a width that ranges from 450 nm to 500 nm. Sidewall irregularity is the primary source of optical losses. The loss is minimised when rib waveguides are employed, as illustrated in Fig. 1.6, whereas it increases as the exterior areas of waveguide structures increase. For instance, an optical loss of approximately 2 dB/cm is the result of light scattering at the sidewalls of a strip waveguide with a cross-section of 500 nm x 220 nm [21]. As a general rule, the optical losses decrease as the optical field confinement increases. Specifically, the optical losses decrease as the amount of light that is confined within the waveguide increases. The optical confinement is the percentage of light that is contained within the waveguide-core [22]. In order to represent the light within a particular area, such as a waveguide core, it

is convenient to calculate the cross-sectional power. The **Poynting vector**, which denotes the instantaneous power flow resulting from instantaneous electric and magnetic fields, can be employed to estimate it. Nevertheless, the time-averaged Poynting vector is employed when an electromagnetic wave is represented as sinusoidally varying fields at a specific frequency. The time-averaged complex Poynting vector is then integrated over the waveguide cross-section to express the cross-sectional power:

$$P = \iint \frac{1}{2} \text{Re} \{E \times H^*\} dx dy \quad (1.39)$$

where E and H are the electric and magnetic field vectors, respectively. Finally, the **field confinement factor**, also known as field interaction factor, is calculated as:

$$\Gamma = \frac{P_{core}}{P_{\infty}} \quad (1.40)$$

where P_{core} is the cross-sectional power inside the core, i.e. the optical power confined inside the core, and P_{∞} represents the complete power, that means the power over the entire cross-section [23].

In addition to the field confinement factor, the waveguide sensitivity also describes the interaction between the guided light and the surrounding medium, and it can be demonstrated that it could be enhanced by a higher field confinement within the cladding material, which is in fact the fluid [24][25]. The waveguide sensitivity is defined in a variety of ways, depending on the sensing mechanism, such as chemical bulk sensing or label-free surface sensing, as the effective refractive index reflects the light propagation inside the waveguide. In particular, it is evaluated according to the following principle:

$$S_{wg} = \frac{\Delta n_{eff}}{\Delta \xi} \quad (1.41)$$

where Δn_{eff} represents the effective refractive index change and $\Delta \xi$ represents either the change of the cladding refractive index n_{clad} in case of chemical bulk sensing or the thickness of the adhered layer or the mass density when label-free surface sensing is considered.

The waveguide sensitivity can be expressed in RIU/RIU, RIU/nm, or RIU (pg/mm²), as a result of the varying units of the sensing mechanism $\xi = \{n_{clad}, t, \rho\}$. RIU corresponds to the refractive index unit.

Optimising the waveguide sensitivity typically involves calculating the optical field distribution, through the use of the **finite-element method (FEM)**. In this scenario, the Helmholtz equation can be solved for various n_{clad} to determine the effective refractive index, n_{eff} . By plotting n_{eff} over n_{clad} , it is possible to determine S_{wg} by calculating the slope of this graph [26].

Slot waveguides or subwavelength gratings (SWG) are the waveguide structures that are most commonly used to improve S_{wg} [27][28]. Additionally, the light-analyte interaction is influenced by the polarisation of the guided modes and, for this reason, in some cases the use of the transverse-magnetic (TM) rather than transverse-electric (TE) could be useful to enhance the waveguide sensitivity [29]. In general, both fundamental modes—namely, the initial TE mode and the initial TM mode—may be implemented. The dominant transverse electric field component is parallel to the substrate in the fundamental TE mode, whereas the dominant transverse magnetic field component is parallel to the substrate in the fundamental TM mode.

Higher light-analyte interaction is demonstrated in the TM mode, but this is at the expense of optical losses. Moreover, the TE mode is the preferable option due to the fact that the majority of photonic devices, such as beam splitters, grating couplers, and spot-size converters, are optimised for it. This because it is frequently employed in telecommunications applications, which is a technological driver of photonic integrated circuits (PICs). The electric field intensity distributions of the TE mode and TM mode in rib, strip, and slot waveguides with water as the top cladding are illustrated in Table 1.1.

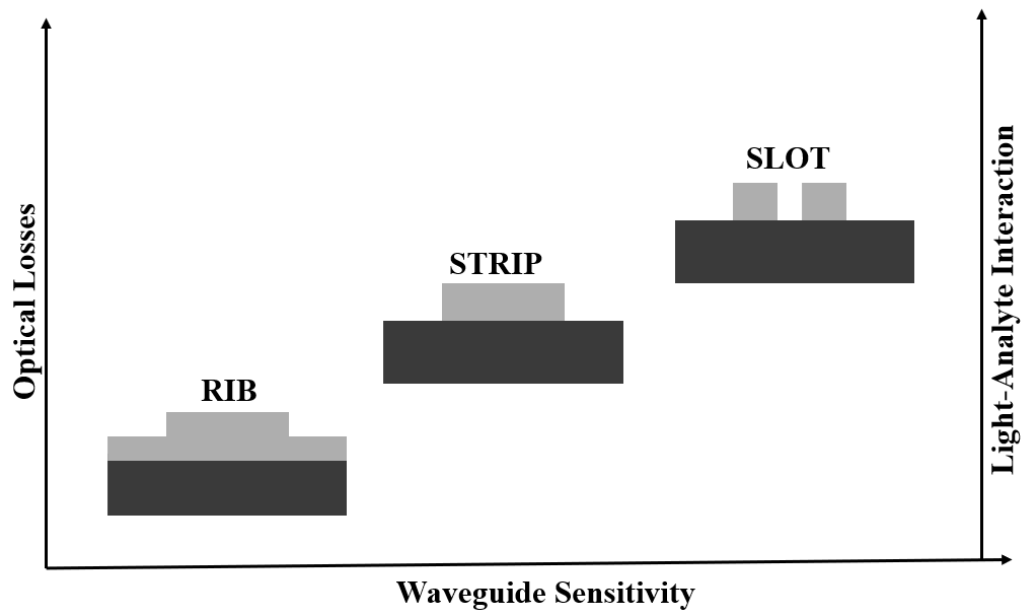


Figure 1.6: Commonly used waveguide geometries for optical biosensing: rib, strip, and slot waveguides. The waveguide sensitivity is enhanced by the increased light-analyte interaction; however, the optical loss is also increased.

Table 1.1: Electric field intensity distributions of the TE mode and TM mode in the case of rib, strip, and slot waveguides using water ($RI = 1.332$) as top cladding.

	TE mode	TM mode
Rib Waveguide		
Strip Waveguide		
Slot Waveguide		

Ring Resonator Sensitivity

The resonance wavelength shift can be calculated from resonator metrics, that is [30]:

$$\Delta\lambda_{res} = \frac{\lambda_{res}}{n_g} \Delta n_{clad} \quad (1.42)$$

where n_g is the group index, λ_{res} is the resonance wavelength and Δn_{clad} determines the refractive index change of the cladding material. The group index can be calculated by:

$$n_g = n_{eff} - \lambda \frac{\delta n_{eff}}{\delta \lambda} \quad (1.43)$$

Here, the effective refractive index of the optical waveguide is denoted as n_{eff} . The second term of Eq. (1.43) is referred to as dispersion of the group index. Assuming a small resonance wavelength shift and, hence, a flat dispersion, the group index can be approximated by:

$$n_g \approx n_{eff} = \frac{\lambda^2}{FSR L_{ring}} \quad (1.44)$$

where L_{ring} is the ring circumference and FSR is the free spectral range. From this formula it is apparent that the free spectral range has a quadratic dependency on the wavelength, i.e. $FSR \propto \lambda^2$.

However, the ring resonator sensitivity depends not only on the waveguide geometry and, therefore, another way to define the ring resonator sensitivity is given by:

$$S_{rr} = \frac{\Delta\lambda_{res}}{\Delta n_{eff}} \quad (1.45)$$

Overall Sensor Performance

Taken both definitions into account, the overall photonic device sensitivity can be defined by:

$$S = S_{wg} S_{rr} = \frac{\Delta n_{eff}}{\Delta \xi} \frac{\Delta\lambda_{res}}{\Delta n_{eff}} = \frac{\Delta\lambda_{res}}{\Delta \xi} \quad (1.46)$$

It is important to acknowledge that the binding of antigens to the functionalised waveguide surface induces a change in the cladding refractive index, n_{clad} . In this scenario, the **limit-of-detection (LoD)** is determined by considering the minimum detectable change in the cladding refractive index, which is directly proportional to the minimum detectable resonance wavelength shift, $\Delta\lambda_{min}$, that can be resolved by the characterization setup. The *LoD* can be obtained as follows:

$$LoD = \Delta\xi \quad (1.47)$$

Consequently, the *LoD* may be represented by three distinct units, contingent upon ξ . For chemical bulk sensing, a minimum change of the refractive index in the cladding ($\xi = \Delta n_{clad}$) is considered and the unit of measurement is RIU.

Label-free surface sensing considers the minimum change in the thickness of the adhere layer ($\xi = \Delta t$) or of the mass density ($\xi = \Delta\rho$), with the *LoD* unit being pg/mm². In addition, the *LoD* can be determined by dividing the minimum resonance wavelength shift, $\Delta\lambda_{min}$, by the sensitivity, S :

$$LoD = \frac{\Delta\lambda_{min}}{S} \quad (1.48)$$

The definition of an **intrinsic limit-of-detection (ILoD)** is required to obtain a metric what is not dependent on the characterization setup [31]. It can be acquired by setting the measurement resolution as full width at half maximum (*FWHM*) of the resonance peak, which results in:

$$ILoD = \frac{FWHM}{S} = \frac{\lambda_{res}}{Q - factor \cdot S} \quad (1.49)$$

When working with this type of device, it is crucial to consider several factors to enhance the overall performance. The waveguide sensitivity, S_{wg} , directly influences the wavelength shifts and considerably impacts the overall sensitivity, resulting in a proportional increase of the interaction between the light and the analyte. As a result, the attainment of high S_{wg} values is contingent upon the execution of precise preliminary simulation studies.

Additionally, utilizing the transverse-magnetic (TM) mode rather than the transverse-electric (TE) mode can further enhance waveguide sensitivity due to a greater field confinement within the aqueous solution. It is important to note that while an increase in waveguide sensitivity may improve the limit-of-detection (LoD), it must not lead to additional losses in the waveguide mode [32].

It is also crucial to improve the sensitivity of the ring resonator, S_{rr} , as it is responsible for determining the wavelength shift, $\Delta\lambda$, based on the effective refractive index, Δn_{eff} . This can be achieved by simulating the spectrum of the ring resonator at a variety of Δn_{eff} . Additionally, the Q-factor can be increased to reduce the influence of noise on the resonance wavelength determination [33][34]. In order to accomplish this, it is imperative to mitigate optical loss, which consequently decreases the width at half maximum. Reduced attenuation within the ring resonator is the consequence of a lower $FWHM$, which in turn minimises the smallest detectable wavelength shift, the intrinsic limit-of-detection ($ILoD$), and the limit of the detection (LoD).

Minimising the footprint by decreasing the circumference of the ring (L_{ring}) substantially decreases space use and device expenses, eventually enhancing integration density, which is especially advantageous for multiplexing applications. Furthermore, reduced ring radii enhance the free spectral range, which is beneficial for identifying big compounds (large biomolecules) that generate substantial resonance shifts. To ensure successful detection, the FSR must exceed $\Delta\lambda_{res}$, which can be accomplished by reducing the ring circumference, at the expense of the sensitivity and the limit-of-detection. For this reason, a compromise between sensitivity and free spectral range is necessary, which is heavily influenced by the application of interest.

Finally, the $ILoD$ can be improved by reducing optical loss, which is strongly dependent on the light wavelength; consequently, photonic biosensors should ideally operate in the visible spectrum, where water absorption is considerably lower compared to the infrared region [32].

Factors influencing Sensitivity and Limit-of-Detection

In the realm of ring resonators, sensitivity and limit-of-detection are key metrics that define their performance in sensing applications, and that could be influenced by different factors, including design parameters, materials used, and fabrication imperfections.

- Design parameters

The radius of the ring is one of the most critical geometric factors. A smaller radius allows for more effective light confinement within the ring, enhancing the interaction between the light and any substances in the vicinity of the resonator. This increased interaction improves the sensitivity of the device, enabling the detection of minute changes in refractive index caused by binding events.

From the *LoD* perspective, a smaller radius typically leads to a lower limit of detection, as the enhanced sensitivity allows for the identification of smaller concentrations of analytes. However, larger ring radii can reduce bending losses, which is particularly important for the integration with other optical components. Consequently, even if a larger radius may lead to lower sensitivity compared to a smaller radius, it could also enhance overall device stability and ease of integration. For the reasons above mentioned, there is often a trade-off that must be balanced based on specific application requirements.

The width of the waveguide is another significant factor to take into account. A narrower waveguide often provides better mode confinement, enhancing the resonator's sensitivity by allowing light to remain more localized, thus increasing the interaction with the sample analyzed. However, a very narrow waveguide may also introduce increased scattering losses, potentially reducing the overall performance.

The coupling region, where light enters and exits the ring, is a critical design aspect that affects performance. The efficiency of the coupling determines how well light can interact with the resonator. If the coupling is too weak, much of the light may not effectively interact with the sample, leading to lower sensitivity and, consequently, a higher limit of detection.

The shape of the ring can also impact performance. While circular rings are common, other shapes, such as elliptical or racetrack geometries, can offer different optical properties, affecting mode distribution and field intensity. Using multiple rings in a cascaded configuration can further increase the effective interaction length, providing a powerful method to enhance sensitivity and lower the *LoD*.

- Material used

The optical properties of the material used to fabricate ring resonators are crucial in determining their overall quality and performance. The refractive index of the material directly affects how well light is confined within the resonator. A high refractive index contrast between the resonator material and the surrounding medium enhances the confinement of light. This strong confinement results in lower propagation losses and a higher Q-factor, which is essential for achieving sharp and distinct resonance peaks. The refractive index also influences the mode propagation within the resonator. Thus, a higher refractive index ensures that the guided modes are well confined, reducing losses and maintaining the integrity of the resonant modes.

The material must be transparent at the operating wavelength to minimize absorption losses. High transparency ensures that most of the light remains within the resonator, contributing to a higher Q-factor. For example, silicon and silicon nitride are popular choice for visible and near-infrared applications due to their low absorption in that wavelength range. The absorption coefficient of the material should be low to avoid significant attenuation of the light signal. Lower absorption losses mean that the resonator can maintain its high Q-factor, which is crucial for applications requiring precise detection, such as biosensors.

- Fabrication imperfections

The performance of ring resonators is critically dependent on their fabrication quality. Fabrication imperfections such as surface roughness and sidewall roughness can increase scattering losses. These losses reduce the Q-factor of the resonator, and lower Q-factors values lead to broader resonance peaks, reducing the sensitivity and the resolution of the device. Therefore, achieving high precision in the fabrication process is essential for optimizing the performance of ring resonators.

To mitigate these effects, advanced fabrication techniques, such as electron beam lithography and precise etching processes, are employed to minimize roughness and enhance the smoothness of the resonator surfaces. Additionally, post-fabrication treatments, like thermal annealing, can further improve surface quality, contributing to higher Q-factors and, consequently, better device performance.

Surface Functionalization for Label-Free Detection

Optical micro-ring resonator sensors are a novel class of label-free optical sensors for bio/chemical detection that has lately garnered significant research attention [35]. In general, label-free assays are often preferred since they provide direct measurement of the target, hence removing labelling processes and reducing sample preparation labour.

In a basic label-free test, the sensor surface is covered with an affinity structure that selectively binds the target at low concentrations. The ring resonator detects the resultant mass gain or local alteration of the refractive index, registering a signal shift. The selection of the bioreceptor and its immobilisation method on the transducer surface depends on the intended uses, the kind of transducer, and the surface material.

Bioreceptors

Alongside the specificity between the analyte and its bioreceptor, several crucial characteristics should be considered in bioreceptor selection, including the affinity between the analyte and the bioreceptor, the stability of the complex formed by the two molecules, and the necessity for the complex formation to be detectable by the transducer.

Among the variety of bioreceptors that can be used for biosensing applications, it is important to remember antibodies, cellular components or whole cells, aptamers, and enzymes [36].

Antibodies or immunoglobulins (Ig) are Y-shaped protein structures made up chains of polypeptides that consist of heavy and light chains used to detect a specific antigen [37]. An antibody is made up of the Fab region present at the top of a structure that binds the antigen and stem Fc region, which activates immune cells and their binding [38]. It can be polyclonal, monoclonal, or recombinant, depending upon the number of epitopes that it can bind. Monoclonal and polyclonal antibodies detect a single epitope and multi-epitopes [39]. Recombinant antibodies detect a single epitope due to their monoclonal nature produced in the lab synthetically using synthetic genes [40]. Polyclonal and monoclonal antibodies have advantages and disadvantages associated with them. A monoclonal antibody can be synthesized at a high cost, while polyclonal antibodies have high cross-reactivity issues. Monoclonal or recombinant antibodies bind only one epitope and, therefore, are used to design highly specific biosensors. The orientation of antibodies

and immobilization plays a significant role in the detection of a target with high specificity and high performance [41].

The combination BSA/anti-BSA, HSA/anti-HSA, and IgG/anti-IgG serve as commonly used model systems for biosensing proofs-of-concept.

Cellular components or even **whole cells** can also be employed as bioreceptors to detect any type of microorganism (bacteria, virus) or to study extracellular or intracellular membrane transport proteins.

Recently, **synthetic receptors** derived from engineered molecules have surfaced as a compelling alternative to biological receptors. **Aptamers** are synthetic DNAs, RNAs, or peptide nucleic acids (PNAs) created with unique sequences to detect specific targets with high specificity and affinity [42][43]. Aptamers are produced using systematic evolution of ligands by an exponential enrichment (SELEX) procedure, an iterative procedure that consists of oligonucleotide sequences around 10^{15} – 10^{18} to generate excellent affinity to detect a target [44]. Aptamers have tertiary structures with basis sequences bound through hydrogen bonding [45][46][47][48]. They can bind to a wide variety of targets, which include from small molecules to toxins and micro-organisms, and are more stable than antibodies as they can survive at high temperatures, in harsh environments, and across a wide pH range [49].

Enzymes are molecules that catalyze various reactions and mainly exist in the form of proteins [50]. Enzymes can be conjugated with antibodies, cells, and aptamers and, therefore, are preferred for labeling purpose to detect an analyte. Lactate dehydrogenase, horseradish peroxidase, glucose oxidase, and acetylcholinesterase enzymes are commonly used for various biosensing applications. Various enzymatic optical biosensors have been reported for different applications.

Nucleic acids are complementary sequences of DNA or RNA which transform the genetic information as they involve information to produce an organism inside the body. They are made of polymer chains of nucleotides and named as cytosine, guanine, adenine, thymine, and uracil. A DNA is a double stranded helical molecule that uses thymine as a base, and a single stranded RNA molecule makes use of uracil to form sequences [51].

Immobilization techniques

After selecting the application (i.e., the bioreceptor) and the transducer (i.e., the surface material), it is essential to use the most suitable immobilization approach. The primary goal of the immobilization approach is to establish a recognition layer that provides effective coverage of the transducer surface, enabling interaction with the target with high specificity and rapidity, while preserving the bioreceptor qualities and transducer sensitivity. It should also reduce nonspecific adsorptions during the analysis of complex materials, such as blood or serum, without prior processing. Furthermore, the recognition layer must exhibit temporal stability and, in some instances, enough robustness to allow for regeneration without significantly compromising the binding characteristics of the bioreceptor. The choice of the most effective strategy of immobilization is the key factor that turns a sensing device into a valid and applicable analytical tool as the bioreceptor layer directly affects the reproducibility, the selectivity, and the resolution of any sensor device. Several strategies can be employed to immobilize the bioreceptor on the sensor surface [52], such as physical adsorption, covalent binding, noncovalent interactions, physical trapping, etc.

Focusing on silicon based-ring resonator, two key steps should be considered: a) modification of the surface to allow for controlled surface chemistry, and b) immobilization of a suitable high affinity binder on the surface while maintaining its activity.

a) Surface modification

Surface functionalization of silicon can be achieved with established organofunctional silane, which is based on the formation of covalent *Si-O-Si* bonds between oxidized silicon structure and the coating substance [53][54][55]. Silicon has a thin native oxide layer, if exposed to air and/or moisture [56]. Therefore, a condensation type-reaction of oxidized bulk silicon surface and pre-hydrolyzed alkoxysilanes is typically used. In the first step, the surface of the silicon may be cleaned and activated, e.g. with plasma cleaning [57] or chemically with strongly acidic hydrogen peroxide solution (Piranha solution) to yield a pristine surface with silanol groups [58][59]. In the second step, either methoxysilanes or ethoxysilanes in a pure solvent or with a small percentage of water are added [60]. Common methoxysilanes are (3-aminopropyl)-trimethoxysilane (APTMS), which leads to amino-modified surfaces [53] or (3-glycidyloxypropyl)- trimethoxysilane

(GLYMO) to obtain epoxy-modified surfaces [59]. After an incubation ranging from minutes to hours, the sample is thoroughly washed and dried; an additional curing step at increased temperature may be performed to aid the condensation reaction [55][60]. The obtained functionalized surface is now available for further modifications.

b) Immobilization of high-affinity binder

As already mentioned, several binders can be immobilized on the sensor surface for sensing experiments, but the most prominent class is represented by antibodies. Typically, these ones are covalently immobilized by coupling accessible amino groups from lysine residues or if present, free sulfhydryl groups from cysteine residues on reactive surfaces. For amine surfaces, various coupling paths have been demonstrated using an amine group of the protein and a linker molecule. The most prominent are hereby introduced:

- 1) Glutaraldehyde (GAD) activation of the surface followed by coupling with the target protein (P) and final reduction of the generated imine-bonds to yield stable amine-bonds with sodium cyanoborohydride ($\text{NaBH}_3(\text{CN})$) [55].
- 2) Succinic anhydride (SCA) modification of the surface and activation of the carboxylic acid with NHS/EDC (NHS = N-Hydroxysuccinimid, EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid) to yield an NHS ester subsequently reacting with free amines of the protein to yield stable amide bonds [53].

While the results of both reaction paths seem very similar, surface charges can play an important role in the correct orientation of the immobilized proteins [61]. An alternating head-on tail-on immobilization pattern could be observed for antibodies in the SCA path, due to the neutral surface charge of NHS activated surfaces at neutral pH, or in the conjugation step [61]. In the GAD path, the final surface may be positively charged due to the generated secondary amines, possibly leading to increased unspecific binding of proteins in the final assay. Also, higher head-on immobilization for antibodies could be observed for GAD surfaces, possibly due to the more reactive α -amino groups in the head [61]. The direct immobilization of the antibody may lead to deformation and loss of function of the antibody. Therefore, direct immobilization of the antibody should be balanced against the immobilization with more robust affinity proteins like Protein A or Protein G [62]. Oriented immobilization of antibodies on the surface might be favorable if the highest activity of the surface is desired [61][63].

Advanced techniques, such as self-assembled monolayers (SAMs) and the deposition of conductive polymers, are commonly employed to optimize the interaction between the sensor and target analytes. A particularly promising approach in this area is the use of molecularly imprinted polymers (MIPs). MIPs are synthetic polymers that are engineered to possess specific recognition sites for target molecules, allowing them to selectively bind to those analytes with high affinity. The process of creating MIPs involves the polymerization of functional monomers in the presence of a template molecule, which is the target analyte. Once the polymer matrix is formed, the template is removed, leaving behind cavities that are complementary in shape, size, and functional groups to the original target molecule. This tailored design results in MIPs that can selectively capture the target from complex biological samples, making them particularly valuable in biosensing applications.

The incorporation of MIPs into the functionalization of ring resonators can greatly improve the selectivity and sensitivity of these sensors. Furthermore, the high stability and robustness of MIPs make them well-suited for use in challenging environments where traditional sensing materials may fail.

Nevertheless, the functionalization process poses notable practical challenges. Ensuring the long-term stability of the functionalized layer is essential for maintaining reliable sensor performance. Factors such as temperature fluctuations and humidity can adversely affect the integrity of the functionalized surface, leading to sensor drift and reducing sensitivity over time. To mitigate these issues, strategies such as the employment of cross-linking agents to reinforce the binding of the functionalization layer and the use of protective coatings to shield the surface from environmental influences can be highly effective. Addressing these challenges is vital for the development of robust ring resonator sensors, particularly for applications in viral detection.

Evanescent Field Biosensing Principle

Light is confined in ring resonator biosensors by total internal reflection (TIR) at the waveguide interface. A significant portion of the guided electromagnetic mode power extends outside the waveguide, into the upper cladding medium surrounding the core, as an evanescent field, which allows to detect the deposition of analytes on the surface [64].

The evanescent wave extends only to a short distance (between tens and hundreds of nanometres) from the interface, and its power decreases exponentially with distance from the surface [65]. This phenomenon is exploited in biosensing, enabling real-time interrogation of antigen-antibody biorecognition events at the nanoscale, as shown in Fig. 1.7.

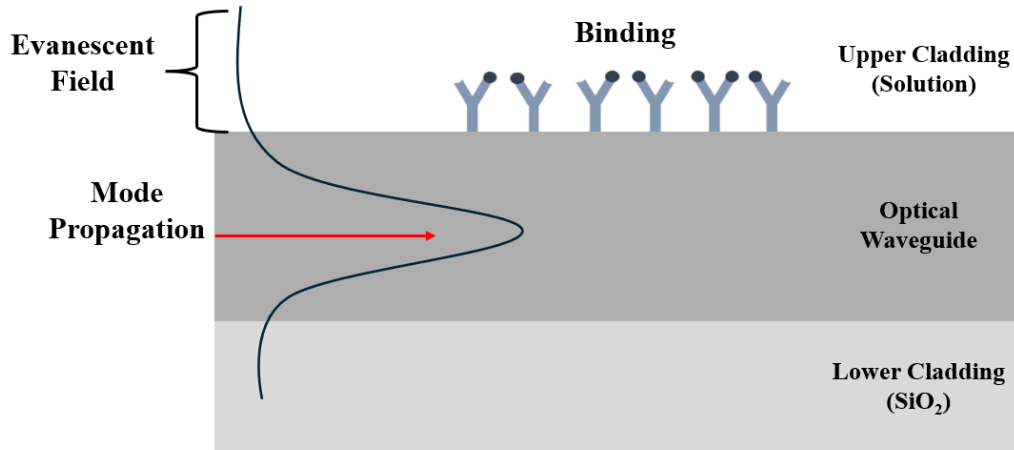


Figure 1.7: *The evanescent field around the waveguide is sensitive to refractive index changes caused by analyte binding to the functionalised waveguide surface.*

Refractive index variations of the external medium close to the surface cause changes in the optical properties of the excited mode via the evanescent field. Due to the exponential nature of the evanescent field, only changes in the local refractive index can be detected. Therefore, there is a region around the waveguide sensitive to analyte interactions. As a result of the target analyte binding to the functionalized waveguide surface, an increase in the effective refractive index is produced, causing a perturbation of the evanescent field and a shift in the resonant wavelength, proportional to the concentration of the analyte. The effect observed on the transmission spectrum of the waveguide ring resonator biosensor is represented in Fig. 1.8.

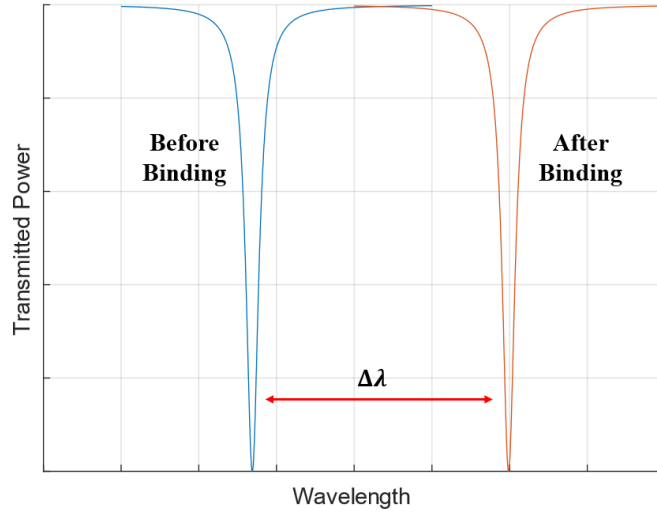


Figure 1.8: *Optical transmission spectrum of a ring resonator before and after the analyte binding, resulting in a resonant wavelength shift ($\Delta\lambda$).*

Light is guided in the core of the optical fiber, which is surrounded by a cladding of a slightly lower refractive index. Since the transverse dimensions of the optical fiber are much larger than the wavelength of the guided light, the model of geometrical optics can be used to describe light propagation in terms of rays [66].

As already anticipated, light is guided by the phenomena of total internal reflection, where all the energy from the incident ray is reflected at the interface between the fiber core and the cladding. In line with Snell's law, TIR takes places when the angle of incidence is larger than the critical angle, θ_c , which is defined as:

$$\theta_c = \sin^{-1}\left(\frac{n_2}{n_1}\right) \quad (1.50)$$

where n_1 and n_2 are the refractive indices of the fiber core and cladding, respectively. A schematic representation of light propagation in an optical fiber is shown in Fig. 1.9.

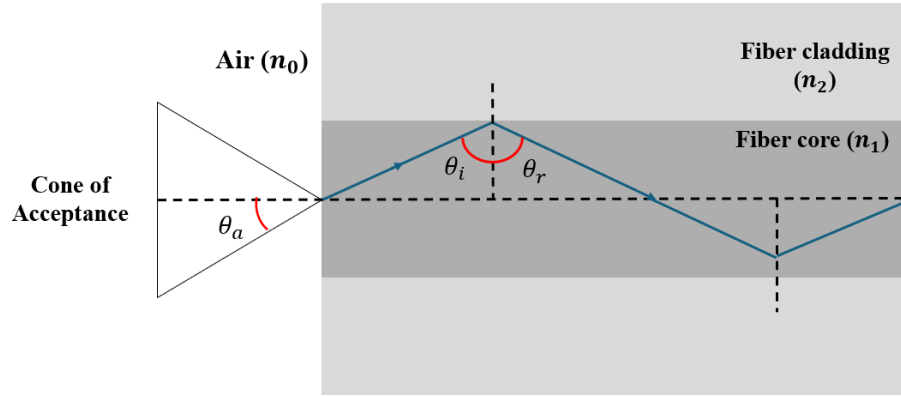


Figure 1.9: *Transmission of a light ray in an optical fiber according to the model of geometrical optics. The ray is coupled into the fiber when the angle of incidence is within the cone of acceptance (between 0 and θ_a) and is propagated by TIR (where θ_r equals θ_i) if the critical angle condition is satisfied.*

The angle with which a ray can enter or exit the optical fiber is also subject to conditions, where the limits are marked by the cone of acceptance. Only rays that enter the fiber within the acceptance cone can propagate along the fiber [66], and this same range of angles also applies at the other end where the light leaves the fiber. An expression for the acceptance cone can be derived from trigonometry and Snell's law, considering the refractive indices of the three media involved (the fiber core and cladding, and the surrounding air). The resulting numerical aperture, NA , can be calculated by:

$$NA = n_0 \cdot \sin(\theta_a) = \sqrt{n_1^2 - n_2^2} \quad (1.51)$$

where θ_a is the acceptance angle, and n_0 , n_1 and n_2 are the refractive indices of the air, the fiber core, and the fiber cladding, respectively.

Binding-unbinding model

The kinetic analysis of binding experiments is based on a simple model, called the **law of mass action** [67][68][69]. Binding occurs when the analyte (A) and the ligand (B) collide due to diffusion, and when the latter has the correct orientation and sufficient energy, the formation of the complex (AB) is determined.

After binding, the analyte and the ligand remain bound for a certain period of time until, following an interaction, these components remain unchanged with respect to the kinetics.

This interaction can be divided into three distinct phases (see Fig. 1.10):

- ❖ **ASSOCIATION**, when two or more molecules bind together;
- ❖ **STEADY STATE**, when the amount of bound molecules is such as the number of bonds that are breaking;
- ❖ **DISSOCIATION**, when the total breakdown of bonds between molecules occurs.

When dissociation is very slow, it takes a long time for both components to be free. As a result, a solution, for example at low pH or with high salt concentration, is flushed to curb interaction; this fourth phase is called **REGENERATION**.

The kinetic evaluation procedure determines association and dissociation constants by fitting the experimental data to a 1:1 interaction model between the analyte and the ligand:



The forward and reverse reaction rates are described by the adsorption (association) rate constant (k_a) and the desorption (dissociation) rate constant (k_d), respectively. The association process results in the formation of the complex [AB] on the sensor surface and is described by:

$$\frac{d[AB]}{dt} = k_a[A][B] \quad (1.53)$$

while the dissociation rate of the complex [AB] is given by:

$$\frac{d[AB]}{dt} = -k_d[AB] \quad (1.54)$$

Once a dynamic equilibrium is established, the rates of the two processes are equal, i.e.:

$$k_a[A][B] = k_d[AB] \quad (1.55)$$

Hence, the equilibrium constants can be expressed by the rate constants according to:

$$K_A = \frac{[AB]}{[A][B]} = \frac{k_a}{k_d} \quad (1.56)$$

$$K_D = \frac{[A][B]}{[AB]} = \frac{k_d}{k_a} \quad (1.57)$$

If the mass transport rate is much larger than the association rate constant or if the surface concentration of the immobilized species is low, the binding rate can be expressed as:

$$\frac{d[AB]}{dt} = k_a[A][B] - k_d[AB] \quad (1.58)$$

Considering that the response R scales linearly with the complex concentration $[AB]$, it is possible to obtain:

$$\begin{aligned} \frac{dR}{dt} &= k_a c (R_{\max} - R) - k_d R = k_a c R_{\max} - k_a c R - k_d R \\ &= k_a c R_{\max} - R(k_a c + k_d) \end{aligned} \quad (1.59)$$

where $R_{\max}$ is the saturation signal characteristic in the moment in which all functional ligand molecules bound analyte molecules. Theoretically, this means that the $R_{\max}$ signal can be reached only at unlimited high analyte concentrations where the degree of dissociation can be fully neglected.

The solution of the last equation becomes, in the association phase:

$$R = \frac{k_a c_0 R_{\max}}{k_a c_0 + k_d} [1 - e^{-(k_a c_0 + k_d)t}] \quad (1.60)$$

and in the dissociation phase:

$$R = R_{\text{end}} e^{-k_d t} \quad (1.61)$$

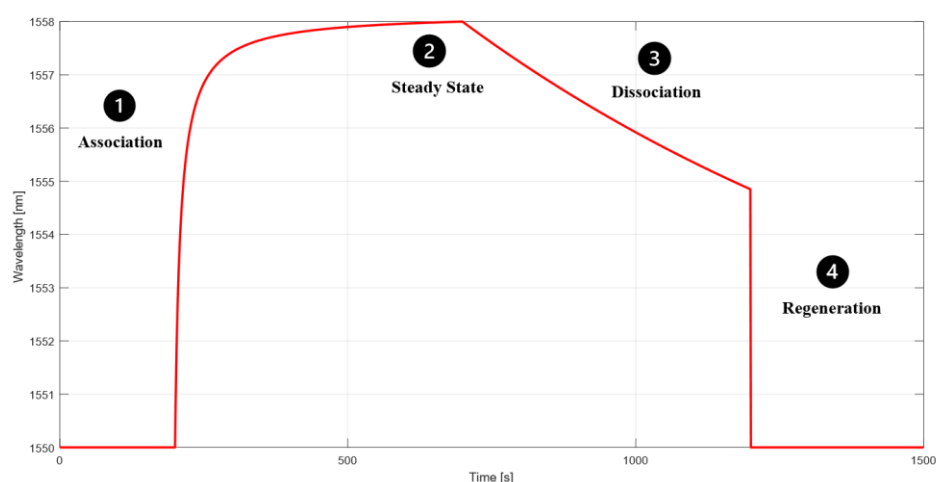


Figure 1.10: Example of a sensorgram reproduced in MATLAB, in which it is possible to distinguish the steps characterizing the binding of a molecule on the surface of a biosensor.

Commercialized Ring Resonator-based Devices

Among the companies focused on the field of silicon photonics applied to medical applications, SiPhox Health stands out with its fully integrated and cost-effective silicon photonics platform, capable of at-home biomarker measurement using fingerstick quantities of blood [70]. The system comprises a portable reader instrument (66 x 180 x 93 mm³, 500g), the sensor chip, and a disposable cartridge.

The reader prototype is a battery-operable instrument comprising a tunable laser subassembly, multipath optical interface to the cartridge, photodiode array, readout electronics, fluid control system, and a USB interface to a computer. The sensor chip uses CMOS-compatible ring resonators to transduce a phase shift from molecular binding into a measured shift in the resonance wavelength. The 5 x 5 mm² sensor chip is fabricated with 193 nm deep UV immersion lithography on 300 mm wafers. Input light is split into 15 channels, each with a ring resonator, and routed to output edge couplers. A top cladding is deposited to protect edge couplers, waveguides, and power splitters, followed by the etching of trenches down to the waveguide layer around the sensors. The chip is diced, cleaned, and optically coupled, whereafter surface functionalization is applied to the sensors.

The microfluidic cartridge is represented by a precise injection piece that features a syringe barrel, rigid wall microfluidic channels, and a sample well. All the features create

a closed loop of microfluidic channels connecting the sample well to the syringe barrel while exposing the sensor to the fluids. Fluid flow is driven at a constant rate by means of an air interface syringe driven by the reader.

To demonstrate the capabilities of the platform, the company develops an assay for measuring CRP, an inflammation biomarker associated with chronic disease conditions and decreased longevity, with a relevant high-sensitivity range in plasma and whole blood ranging from 0.2 to 10 $\mu\text{g/mL}$. A photonic ring resonator immunoassay is performed, using antibodies against the CRP protein immobilized on half of the ring resonator sensors. Additionally, a negative control (Mouse IgG isotype antibody) is immobilized on the other half of the sensors. Immobilization is achieved using standard microarray surface chemistry and micro-spotting techniques. To quantitate CRP in human samples, a dose response curve by testing six known concentrations in triplicate is created, fitting the results to a standard 4-parameter logistic (4PL) sigmoidal curve. These calibration samples are generated using CRP-free plasma spiked with human CRP at six concentrations covering the relevant range. To perform the needed dilution (1:100) and ensure ideal assay conditions, a proprietary running buffer is developed (SiPhox 3.5C Buffer). Subsequently, samples of unknown concentration are automatically compared to the calibration curve to generate a quantitative measurement of CRP content. Thirty-one clinical plasma samples are tested for hsCRP by a CLIA lab using the gold-standard Roche Cobas tool, revealing good agreement between the custom-built measurement system and gold-standard lab tools and techniques.

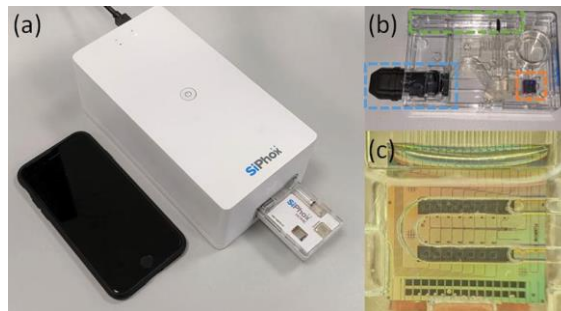


Figure 1.11: (a) Photograph of SiPhox Home reader instrument and disposable cartridge with cell phone for scale. (b) Photograph of cartridge with syringe (green), photonic chip (orange) and pluggable optical connector (blue). (c) Photograph of sensor chip with fiber I/O at the top edge [71].

Another notable company in this sense is Genalyte, which has developed the Maverick™ Diagnostic System (11" high x 16" wide x 23" deep), a multiplex assay detection technology based on silicon photonics, utilizing ring resonators to measure the binding of macromolecules to sensors on a miniature silicon chip [72].

In its current configuration, Genalyte's sensor chip comprises 136 rings etched onto the chip. Each ring is 30 μm in diameter. Eight are used as controls and remained covered by a Teflon-like per-fluoropolymer that coats most of the chip. The other 128 rings are organized into 32 clusters of 4 rings each, which are not covered and so are exposed to the material that flows above them. These rings are functionalized by spotting test-specific reagents on to them, which act as analyte specific capture probes. Thus, each test is run in quadruplicate. The clusters are organized in 2 rows with 16 clusters in each row. The gasket covering each chip has a flow channel for each row of clusters. Thus, 2 samples can be tested for 16 assays each, or 1 sample can be tested on 32 assays in the current version of the chip.

When the assay is being performed, light enters the chip through grating couplers, travels through waveguides to the ring resonators, and then returns to the grating couplers where the intensity at each wavelength of the returning light is measured. Negative peaks in the intensity of light indicate the resonant wavelengths, and the shift in the wavelengths of the negative peaks indicate a change in the refractive index above the ring cluster, which in turn is proportional to the mass that has bound to the reagent above the cluster. The shift in each ring is measured separately, and the average of the shifts from the 4 rings in the cluster is output as Genalyte Response Units (GRU). An outlier within a cluster can be removed automatically by the software by applying Chauvenet's criterion if it is > 3 standard deviation from the mean.

In particular, the company has demonstrated the capability of the system to be used for the multiplex detection of antibodies in serum, the detection of receptor-ligand interactions, and the kinetic characterization of binding.

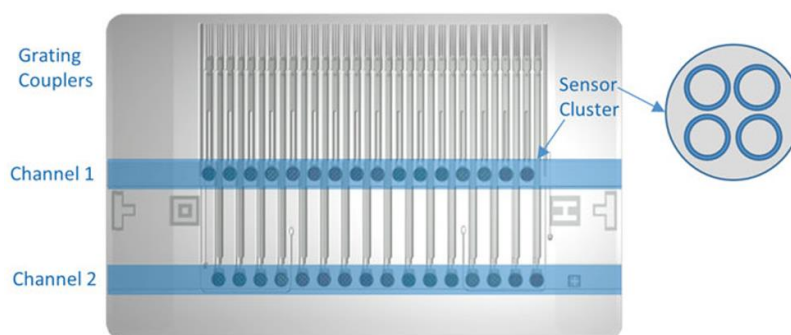


Figure 1.12: Schematic of Maverick™ Detection System produced by Genalyte [73].

Alternative approaches

Detection via the optical properties of biomolecules is only one of the many options that are considered for label-free biosensors. As previously mentioned, one way to classify biosensors is based on their transduction mechanisms. Electrochemical biosensors find a wide range of applications in terms of being portable, highly sensitive, simple, short-response, selective, inexpensive, and specific. They strictly rely on the chemical interactions between a biorecognition layer and the target biomolecules to be measured, and can be differentiated into three different categories, including amperometric biosensors, impedimetric biosensors, and potentiometric biosensors.

Potentiometric biosensors, which can detect the potential difference determined between a reference electrode and an indicator electrode with a very high impedance voltmeter, in almost zero current flow conditions, are currently the subject of growing scientific interest due to their very high sensitivity and specificity obtained when an extremely stable reference electrode is used [74][75][76].

In recent years, numerous potentiometric biosensors, even wearable sensors, have been developed for the monitoring of different biochemical substances, exploiting the activity of bioreceptors including enzymes, antibodies, and nucleic acids. Seema et al. [77] prepared nanoparticles of urease from jack beans and developed a potentiometric biosensor to detect urea in human urine samples. Canovas et al. [78] developed a potentiometric biosensor for the direct detection of glucose in whole, undiluted blood without any sample pre-treatment. Mishra et al. [79] fabricated a wearable potentiometric tattoo biosensor for real-time on-body monitoring of G-type nerve agents simulants. Bandodkar et al. [80] described the fabrication of an epidermal temporary-transfer tattoo-

based potentiometric sensor, coupled with a miniaturized wearable wireless transceiver, for real-time monitoring of sodium in human perspiration. Papp et al. [81] fabricated a potentiometric biosensor for detecting tumor, hepatitis B, digoxin, and troponin I.

Among potentiometric biosensors, particular relevance is assumed by those based on field effect transistors, mainly studied for sensing applications, as for example the ion-sensitive field-effect transistor (ISFET). This device was invented in 1970 [82] and was first used for the sensing of pH and later for the measurement of the concentration of a plurality of biomarkers of biomedical interest, including potassium iodide (KI), ethanol, serum glucose, cholesterol, and hydrazine [83]. ISFET has many advantages in the field of monitoring electrochemical reactions; in fact, it can be produced on a large scale and integrated into other detection systems; moreover, it is beneficial in terms of size, due to the presence of only one reference electrode. As a solid-state sensor, without fragile materials involved, it is acids-alkali resistant, water repellent, and shock resistant. Currently, after the possibilities of clinical detection have been verified, the research emphasis has shifted to the technique for improving the performance of the ISFET biosensors. The related studies mainly include the material, structure, and functionality of the gate. Over the past few years, ISFETs have rapidly progressed and become one of the most widely used biochemical sensors, with hundreds of related papers being published annually. The application is not limited to single detection. By using ISFET arrays, multiplexed detection with a single chip can also be achieved because ISFETs are easily integrated. By integrating multiple ISFETs onto one sensing chip, the on-off state of each one can be controlled electrically. Only the “on” ISFET will operate and transmit biochemical signals from the corresponding analytes as electrical signals. By operating the ISFETs with different functionalities one by one, it is possible to detect different analytes simultaneously with a single chip. Additionally, by fabricating ISFETs in a small size, with high performance, portable and wearable devices can be developed [84]. The ISFET architecture is similar to that of a MOSFET, with the difference being that the gate metal is removed in such a way as to establish a direct contact between the insulating surface and the electrolytic solution to be tested; in particular, it takes advantage of the fact that the current between the source and the drain is modulated by the potential of the gate, which in turn depends on the concentration of the analyte that binds to the sensitive material. The clinical case of interest for which the implementation of an ISFET has been carried out is cystic fibrosis, a disease generally diagnosed and monitored through a

conventional exam-defined sweat test. The distribution of sweat glands in the human body is rich (>100 glands/cm²), and the sweat contains abundant biochemical compounds; thus, human sweat has become a promising avenue for non-invasive biosensing. This is because the widespread presence of eccrine glands on human skin makes this biofluid easily accessible, without having to resort to painful or invasive devices, such as needles. Sweat is a biological fluid that is secreted by the skin through the transepidermal water loss (TEWL), which is regulated by the diffusion of water vapor in the stratum corneum due to a concentration gradient that occurs between the inner and the outer surface of the epidermis. Produced by the sweat glands, perspiration is therefore the main vehicle for the transport of salts through the body. Under normal conditions, the sweat that evaporates and reaches the surface of the skin is slightly salty. Subjects with cystic fibrosis have a mutation in the gene encoding the chloride conductive transmembrane channel, called the cystic fibrosis transmembrane conductance regulator (CFTR), which regulates the transport of water and salts inside and outside the cells; as a result, the epithelial tissue fails to absorb chloride, at the same time causing insufficient sodium adsorption from the ducts. When this is achieved, NaCl concentrations above 70 mol/m³ are found on the skin surface [85], which is why sweat will be heavily salted. The concentration of sodium and chloride ions in sweat can vary depending on several factors, including hydration status, diet, and overall health. However, there are some general norms for the concentration of these ions in human sweat. Typically, the concentration of sodium ions in sweat ranges from 50 to 200 mM/L. The concentration of chloride ions in sweat is typically similar to that of sodium, ranging from 40 to 140 mM/L. These values can vary depending on the individual and the specific conditions under which the sweat was produced. When sweat analysis is carried out through conventional testing, diagnostic errors may occur that could compromise the outcome of the diagnosis of cystic fibrosis; the use of an ISFET for the monitoring of salts in the sweat of patients subject to such pathology could be useful to optimize the clinical trial, minimizing the number of false positives, ensuring continuous and real-time monitoring, and checking in advance whether or not the therapy administered is effective.

In this research work, the modeling and design of an ISFET-based potentiometric biosensor intended for Cl^- sensing in sweat is reported. The study is organized as follows: it starts with the description of the configuration and operating principle of the designed ISFET, explaining the analogy with respect to MOSFETs and the theories which

explain the chemical reactions that take place between the gate oxide and the electrolytic solution; then, the modeling of the device through the finite element method is reported by describing the equations referred to in the two adjacent but distinct domains: the electrolyte domain and the semiconductor domain; finally, the obtained numerical results are presented.

ISFET-based Sensor: Configuration and Operating Principle

The ISFET is a solid-state potentiometric sensor that uses the principle of an FET to convert a concentration of charged ions into an electrical signal. Its structure is very similar to that of a MOSFET, but it is modified with respect to the latter by replacing the gate with an electrolyte solution containing the target ions to be measured, along with a reference electrode. In this way, the electric potential at the gate oxide–solution interface depends on the concentration of ions in the electrolyte.

Due to the presence of the electrolyte solution between the reference electrode and the insulator, the expression of the threshold voltage in an ISFET is different from that of a MOSFET, and it may be written as follows [86]:

$$V_{TH} = E_{ref} - \psi_0 + \chi^{sol} - \phi_{si} - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{ox}} + 2\phi_f \quad (1.62)$$

where E_{ref} is the reference electrode potential relative to vacuum, ψ_0 is the electrostatic potential, χ^{sol} is the surface dipole potential of the solution and it is a constant, ϕ_{si} is the silicon work function, and C_{ox} is the gate insulator capacitance per unit area. Other parameters that affect the value of the threshold voltage are the charges located in the oxide (Q_{ox}), the surface states and interface states (Q_{ss}), and the depletion charge (Q_B). ϕ_f is the potential difference between the Fermi levels of doped and intrinsic silicon, given as:

$$\phi_f = \frac{kT}{q} \ln \left(\frac{N_A}{n_i} \right) \quad (1.63)$$

where k is the Boltzman constant, T is the absolute temperature, q is the elementary charge, N_A is the acceptor concentration, and n_i is the intrinsic carrier concentration of silicon. Except for the electrostatic potential, ψ_0 , all the parameters in the threshold voltage expression remain the same, regardless of the ions' concentration in the

electrolyte solution [87]. As a result, the variation in the ions' concentration is the only thing that can be credited with the changes that occur in the V_{TH} expression.

In Fig. 1.13, the sensor cross-section is shown, and for its modeling, the body of the semiconductor is considered to be $0.7\ \mu\text{m}$ in height, and with a width of $3\ \mu\text{m}$. The source and drain are $0.5\ \mu\text{m}$ in length towards the gate. The gate region is $1.3\ \mu\text{m}$ wide and is large enough to act as a reacting surface to the electrolyte solution.

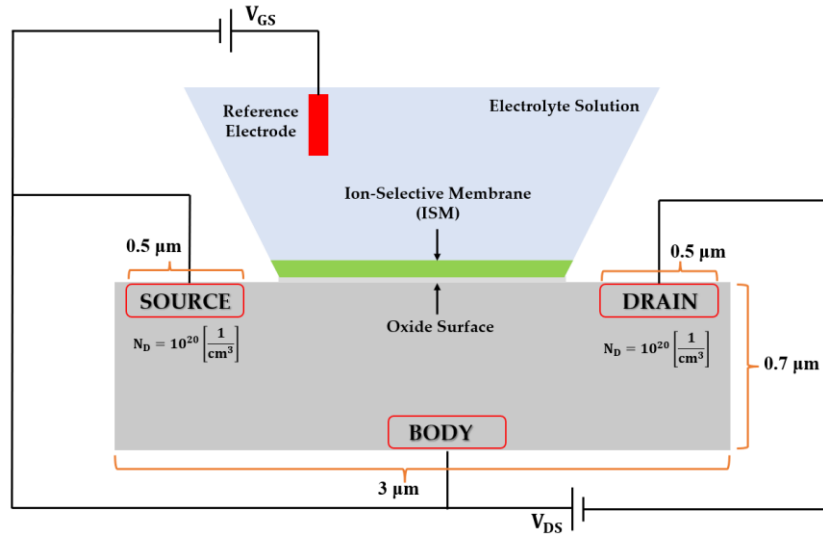


Figure 1.13: Schematic diagram of the designed ISFET

The selectivity of the ISFET is primarily determined by the ion-sensitive membrane, which makes the sensor responsive only to the specific target ions.

Since the ISFET is not water repellent, its encapsulation is necessary. Encapsulation techniques for ISFETs are critical to ensuring stable and consistent electrical properties. Some encapsulation techniques that can minimize variations in electrical properties are described in the literature. For example, the dam-and-fill technique is widely used in ISFETs encapsulation, and it guarantees a small degradation of the sensor performance [88][89].

Thus, the performance prediction achieved by this accurate model is realistic, despite the fact that the sensor is modeled without considering encapsulation. Moreover, the sensor is always polarized in the saturation operating region. In this way, any V_{TH} change due to

variations in the ion concentration in the electrolyte solution induces a change in the drain-source current, I_{DS} , which is given by [86]:

$$\begin{aligned} I_{DS} &= K(V_{GS} - V_{TH})^2 \\ K &= \frac{1}{2} \left(\mu_n C_{OX} \left(\frac{W}{L} \right) \right) \end{aligned} \quad (1.64)$$

where μ_n is the electron mobility, C_{OX} is the oxide capacitance per unit area, and W and L are the width and the length of the channel, respectively.

The chemical reactions that take place between the gate oxide and the electrolytic solution can be described according to two major theories [87][90][91]:

(a) The **site-binding theory**, which analyzes the mechanism of oxide surface charge creation, considering the equilibrium between the amphoteric surface sites and ions in the solution;

(b) The **Gouy–Chapman–Stern theory**, which models ion distribution in the electrolyte solution through different layers, such as the Helmholtz layer and the diffuse double layer, where the first one contains the ions which are strongly adsorbed by the electrode surface, and the second one contains the ions which are distributed with a concentration gradient driven by the thermal motion. In particular, Stern observed that ions cannot approach the electrode surface closer than their ionic radius, and the distance of the closest approach is called the outer Helmholtz plane (OHP). The occurrence of this phenomena is illustrated in Fig. 1.14. It should be noted that the solvation shell of water molecules also contributes to this distance of closest approach. To break the ion free from its watery prison, a greater quantity of energy will be necessary. Because of this, an area adjacent to the electrode surface will be devoid of any ionic charges, and this will give rise to a constant capacitance, known as Stern capacitance, which typically has a value of $20 \mu\text{F}/\text{cm}^2$ [92].

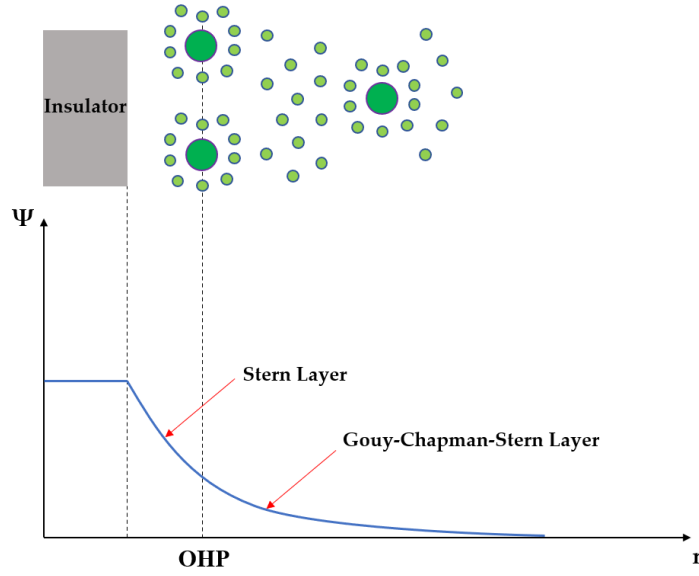


Figure 1.14: *Illustration of the Stern layer.*

ISFET Modeling

The ISFET-based sensor is simulated and designed by using the finite element method (FEM), considering two adjacent domains:

- the electrolyte domain, obtained by approximating sweat as an aqueous solution at acid pH containing the ions of interest;
- the semiconductor domain, set up as a MOSFET. Sweat pH is slightly acidic, usually between 4 and 6.5, so in the simulations a pH of 6 is considered.

Semiconductor Domain

In the semiconductor domain, Poisson's equation for electric potential (Eq. (1.65)) and the drift-diffusion equations for electrons and holes in the semiconductor material (Eq. (1.66)) are solved [93]:

$$\nabla \cdot (-\epsilon_0 \epsilon_r \nabla V) = \rho \quad (1.65)$$

$$\begin{aligned} J_n &= qn\mu_n \nabla E_c + qD_n \nabla n - qnD_n \nabla \ln(N_c) + qnD_{n,th} \nabla \ln(T) \\ J_p &= qp\mu_p \nabla E_v - qD_p \nabla p + qpD_p \nabla \ln(N_v) - qpD_{p,th} \nabla \ln(T) \end{aligned} \quad (1.66)$$

where ϵ_0 and ϵ_r are the absolute and relative permittivity, ρ is the charge density, q is the elementary charge, n is the number of electrons, μ_n is the electron mobility, E_c is the minimum conduction electron energy, D_n is the diffusion coefficient for electrons, N_c is

the effective density of states (conduction band), and T is the temperature. All parameters are defined in the same manner for the drift-diffusion equation of the holes.

Electrolyte Domain

The formation of the diffuse double layer is treated by combining:

- the electrostatic physics, hence, the Poisson's equation for the charge density and the electric field;
- the physics of the transport of chemical species within a solution, thus, the Nernst Planck's equation for the mass transport of ions:

$$J_i = -D_i \nabla c_i - u_{m,i} z_i F c_i \nabla \varphi_l \quad (1.67)$$

where D_i , c_i , and z_i refer to the diffusion coefficient, the concentration, and the charge number of the i -th ionic species, F is the Faraday constant, and φ_l is the electric potential of the electrolytic phase. Eq. (1.65) and (1.67), characterizing the two physics above mentioned, are coupled through the common variable φ_l .

The mobility is calculated as a function of the diffusion coefficient of the ionic species and the temperature, using the Nernst–Einstein's equation [94]:

$$u_{m,i} = \frac{D_i}{RT} \quad (1.68)$$

where R is the molar gas constant.

Assuming that there are no homogeneous reactions of ions in the solution, for mass preservation, the following condition must be satisfied:

$$\nabla \cdot J_i = 0 \quad (1.69)$$

In this case, the transport of four ionic species, namely H^+ , OH^- , Na^{2+} , and Cl^- , is considered. At this point, since in cystic fibrosis, the major effects are caused by the adsorption of negative ions [95], i.e., chloride, Cl^- , a modified version of the site-binding model must be considered (see Eq. (70)), which consequently produces a variation in the Boltzmann equation (Eq. (71)) [95]:



$$[Cl_S^-] = [Cl_B^-] \exp \left(\frac{q\psi_0}{kT} \right) \quad (1.71)$$

where $[Cl_S^-]$ and $[Cl_B^-]$ represent the concentration of chloride ions on the insulating surface and in the electrolyte, respectively, q is the elementary charge, $\psi_0 = \varphi_M - \varphi_{l_{bulk}}$ is the surface potential, and k is the Boltzmann constant. The effect of the interface between the reference electrode and the sample solution is taken into account with the silver electrode work function ($W_{Ag} = 4.6$ V).

Thin Oxide: Semiconductor Domain and Electrolyte Domain Coupling

At the level of the semiconductor domain, the oxide is modelled through the “think insulator gate” boundary condition, which forces the potential to be φ_M -equal. The Bode module binds the latter to the electrolyte potential at the upper edge of the think oxide, φ_l , through the equation:

$$C_{st} = \frac{\sigma_0}{\varphi_{l(y_{ox^-})} - \varphi_M} \quad (1.72)$$

which therefore imposes the difference in potential ($\Delta\varphi_{St} = \varphi_{l(OHP)} - \varphi_M$) on the C_{st} capacity, representing the Stern capacity, with the charge density on the electrodes. It is possible to obtain a clearer vision of the potentials mentioned in this paragraph by evaluating their trend along the vertical axis of the device, as shown in Fig. 1.15; moreover, a detailed description of the parameters of the model is given in Table 1.2.

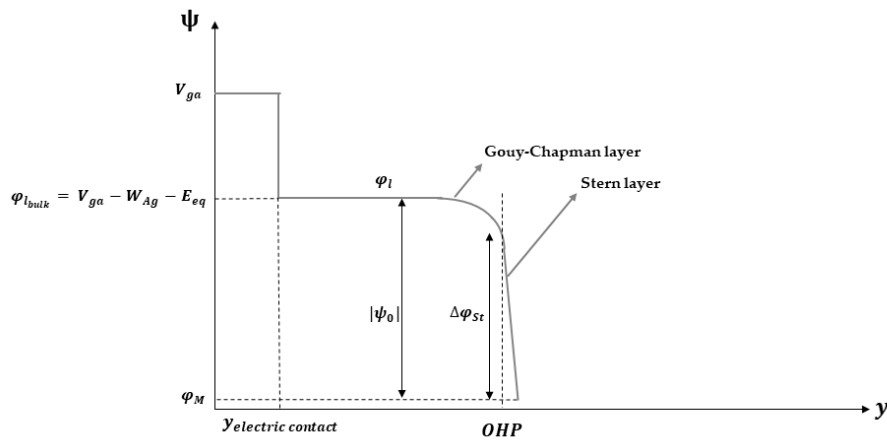


Figure 1.15: Potential diagram of ISFET along the vertical axis in the electrolyte domain.

Table 1.2: *Description of the potentials involved in the study*

Potentials	Description
V_{ga}	Gate voltage applied
W_{Ag}	Work function of Ag electrode
E_{eq}	Equilibrium potential of the reference electrode
φ_l	Electrolyte potential
$\varphi_{l_{bulk}}$	Bulk electrolyte potential
φ_M	Potential imposed at the upper edge of the oxide
ψ_0	Difference in potential between φ_M and $\varphi_{l_{bulk}}$
$\Delta\varphi_{St}$	Difference in potential applied on C_{St} capacity

Eq. (1.70) and Eq. (1.71) show the role of Cl^- ions at the oxide surface in determining the surface charge density, σ_0 , which can be expressed by the following [91][96]:

$$\sigma_0 = qN_s \frac{[H_S^+]^2[H_B^+] - K_a K_b [H_B^+] - K_c [Cl_S^-][H_S^+]^2}{[H_S^+]^2[H_B^+] + K_a K_b [H_B^+] + K_c [Cl_S^-][H_S^+]^2 + K_b [H_S^+][H_B^+]} \quad (1.73)$$

where q is the elementary charge, N_s represents the density of the surface sites per unit area, $[H_S^+]$ and $[H_B^+]$ are the concentrations of hydrogen ions on the insulating surface and in the electrolyte, respectively, K_a and K_b are the dissociation constants for deprotonation and protonation reactions, while K_c is the reaction constant for chloride, and it is a dimensionless quantity.

At the level of the electrolyte domain, the oxide is modeled through the definition of the “electric displacement field from semiconductor” boundary condition, which specifies the continuity of the normal component of the electric induction field at the boundary where the oxide is ideally located.

Ion-Selective Membrane (ISM)

When ISFETs are modified to be chemically sensitive to ions other than H^+ , an ion selective membrane, also known as an ISM, may be modeled and placed in various locations, such as above the oxide layer [97][98]. ISMs can either be in the solid (glassy

or crystalline) or liquid phase. In the first case, ionic sites are present as part of the crystal structure and are covalently bound to the solid network, whereas in the liquid phases, they are usually added in the form of lipophilic salts [99]. However, solid state membrane selectivity cannot be easily tuned and is not flexible. The most prevalent types of ISMs are liquid membranes, typically made of polymeric materials that incorporate a microporous support matrix. This support should be chemically inactive and avoid the dispersion of all membrane components; the most common polymer used in ISMs is poly(vinylchloride) (PVC).

In this study, a PVC-ISM, with $l_{ISM} = 1.67 \mu\text{m}$ and $d_{ISM} = 0.5 \mu\text{m}$, is considered, so as to better filter the flux of Cl^- ions from the electrolyte. This is achieved by using a selectivity coefficient, K_i , which is defined as the ratio between the concentration on the upside and on the downside of the boundary considered ($c_{i,u}$ and $c_{i,d}$, respectively):

$$K_i = \frac{c_{i,u}}{c_{i,d}} \quad (1.74)$$

The selectivity coefficient allows for specifying at which ion the membrane must be more selective, so it acts as a multiplicative term, defined in a range between 0 and 1, which decreases the concentration of the i -th species from the sample solution into the ISM [100].

Numerical Results

As shown in Fig. 1.16, the performance of the ISFET when high-k oxides (silicon dioxide, aluminum oxide, hafnium (IV) silicate, zirconium (IV) silicate, yttrium (III) oxide, tantalum (V) oxide, hafnium (IV) oxide, lanthanum (III) oxide, titanium dioxide) are used as the insulating layer are analyzed, so the correlation between the derivative of the drain-source current with respect to the chloride ion concentration c_0 (sensitivity, S) and the relative permittivity is determined. It is possible to observe that as the permittivity increases, the derivative of I_{DS} with respect to c_0 reduces.

The oxide that shows better performances in terms of sensitivity ($S = 1.2 \times 10^{-7} \frac{\text{A}\cdot\text{m}^3}{\text{mol}}$) is the Hafnium oxide ($\epsilon_{ins} = 25$, $d_{ins} = 30 \text{ nm}$, $l_{ins} = 1.6 \mu\text{m}$). In Fig. 1.17, assuming $V_{GS} = 1.6 \text{ V}$, the evolution of the $I_{DS} - V_{DS}$ characteristics for four values of Cl^- concentration ($c_0 = 50 \text{ mol/m}^3$, $c_0 = 70 \text{ mol/m}^3$, $c_0 = 90 \text{ mol/m}^3$, $c_0 = 110 \text{ mol/m}^3$) is observed. From this result, it is possible to state that the designed device proves to be

successful for the management of cystic fibrosis, exhibiting a difference in saturation current, ΔI_{DS} , of 7.8 μA when c_0 passes from 50 mol/m^3 to 110 mol/m^3 . Moreover, assuming a minimum-detectable change in current, $\min(\Delta I_{DS})$, of 0.5 nA [101], a corresponding resolution in concentration, Δc_0 , of 0.004 mol/m^3 is determined.

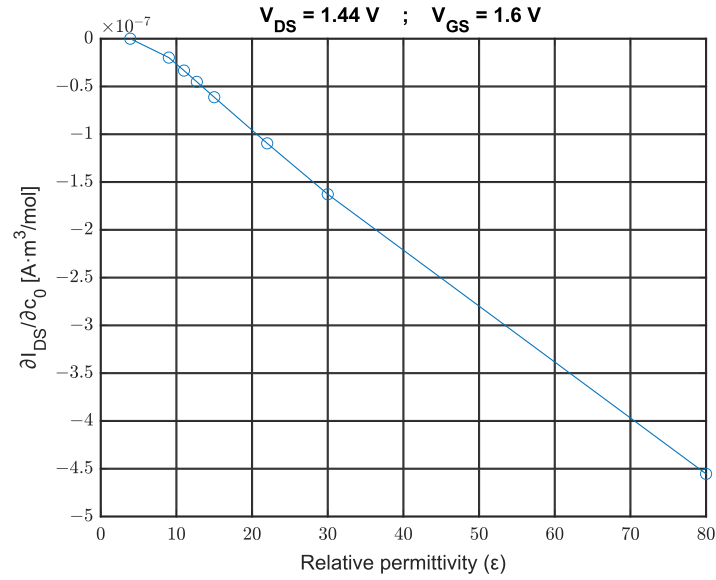


Figure 1.16: Drain-source current variation for two concentration values as a function of the high- k oxide used as an insulating layer.

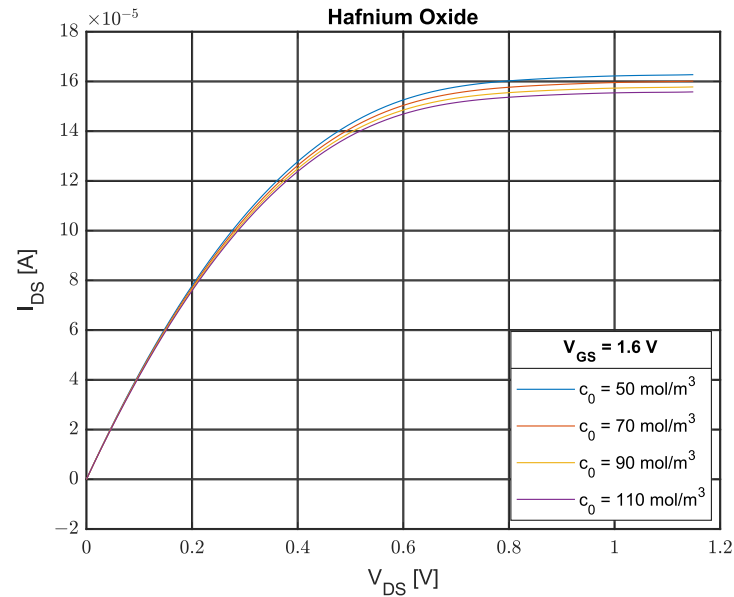


Figure 1.17: Optimal performances of ISFET: drain-source current vs. drain-source voltage for four different Cl^2 values using HfO_2 as the insulating layer.

Another aspect that was thought to affect the performance of the device is the variation of its geometry, such as the width of the oxide. In Fig. 1.18, always considering HfO_2 as the insulator, it is possible to see how the dependence of the drain-source current, I_{DS} , on the drain-source voltage, V_{DS} , varies depending on four values of d_{HfO_2} and, in particular, the sensitivity of the device reduces as the thickness increases. This agrees with the classical behaviour of MOSFETs.

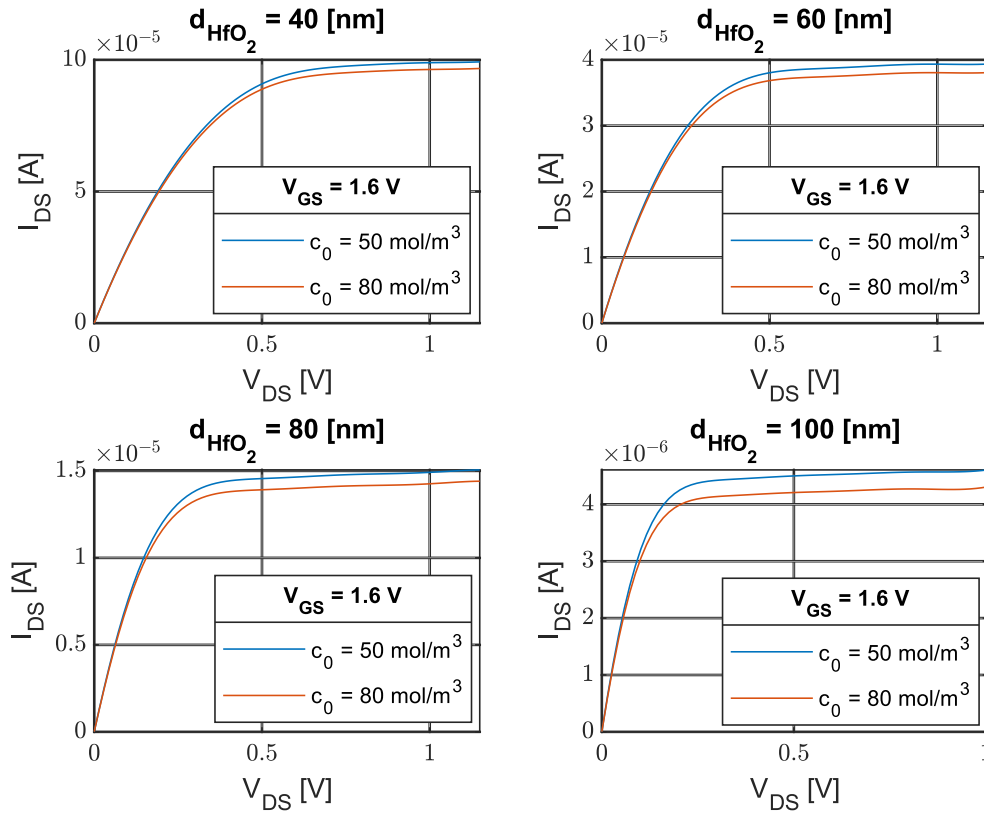


Figure 1.18: Drain-source current vs. drain-source voltage for two different Cl^- values using various values of HfO_2 's thickness.

Then, the drain-source current, I_{DS} , in function of five values of Cl^- concentration, with a fixed value of the drain-source voltage, $V_{DS} = 1.44$ V, and of the gate-source voltage, $V_{GS} = 1.6$ V, is calculated. As shown in Fig. 1.19, there is a direct correlation between these two parameters; in fact, the higher is the concentration to detect, the higher is the saturation current.

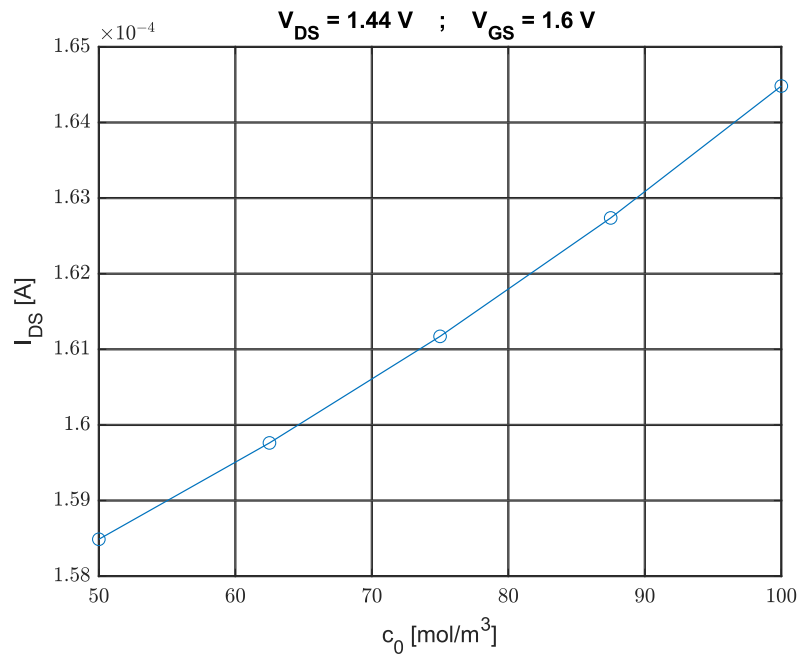


Figure 1.19: I_{DS}/c_0 curve with a fixed value of V_{DS} for ISFET-based Cl^- .

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CHAPTER 2

Ring Resonators in Silicon-on-Insulator Technology

Photonic Integration

Photonic integration has made tremendous progress in the last few years. Large-scale monolithic integration of complex photonic functions is a reality now [1][2][3][4]. The range of applications has broadened from long-haul telecommunication [5] to short-reach data communication [6][7] and from optical coherence tomography [8] to lab-on-a-chip systems [9][10]. Unlike electronic integration, photonic integrated circuits have been based on a plethora of material platforms [11][12], each platform having its own advantages and challenges.

In the last 15 years, silicon photonics has established itself as an important photonic integration platform [13]. It has made its way from research labs to manufacturing foundries and ultimately to the market. It may be described as a technology that uses a high index contrast material platform for wafer-scale fabrication of high-density and low-cost Photonic Integrated Circuits (PICs) in a CMOS fab delivering high yield.

The success of silicon photonics can be attributed to two main features. First, leveraging existing CMOS infrastructure [14] for the fabrication of silicon photonic chips has turned out to be the major driver for the growth of this field. It allows the fabrication of high, moderate and low volumes of silicon photonic chips in existing CMOS fabs that are primarily loaded with the fabrication of electronic ICs. For prototyping, typically executed by means of Multi-Project Wafer (MPW) services to deliver a small number of chips, the cost per chip is of the order of 100 to 1000 US Dollars [15]. But for manufacturing this cost will rapidly drive down by a factor of 100 or so even for moderate volume. Such a scenario circumvents huge financial investment and risk involved in building a dedicated fab for photonic integration only. Second, a paramount attribute to the success of silicon photonics is the use of a high index contrast material platform for the implementation of PICs. This feature ensures the implementation of complex optical functions while keeping the chip form factor small, resulting in more chips per wafer. Furthermore, the high index contrast allows the implementation of functions such as

photonic crystal cavities [16][17][18] and high-efficiency grating couplers [19][20] that are difficult or simply not possible to implement in a low-index contrast material platform.

Silicon-on-Insulator (SOI) Platform

In place of conventional silicon substrates in semiconductor manufacturing, mainstream silicon photonics products are built on silicon-on-insulator (SOI) wafer. Its layer stack comprises a thin layer of crystalline silicon, which is separated from the silicon substrate by a buried oxide (BOX) layer. SOI wafers with a 0.22 μm silicon guiding layer and 2 μm BOX is the pseudo standard used for SOI-based silicon photonics. However recently thicker silicon layers of 0.31 μm [21] and 0.4 μm [22] are also getting prominence due to the ease of heterogeneous III-V laser integration on these waveguide circuits. The high index contrast of about 2 between the guiding silicon layer ($n_{Si} \sim 3.5$) and the BOX ($n_{BOX} \sim 1.45$) allows for a tight bending radius of 5 μm (for 0.45 μm wide strip waveguides operating at 1.55 μm). This enables flexibility in the layout of complex and highly integrated photonic circuits. In its basic form SOI-based silicon photonics provides passive components such as waveguides, splitters, wavelength filters, interferometers, resonators, polarization management devices and couplers to guide light in and out of the silicon chip [23][24][25]. In its more advanced form, it provides advanced photonic functions such as high speed (40 Gb/s and beyond) modulators and monolithically integrated detectors [26][27][28]. Moreover, the high thermo-optic coefficient of silicon is exploited for realizing tunable filters, tuning of fabrication-induced errors for interferometric devices and for low-speed switching operations [29]. Low-cost access to SOI-based silicon photonics is commercially available through the MPW services offered by various CMOS pilot lines and foundries [30][31].

SOI has undoubtedly shown impressive performance for passive and active functions on a photonic integrated chip in the last few years. Some of the test bed demonstrations using SOI-based silicon photonics in research labs have made their way to products, which is a very promising sign for SOI-based silicon photonics. The high index contrast of SOI not only makes it superior, due to the reasons mentioned above, to other photonic integrated material platforms, but also makes it a challenging material platform. It demands nm-scale precision in fabrication to achieve high performance components. Moreover, the success of silicon photonics has opened new avenues for applications, e.g. in wavelength

regimes where silicon or the buried oxide of SOI is no longer transparent. The above-mentioned reasons cause an increasing interest to explore alternate material platforms which still possess relatively high index contrast and are CMOS compatible to enable high-density photonic integration.

Photonic sensors based on SOI technology

Photonic sensors based on SOI technology are commonly implemented as interferometers, specifically Mach–Zehnder interferometers (MZIs) [32], or resonators, such as ring resonators, disk resonators, 1-D and 2-D photonic crystal (PhC) resonators, and Bragg grating resonators [33][34][35]. The use of an asymmetric MZI-based biosensor platform has been recently described for the sensitive and multiplex detection of anti-SARS-CoV-2 antibodies in human plasma samples using the spike protein, the receptor-binding domain, and the nucleocapsid protein as target antigens [36]. Quantitative real-time label-free detection of DNA sequences using a liquid core optical ring resonator (LCORR) sensor is reported in [37]. The authors experimentally and theoretically analyzed the LCORR response to a variety of DNA samples with different strand lengths, numbers of base mismatches, and concentrations, with a sensitivity of 37.1 nm/RIU. The design of a high sensitivity graphene silicon hybrid microdisk in a square cavity biosensor used to detect pathogens such as cancer cells, glucose, influenza, and corona is shown in [38]. Recently, sensor technology based on PhC biosensors has become more versatile and shows excellent accuracy compared to its electronic counterparts. A radius-graded PhC sensor array applied on a nanoscale optical platform for label-free biosensing is proposed in [39]. The simulation results demonstrate that the refractive index sensitivity of the biosensor varies from 66.67 to 136.67 nm/RIU. Other important works based on PhC technology are presented in [40][41][42][43][44][45].

Among the above-mentioned options, it is well known that ring resonators offer advantages in terms of enhanced sensitivity and compact dimensions, making such optical cavities more appropriate for integrated sensing platforms. Moreover, it is notable that compared to traditional benchtop electrochemical instruments (enzyme-linked immunosorbent assays [46], electrochemical sensors [47], bilayer lipid membranes [48], high-performance liquid chromatographs [49], microelectrode immunoassays [50], field immunoassays [51], and surface plasmon resonance spectroscopes [52]), SOI-based rings provide several noteworthy benefits, including their small size, ability to be produced at

a large scale, rapid real-time readout capabilities, and potential for developing low-cost, portable devices for PoC applications. These advantages stem from the utilization of CMOS-compatible processes in the fabrication of SOI-based RRs. In Table 2.1, a comparison of SOI ring resonators presented in literature is reported.

For the purposes of our work, the focus is on ring resonator technology. A ring resonator is composed of a silicon-based waveguide on top of a buried oxide substrate, operating as a spectral filter by exploiting the principles of resonance and constructive interference within a looped optical pathway. Light introduced via the bus waveguide can couple into the ring when specific resonance conditions are met. This results in the buildup of light at resonant wavelengths inside the ring, creating dips in the transmitted light spectrum through the bus waveguide. If n_{eff} represents the effective refractive index of the propagating mode and L is the physical length of the ring, the resonant wavelengths can be mathematically stated as $\lambda_{res} = (\frac{n_{eff} \cdot L}{m})$, where m is the order of the resonant mode, and an integer number [53]. In this scenario, sensing could be performed by exploiting the interaction of the evanescent field of the propagating wave with the environment. A refractive index change in the cladding environment can be measured using these resonant devices, by tracking the shift in the optical spectrum. The figure-of-merit (FoM), defined as the sensitivity divided by the resonance width, is the most well-established performance parameter for assessing the performance of integrated microphotonic resonant refractive index sensors and biosensors. For RRs in SOI technology, the state-of-the-art FoM is $\simeq 1000 \text{ RIU}^{-1}$ [54][55][56][57].

In this context, much effort has been dedicated to improve waveguide geometries for optical sensing through simulation studies, and different ring-based resonant configurations have been explored, but a definitive comparative assessment of them was previously lacking in the literature. The novel aspect of this work is the accurate and scientifically founded comparison between various designs of ring resonators, aiding in the optimization of design parameters and the selection of the most suitable configuration for specific applications. The aim of one of our works is to experimentally compare four different ring configurations in terms of sensitivity and FoM , demonstrating that the slotted ring outperforms other competitive approaches. A silicon photonic chip including tens of RRs has been fabricated and optically characterized, with air and aqueous solutions as cladding.

Table 2.1: *Comparison of SOI ring resonators in literature*

Optical Device	Operating Wavelength (nm)	Q-factor (in water)	Sensitivity (nm/RIU)	Figure-of-Merit	Reference
All-pass RR with slot waveguides	1550	1900	476	583	[58]
All-pass RR with SWG waveguides	1550	3900	402	1045	[59]
Add-drop RR with strip waveguides	1550	20.000	70	933	[55]
Add-drop RR with slot waveguides	1550	1200	298	231	[60]
All-pass RR with slab waveguides	1550	4000	380	981	[61]
All-pass RR with SWG waveguides	1550	2180	423	615	[62]
Multi-box RR	1550	2600	579.5	1004	[57]

Fabricated Devices

The comparison is based on four different configurations of RRs, namely, three all-pass filters, the single ring, the slotted ring, the ring with an “S” junction (also known as the Taiji resonator) [63][64][65], and an add-drop filter, the panda ring [66], to evaluate their sensitivity in detecting changes in the refractive index of the top cladding. All the resonators, except the slotted one, are fabricated using a silicon strip waveguide characterized by a height of 250 nm and a width of 450 nm. The slot waveguide is composed of two rails, each having a thickness of 250 nm, a width of 225 nm, and spacing of 100 nm. A schematic representation of the waveguides cross section is provided in Fig. 2.1.

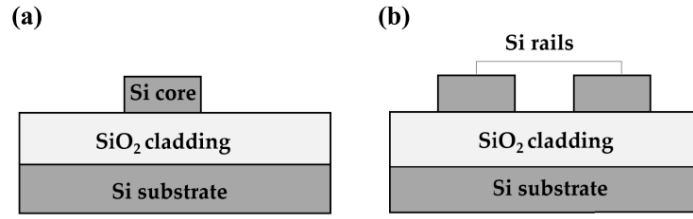


Figure 2.1: *Cross-sectional view of SOI waveguides (a) strip waveguide, and (b) slot waveguide*

All rings are designed with a radius of 20 μm . This value is a compromise between two contrasting needs: a small footprint for the optical cavity and a high Q-factor for the resonators. The coupling between the rings and the bus waveguide has been evaluated for different gap values, ranging from 0.06 to 0.3 μm for all configurations, except the slotted ring, for which the gap reaches 0.7 μm . Furthermore, the panda ring is obtained by considering a cascade of three RRs separated by 0.1 μm , where the dimension of the central one is identical to the other configurations and the side rings have a radius of 10 μm . The geometrical sizes of the rings are selected after an accurate design activity assuming that the propagation loss of the silicon waveguide is in the range of 2.4 dB/cm for the silicon wire and 3.5 dB/cm for the slot waveguide.

As already mentioned, two types of widely used waveguides, namely, strip and slot waveguides, are tested. Using the finite element method (FEM), it is possible to confirm that these are single mode waveguides, and to calculate the effective refractive index of the quasi-TE mode supported by the waveguiding structures, which, for the strip waveguide, is equal to 2.389 or 2.439 with air or aqueous solution as the top cladding, respectively; in the case of the slot waveguide, this value is equal to 1.729 or 1.818 with air or aqueous solution as top cladding.

The amount of light penetrating into the cladding differs for each waveguide configuration and correlates with unwanted optical losses and waveguide sensitivities. The E_x -field intensity of the quasi-TE mode for the strip and slot waveguides is provided in Fig. 2.2. It is evident that light is mainly confined inside the silicon core in the case of strip waveguides, whereas in the case of slot waveguides, the light can be significantly confined in the vicinity of two silicon rails.

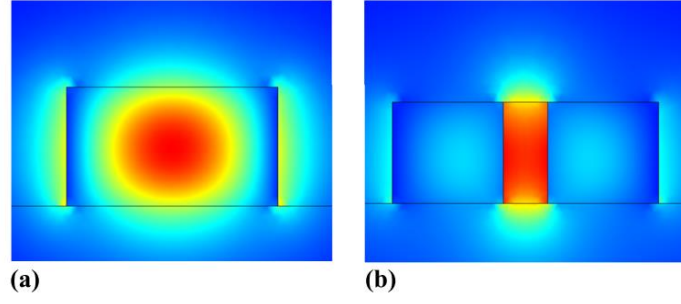


Figure 2.2: *Simulation of the Ex-field intensity of the quasi-TE mode for (a) strip waveguide and (b) slot waveguide.*

The chip fabrication was carried out at SiPhotonIC in Technical University of Denmark using e-beam lithography, a technique that enables precise patterning of the waveguides in the upper silicon layer. Subsequently, the process of etching is carried out to delineate the strip waveguides, entailing the total removal of the surrounding silicon material.

Optical Characterization

For chip characterization, a single-mode fiber setup is implemented. The quasi-TE mode is excited in all resonant devices. The TE-polarized light of a tunable laser, working in the wavelength range from 1500 to 1630 nm, is coupled to the silicon-based waveguides via the grating coupler at the edge of the chip. The light is then partly coupled to the RR if the resonance condition is fulfilled, leading to resonance peaks in the transmitted power spectrum. A photodiode is used to detect the optical output of the resonator, generating a current proportional to the intensity of the light. Then, an oscilloscope is used to analyze the electrical signal. A schematic representation of the setup is shown in Fig. 2.3.

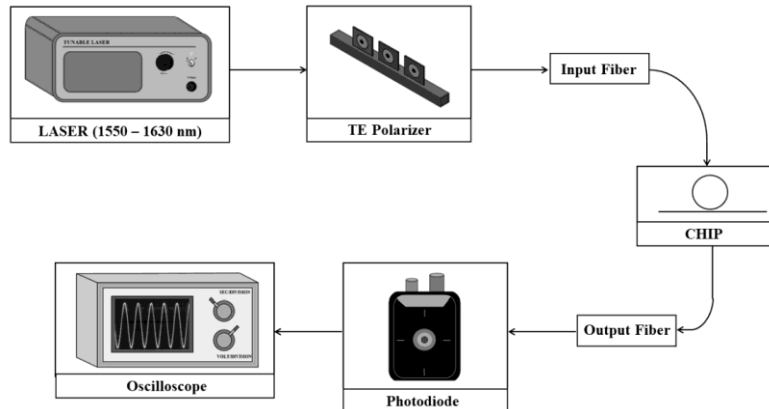
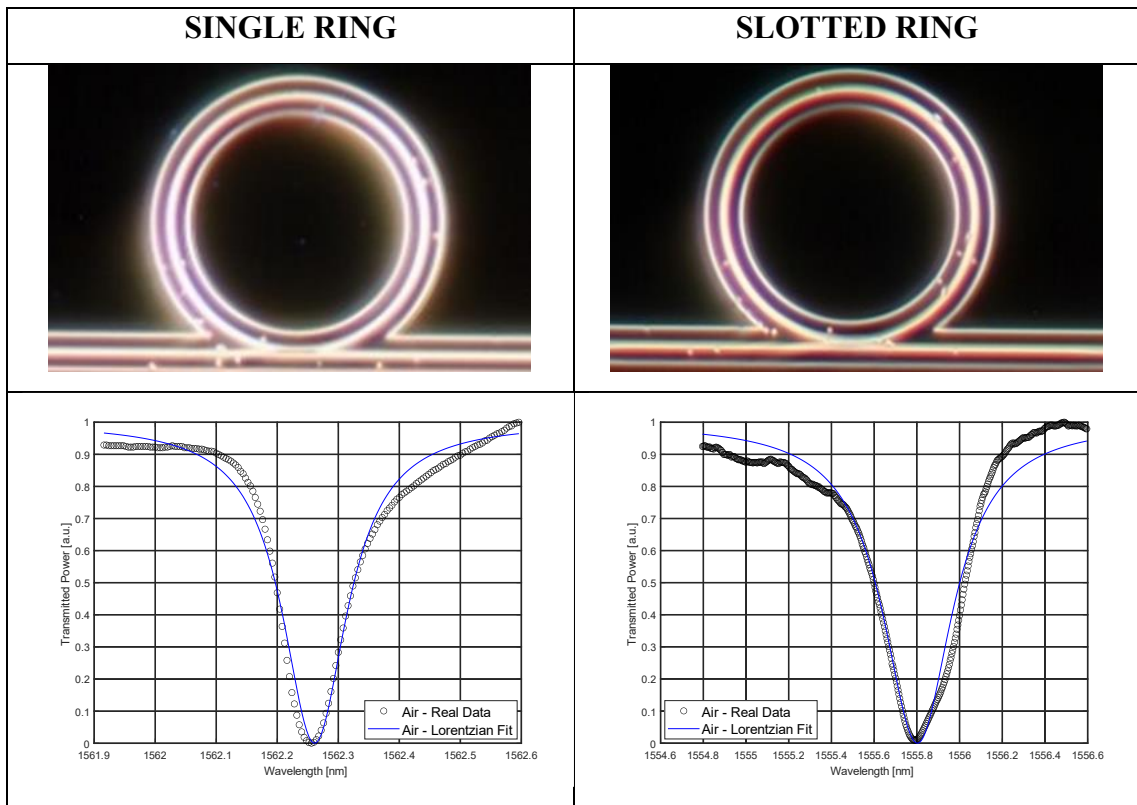


Figure 2.3: *Schematic of the experimental setup used to test the RRs as sensors.*

For each configuration, several measurements are obtained using air as the top cladding. First, the free spectral range (FSR) is estimated, achieving values of approximately 5 nm. Then, from the transmission spectrum, a wavelength range of 2 nm is considered so that it is possible to select the resonance that yields the highest value of the extinction ratio (ER). Next, the spectral response is fitted by using the Lorentzian function, which effectively approximates the trend of this type of experimental data. In addition, to assess the spectral resolution of the devices, the full width at half maximum ($FWHM$) of the selected resonance is measured, ensuring that it is approximately 0.5 nm for all configurations. As an example of the results obtained with air as top cladding, in Fig. 2.4, the spectral responses of the four types of resonant devices, for selected values of the RR gap, are presented. The spectra all have a Lorentzian shape, with a very high ER . Fig. 2.4 also shows the image of the characterized resonators at microscopic level.



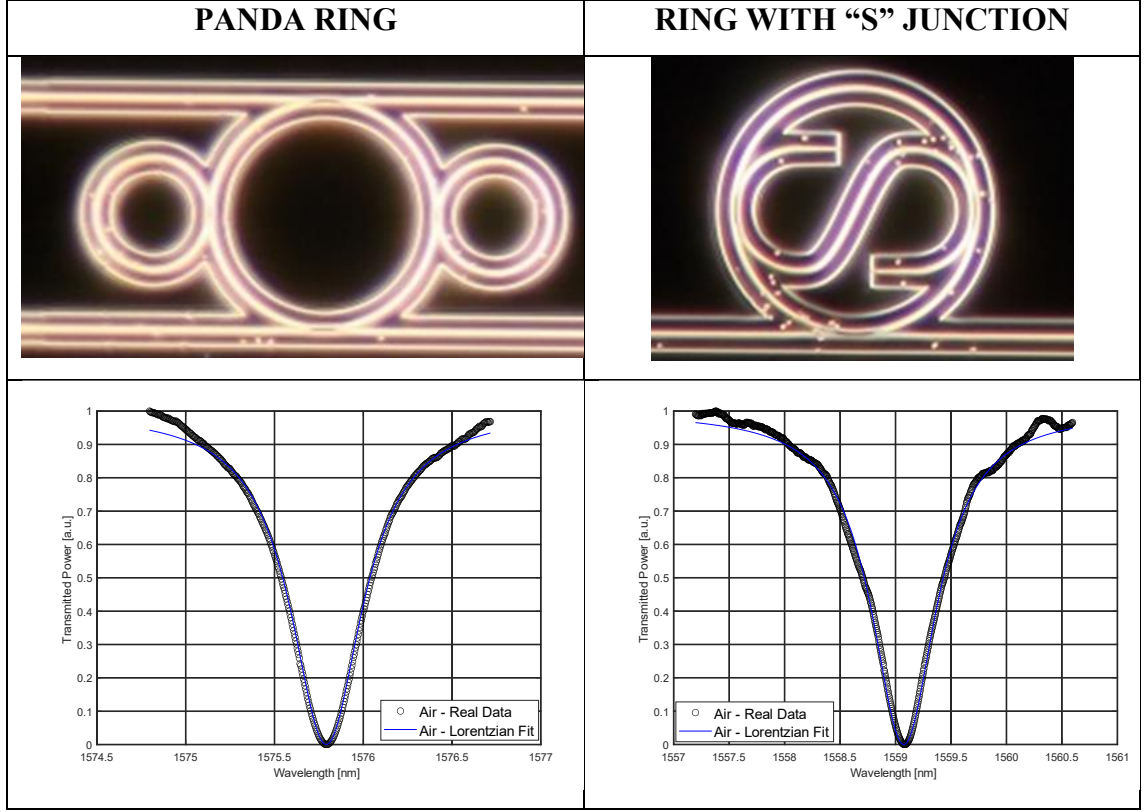


Figure 2.4: *Experimental results obtained with air as the top cladding. For each RR configuration, below, the transmitted power, evaluated in a certain range of wavelengths, is reported (both real data and the results of Lorentzian fitting) by considering a specific gap value (gap = 0.18 μm for the single ring, gap = 0.3 μm for the slotted ring, gap = 0.16 μm for the panda ring, and gap = 0.08 μm for the ring with the “S” junction); above, a detailed image of the RR at the microscopic level in the dark field.*

In the specific case of single and slotted RRs, the ER and the Q -factor are reported as a function of the gap considered (see Figs. 2.5 and 2.6), underlying the critical coupling condition for gap = 0.18 μm and gap = 0.25 μm , respectively. In both configurations, the same trend is noticed and, in particular, the Q -factor increases with the increase in the gap between the ring and the bus waveguide, according to a quadratic dependence. The ER exponentially grows up to the gap value assumed as corresponding to the critical coupling condition, and then decreases for higher gap values.

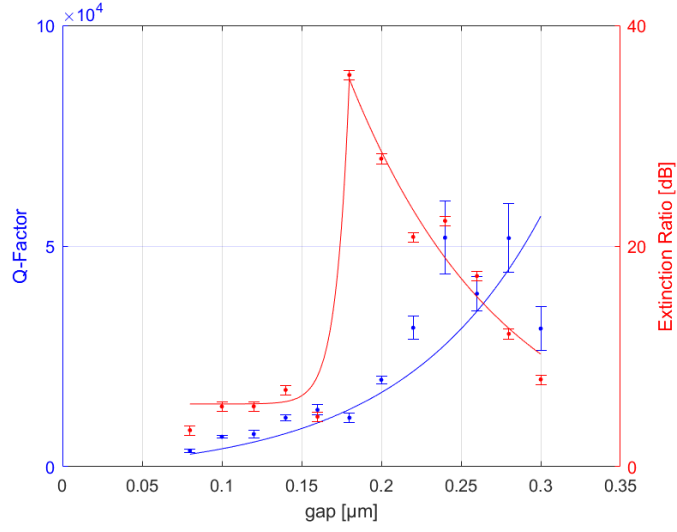


Figure 2.5: *Q-factor and ER trends versus gap values in the case of the single ring.*

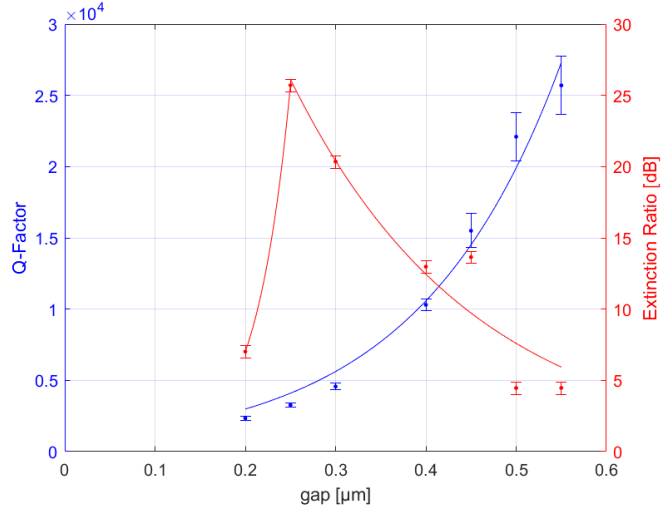


Figure 2.6: *Q-factor and ER trends versus gap values in the case of the slotted ring.*

At this point, to test the efficiency of devices, a preliminary evaluation of losses is needed. In practice, considering the transfer function of all-pass RRs (Eq. 2.1), it is necessary to evaluate the value of a , which represents the single-pass amplitude transmission, including both propagation loss in the ring and loss in the couplers [53]:

$$T_n = \frac{a^2 - 2racos\phi + r^2}{1 - 2rcos\phi + (ra)^2} \quad (2.1)$$

where r is the self-coupling coefficient and $\varphi = \beta L$ is the single-pass phase shift, with L being the length of the ring and β being the propagation constant of the circulating mode (assumed to be 1).

Using this method, the estimated loss is equal to 2.5 dB/cm in the case of the single ring and 4.5 dB/cm in the case of the slotted ring. This finding agrees with the results in the literature and indicates that slot waveguides are better in terms of sensitivity but are associated with higher optical losses [67]. Similarly, it is possible to define r as the cross-coupling coefficient, so that r^2 and k^2 are the power splitting ratio of the coupler, and they are assumed to $r^2 + k^2 = 1$, which means that there are no losses in the coupling section. Consequently, given the value of r^2 , k^2 is derived, representing the coupling efficiency (η) as a percentage. In particular, the results indicate that η approaches 3.17% in the single ring configuration, while it increases up to 7.86% in the slotted ring configuration.

For each ring configuration, the best value of the gap based on the results of the characterization in air is selected and, in particular, the device with the highest Q-factor value among those with $ER > 8$ dB.

Sensing Experiments with NaCl Solutions

These four devices are first characterized using water as the top cladding and then using a series of NaCl solutions of varying concentrations (0.25, 0.5, and 1 M). This is done to assess the bulk sensitivity to refractive index changes in the cladding in terms of resonance shift. It should be noticed that the resonator sensitivity, S_r , is independent of the gap value characterizing the distance between the ring and the bus waveguide. It is strictly correlated with the operating wavelength (λ_{res}), the waveguide sensitivity (S_w), and the group index (n_g) as follows [68]:

$$S_r = \frac{\lambda_{res}}{n_g} \cdot S_w \quad (2.2)$$

where $S_w = (\partial n_{eff} / \partial n_c)$, with n_c the cover medium refractive index.

In Figs. 2.7-2.10, the raw data in the form of transmission spectra are processed to track the wavelength shift of a single resonant peak. Figs. 2.7-2.10 also show the plot of the resonance peak wavelength shifts against the refractive index change for each solution with respect to distilled pure water. The refractive indices of the water and NaCl solutions employed are calculated at a wavelength of 1550 nm [54]. From the obtained outcomes, it is evident that the regression line closely fits the working points, with a value of the coefficient of determination (R^2) close to 0.99.

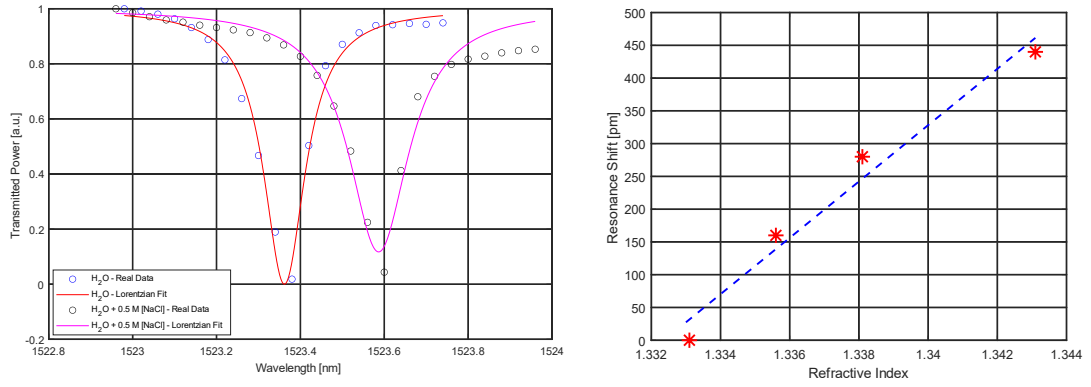


Figure 2.7: Experimental results with aqueous solution as the top cladding for the single ring.

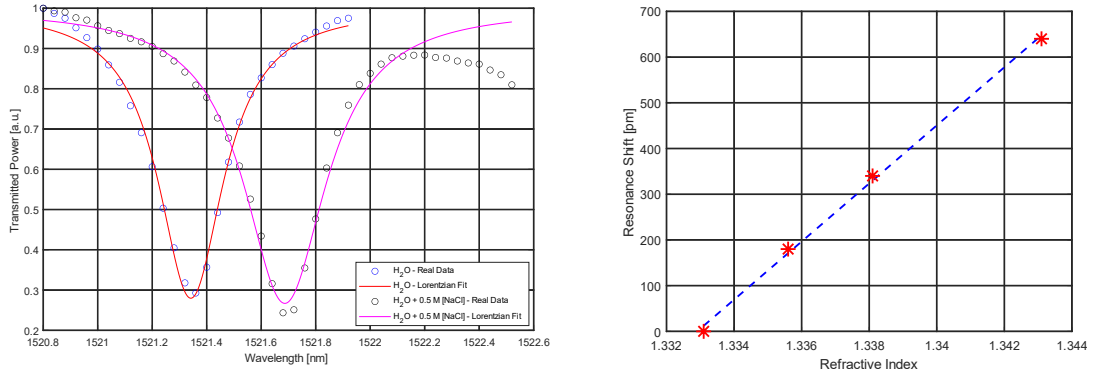


Figure 2.8: Experimental results with aqueous solution as the top cladding for the slotted ring.

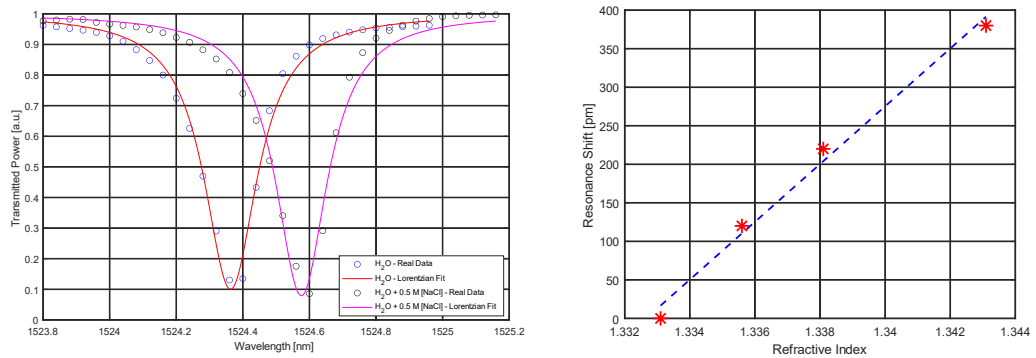


Figure 2.9: Experimental results with aqueous solution as the top cladding for the panda ring.

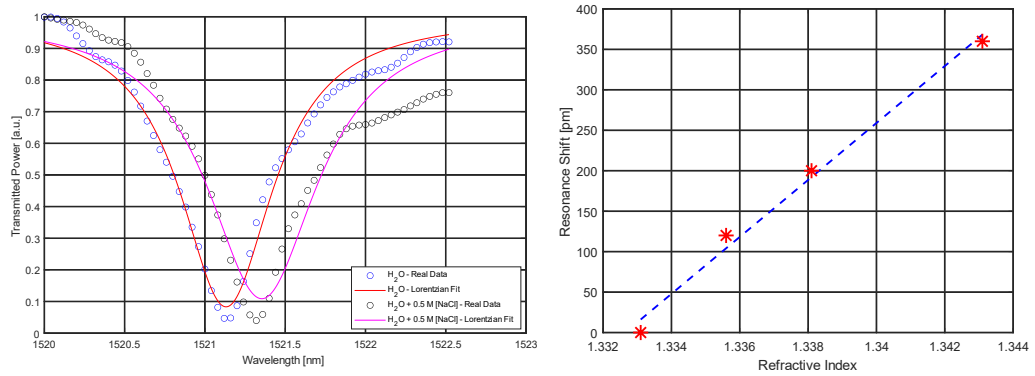


Figure 2.10: *Experimental results with aqueous solution as the top cladding for the ring with the “S” junction.*

For the single-ring configuration, when the top cladding is changed from pure distilled water to water containing salts at different concentrations, the experimental findings show that the measurable shift is approximately 160, 280, and 440 pm. Then, the bulk sensitivity (S) is determined by measuring the ratio of the change in the resonant wavelength caused by the change in the refractive index.

In this specific case, a sensitivity $S = 43$ nm/RIU is obtained. As shown in Table 2.2, the same process is implemented for the slotted ring, the panda ring, and the ring with the “S” junction. The slotted ring proves to be the most sensitive, with a sensitivity of 64 nm/RIU.

Table 2.2: *Summary of the resonance shifts, Q -factor in water, and bulk sensitivity values for the RRs tested*

Ring Resonator Configuration	Gap Value	Q-factor in water	Resonance Shifts for 0.25 M, 0.5 M, and 1 M	Bulk Sensitivity
<i>Single Ring</i>	180 nm	8.4×10^3	160 pm, 280 pm, 440 pm	43 nm/RIU
<i>Slotted Ring</i>	300 nm	3.5×10^3	180 pm, 340 pm, 640 pm	64 nm/RIU

<i>Panda Ring</i>	160 nm	2.5×10^3	120 pm, 220 pm, 380 pm	38 nm/RIU
<i>Ring with "S" Junction</i>	80 nm	1.7×10^3	120 pm, 200 pm, 360 pm	35 nm/RIU

Assuming that the readout systems exhibit a minimum detectable shift in the resonance wavelength, $\Delta\lambda_{min}$, that is, 1/15 of the *FWHM* [69], the minimum detectable change in the refractive index is in the order of 10^{-4} RIU. A common *FoM* to evaluate the sensing performance of the devices is given by the sensitivity divided by the resonance width. For each configuration of RR, the width of the resonance peak obtained while testing in pure water was evaluated. As shown in Fig. 2.11, the results confirm that the slotted ring is the most sensitive of the four configurations but identify the panda ring as the second most effective in this regard. The *FoM* for the slotted ring is 221.5 RIU^{-1} .

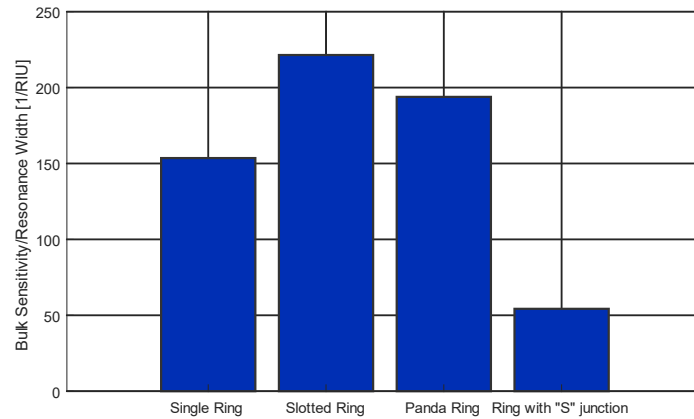


Figure 2.11: *FoM: evaluation of the sensing performance of the devices by dividing the values of bulk sensitivity obtained from the resonance peak width of the experiments in pure water.*

Comparison of SOI Ring Resonators with other optical technologies

Microring resonators based on silicon-on-insulator (SOI) technology offer numerous advantages over other biosensing methods, particularly in the context of sensitivity, miniaturization, integration, and multiplexing capabilities. One of the most significant benefits is their ultra-sensitivity, enabling the detection of very low concentrations of

analytes. This high sensitivity is especially valuable in biomedical applications, where the early detection of biomarkers can be critical for diagnosis and treatment.

Another key advantage of SOI microring resonators is their ability to facilitate high multiplexing. By integrating multiple resonators on a single chip, these devices can simultaneously detect a variety of analytes, enhancing the efficiency in biosensing applications. The multiplexing capability is crucial for comprehensive diagnostics, allowing for the simultaneous monitoring of multiple biomarkers or pathogens, which can significantly improve patient outcomes.

The small footprint of SOI microring resonators also contributes to their effectiveness. The miniaturization enables the development of compact and portable biosensing devices that are essential for point-of-care applications, where space and convenience are paramount. Furthermore, microring resonators are designed for seamless integration into SOI platforms, leveraging established semiconductor fabrication techniques. This compatibility not only streamlines the manufacturing process but also supports mass production at a lower cost, making them economically advantageous for single-use applications.

However, while microring resonators offer these substantial benefits, they suffer from limitations. Their reliance on precise control during the fabrication process can lead to variations that impact sensitivity and overall performance. Moreover, although they excel in sensitivity and multiplexing, there may be specific applications, particularly those requiring the detection of complex biomolecular interactions, where their performance does not match that of advanced interferometric techniques or plasmonic sensors. Additionally, SOI microring resonators may encounter challenges related to temperature sensitivity and environmental stability, which could affect their accuracy in dynamic biological conditions.

In Tab. 2.3, a general comparison in terms of surface and bulk sensitivity is reported for different optical technologies.

Table 2.3: *State-of-the-art photonic biosensors*

Optical Detection Method	Surface Sensitivity (pm/mm²)	Bulk Sensitivity (RIU)
Plasmonic (SPR, LSPR)	0.1-1	$10^{-5} - 10^{-7}$
Grating Couplers	0.3	$2 \cdot 10^{-6}$
MZI interferometer	0.01-0.06	$10^{-7} - 2 \cdot 10^{-8}$
BiMW interferometer	0.01	10^{-8}
Young interferometer	0.013-0.75	$9 \cdot 10^{-8} - 9 \cdot 10^{-9}$
Ring Resonators	1.5-3	$5 \cdot 10^{-6} - 7 \cdot 10^{-7}$
Photonic Crystals	0.4-7.5	10^{-5}

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CHAPTER 3

Ring Resonators in Silicon Nitride Technology

Silicon Nitride Platform

Silicon-on-insulator (SOI) has matured into a sophisticated photonic integrated circuit (PIC) platform used in devices already available on the market; nevertheless, it is not the only alternative for high-index-contrast optical circuits produced via CMOS manufacturing. Silicon nitride (Si_3N_4) is being investigated as a viable alternative photonics structure, with similar attributes and advantages. Comparing SOI and Si_3N_4 in terms of fabrication imperfections and associated losses, it can be stated that silicon nitride shows better performance. It has a refractive index that is an optimal compromise, being lower than that of silicon but higher than that of silicon dioxide, resulting in a lower index contrast compared to that obtained in SOI platforms. This is because a high index contrast allows better light confinement in the optical waveguide, but also makes it more prone to surface roughness and dimensional deviations during the fabrication, leading to significant propagation and scattering losses [1][2][3]. Furthermore, silicon nitride offers substantial benefits for biosensing tests, due to its resistivity to humidity and Na^+ ion diffusion, hence preserving a steady refractive index when in contact with biological fluids [4].

In general, a material platform needs to have a range of characteristics to be effective for photonic integration. This includes a wide transparency range, the ability to provide low loss components, allowing for high integration density, the realization of high performance active and passive components properties to implement novel devices.

On the basis of the above-mentioned attributes for the SOI and Si_3N_4 material platforms, a detailed comparison between these two material platforms follows:

A. Transparency range

SOI-based waveguides have low absorption losses in the wavelength range from 1.1 μm (band edge of silicon) to about 3.7 μm (onset of mid-IR absorption of silica). For applications requiring shorter wavelengths (e.g. data communication at 850 nm, sensors

operating in the therapeutic window etc.) SOI is not an option. Since Si_3N_4 is transparent throughout most of the visible range – down to at least 500 nm – it is a viable candidate to implement silicon photonics at wavelengths below 1.1 μm [5]. This has led to demonstrations of spectroscopic functions [6][7], Raman spectroscopy-on-chip functions [8][9][10] and integration with colloidal quantum dots emitting in the visible [11].

B. Index contrast

The index contrast in SOI waveguides is very high (3.5 vs 1.5) while that in Si_3N_4 waveguides is moderately high (2 vs 1.5). Very high index contrast is both a blessing and a curse: it allows one to implement unique functionalities on a very compact footprint but at the same time it makes the waveguide prone to scattering losses due to nm-scale roughness of the sidewalls of the waveguide. Even a roughness of only a few nm already leads to a waveguide loss of the order of 1 dB/cm. It also implies high sensitivity of the effective index to the waveguide width. This leads to the harsh rule of thumb that a waveguide width deviation of 1 nm leads to a ~ 1 nm wavelength error in the spectral transfer function of interferometric components such as Mach Zehnder- or ring resonator-based devices. It also leads to less-than-ideal crosstalk in arrayed waveguide gratings. In Si_3N_4 waveguides, all of this is relaxed to a certain degree, while the compact footprint is largely maintained. One could say that the index contrast in silicon nitride waveguides sits in a nice middle ground.

The lower index contrast of the Si_3N_4 system as compared to SOI implies that it is harder to make high efficiency grating couplers for out-of-plane optical input/output, a very useful feature that allows for wafer-level testing and alignment-tolerant fiber coupling [12].

C. Low loss

SOI-based photonic wires have typical waveguide losses of 1 to 2 dB/cm, largely due to the scattering losses associated with sidewall roughness. In Si_3N_4 photonic wires, these losses can in principle be an order of magnitude lower. The losses can be reduced further by using shallow rib waveguides or very thin strip waveguides. Losses down to ~ 1 dB/m have been reported for such Si_3N_4 waveguides, but this is obviously at the expense of lateral and/or vertical confinement [13][14].

Photonic sensors based on Silicon Nitride Technology

Photonic sensors such as Mach–Zehnder interferometers [15][16], photonic crystals [17], ring resonators, etc., can be implemented by using silicon nitride technology. Notably, silicon-nitride ring resonator technology could be highly promising due to its compact size and high-throughput analysis capabilities.

The combination of Si_3N_4 ring resonator biosensors with a filter bank spectrometer is exploited for detecting a pentameric protein produced by the liver, the C-reactive protein (CRP), with levels increasing in response to an inflammation in human body. Authors demonstrate the capability of their device to quantify the concentration of that biomarker with a sensitivity of 179.7 nm/RIU [18]. A detailed comparison between silicon nitride ring resonators designed to work in TE mode at 1550 nm and those designed to work in TM mode at 1310 nm is reported in [19]. The outcomes of this work highlight the superior performance of the latter as label-free biosensors, due to the higher sensitivity and quality factor achieved by operating in TM mode at 1310 nm. A T-shaped silicon nitride ring resonator fabricated using suspended waveguides atop a silicon dioxide layer is demonstrated in [20]. Bulk sensing experiments with organic liquids show a sensitivity of approximately 247 nm/RIU, making the sensor suitable for biosensing applications.

Design of Silicon Nitride Ring Resonators

In this work [21], the performance of ring resonators operated in the TE mode around 1310 nm wavelengths using strip and slot waveguides is studied. These waveguides are designed considering 0.3- μm thick silicon nitride layer atop a silicon dioxide bottom cladding layer with a precise thickness of 3.26 μm . Specifically, the strip waveguide has a thickness of 300 nm and width of 900 nm, whereas the slot waveguide is made up of two parallel rails, each 300 nm thick and 550 nm wide, separated by a tiny gap of 150 nm. All ring resonators have a fixed radius of 100 μm to avoid bending loss.

The amount of light penetrating into the cladding varies for each waveguide configuration, affecting both optical loss and waveguide sensitivities. Fig. 3.1 shows the cross-section and the E_x -field intensity of the TE-mode for both strip and slot waveguides. It is clear that in strip waveguides, light is primarily confined within the silicon core, while in slot waveguides, a significant portion of the light is confined near the two silicon rails.

In order to convert the mode of light propagation from the strip waveguide mode to the slot waveguide mode, a taper (strip-to-slot converter) is used. This device is designed in such a way that the conversion is efficient and with minimal loss of light (see Fig 3.2).

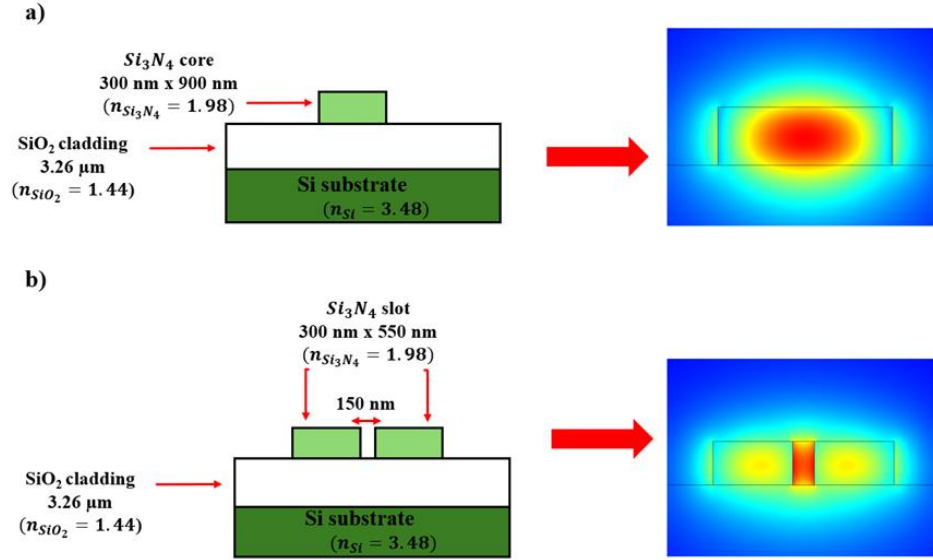


Figure 3.1: Cross-sectional view and simulation of the E_x -field intensity of the TE-mode for strip and slot waveguides.

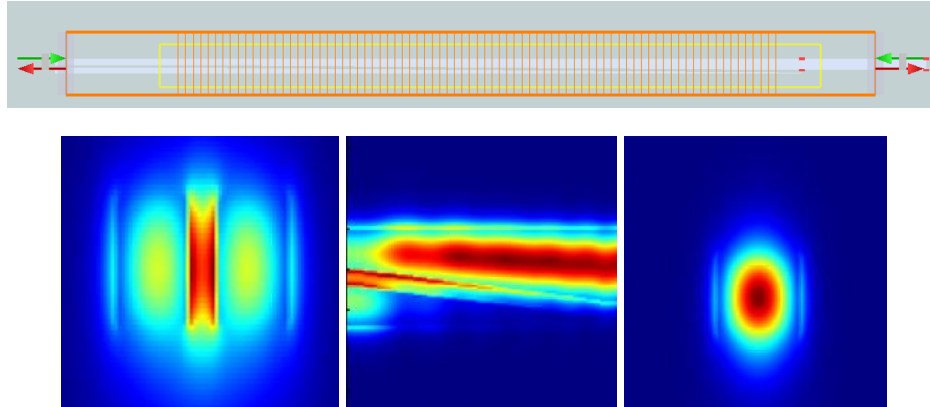


Figure 3.2: Strip-slot coupler geometry. In the insets, E_x field distributions at the starting, at the center, and at the ending section of the coupler are shown.

The coupling efficiency between the ring and the bus waveguide is evaluated across various gap distances, ranging from 0.4 μm to 0.55 μm . rings. The couplers included in the device are formed by a straight waveguide and a bent one (see Fig. 3.3). In this

component, the distance between the centres of the waveguides depends on z , i.e. the coordinate along the propagation direction, and so the coupling coefficient κ between the modes propagating in the two waveguides depends on z , too.

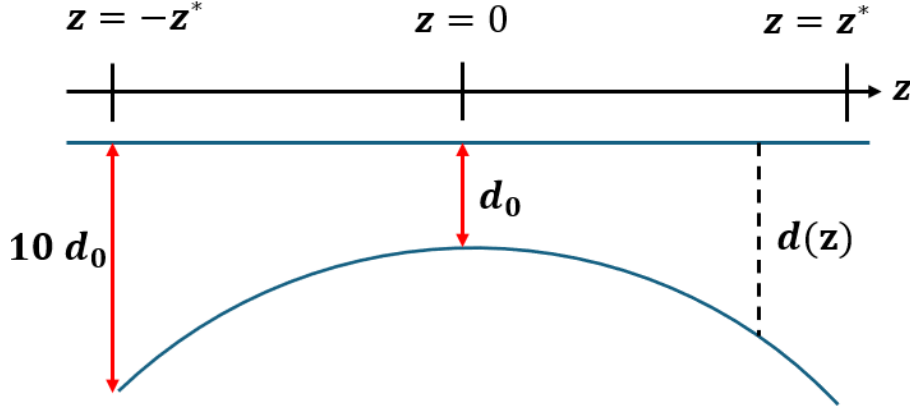


Figure 3.3: Coupler formed by a straight waveguide and a bent one.

The distance between the waveguides is equal to:

$$d(z) = R + d_0 - \sqrt{R^2 - z^2} \quad (3.1)$$

where R is bending radius of the bent waveguide and d_0 is the minimum distance between the centers of the waveguides.

The dependence of the coupling coefficient κ on d_0 has been derived by calculating the propagation constants of the symmetric and the anti-symmetric quasi-TE supermodes ($\beta_S = \frac{2\pi}{\lambda} \cdot n_{effS}$ and $\beta_A = \frac{2\pi}{\lambda} \cdot n_{effA}$, respectively) supported by the coupler for d_0 ranging from 1000 nm to 1700 nm. The coupling coefficient κ is equal to $(\beta_S - \beta_A)/2$ [22]. The κ dependence on d is very well fitted by the following exponential function:

$$\kappa(z) = k_1 \exp[k_2 d(z)] = k_1 \exp \left[k_2 \left(R + d_0 - \sqrt{R^2 - z^2} \right) \right] \quad (3.2)$$

where k_1 and k_2 are fitting coefficients depending on the geometrical and optical properties of the waveguides forming the coupler.

The amplitudes A_1 and A_2 of the two modes propagating in the waveguides can be estimated by using the coupled mode theory (CMT) [23]:

$$\begin{cases} \frac{dA_1(z)}{dz} = -i\kappa(z)A_2(z) \\ \frac{dA_2(z)}{dz} = -i\kappa(z)A_1(z) \end{cases} \quad (3.3)$$

For $z = \pm \sqrt{2d_0^2 R - 9d_0^2} = \pm z^*$, the distance between the waveguides is $10 d_0$. It is possible to assume that the coupling between the waveguides is negligible at that distance. Therefore, it is possible to simulate the coupler in the range from $-z^*$ to $+z^*$ and impose the following initial condition:

$$a_1(-z^*) = 1, a_2(-z^*) = 0 \quad (3.4)$$

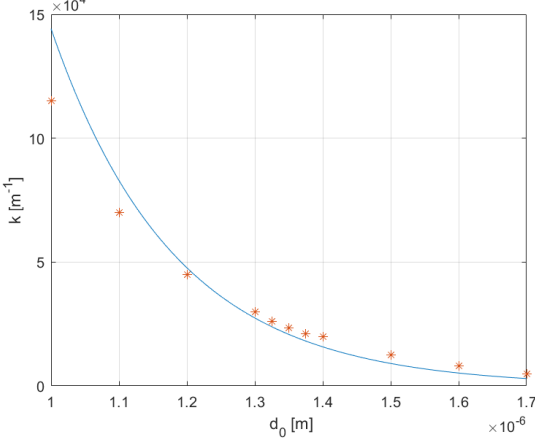
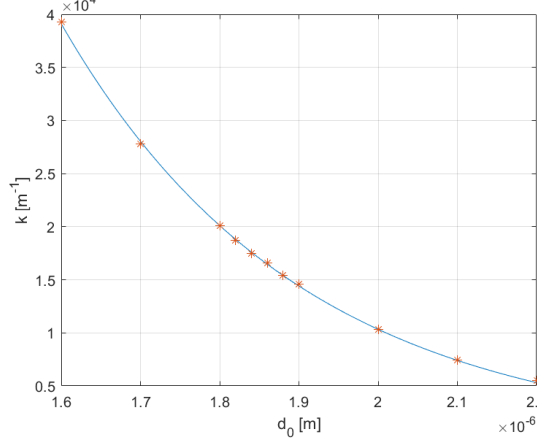
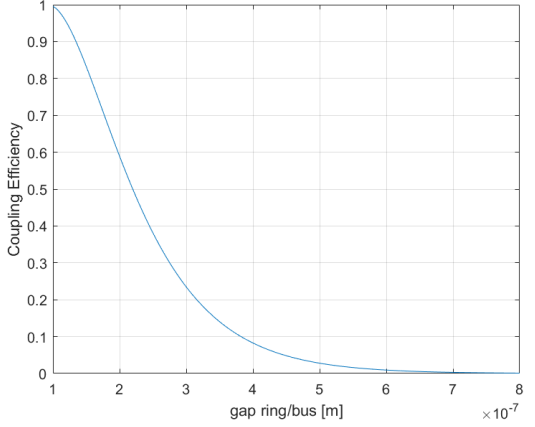
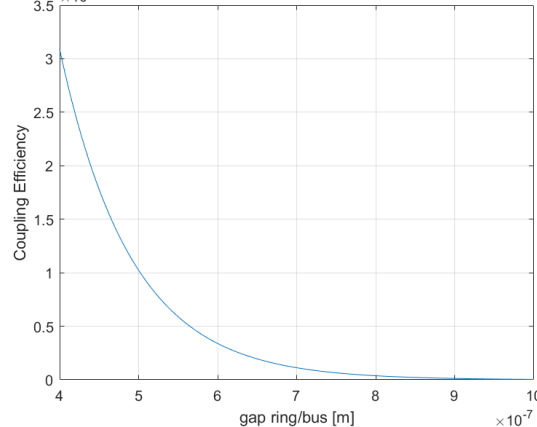
The coupling efficiency η , which is the fraction of the optical power passing from the straight waveguide to the bent one, can be estimated by solving the equation system (Eq. (3.3)) in the range from $-z^*$ to $+z^*$.

After calculating the solution of Eq. (3.3), the coupling efficiency can be evaluated as:

$$\eta = |a_2(z^*)|^2 \quad (3.5)$$

In Table 3.1, for both strip and slot waveguides, the exponential plot of κ vs. d_0 from which the estimation of the coupling parameters, k_1 and k_2 , is obtained. Always in Table 3.1, the trend of the coupling efficiency vs. the gap between the bus waveguide and the ring is reported. As expected, η decreases as the gap increases. In the case of strip waveguides, the condition $\eta = 3.5\%$ is achieved for gap ≈ 480 nm; whereas, in the case of slot waveguides, the condition 4.3% is achieved for gap ≈ 680 nm.

Table 3.1: Estimation of coupling parameters, k_1 and k_2 , and evaluation of the coupling efficiency, η .

Estimation of coupling parameters, k_1 and k_2	
Strip Waveguide	Slot Waveguide
 $k_1 = 3.635e + 07 [m^{-1}]$ $k_2 = -5.53e + 06 [m^{-1}]$	 $k_1 = 8.02e + 06 [m^{-1}]$ $k_2 = -3.327e + 06 [m^{-1}]$
Evaluation of the coupling efficiency, η	
Strip Waveguide	Slot Waveguide
	

The devices' dimensional parameters are selected by an accurate design procedure, taking into account the propagation losses of the silicon nitride waveguides, which are 2 dB/cm for the strip waveguide and 3 dB/cm for the slot waveguide (experimental values). Using the finite element method (FEM), it is possible to verify that these are single-mode waveguides, and to calculate the effective refractive index of the TE mode supported by

the waveguiding structures, which, for the strip waveguide, is equal to 1.537 or 1.584 with air or aqueous solution as the top cladding, respectively; in the case of the slot waveguide, this value is equal to 1.453 or 1.535 with air or aqueous solution as top cladding.

Fabrication of Silicon Nitride Ring Resonators

The fabrication process is carried out at the Nanophotonic Technology Center (NTC), Polytechnic University of Valencia, using standard silicon micro-fabrication methods in a class 10-1000 clean room, according to the following steps (summarized in Fig. 3.11):

1. Wafer Cleaning

First, the wafer used for preparing the silicon nitride sample is cleaned with acetone and isopropanol, followed by an oxygen plasma treatment for 15 minutes to remove any organic and inorganic contaminants from the surface. To improve adhesion, a siloxane primer is then applied to the wafer, which is subsequently heated for 2 minutes at 180 °C.



Figure 3.4: *EVG101 by EVG.*

2. Photoresist Coating

Next, a photosensitive material, known as photoresist, is applied to the substrate. This material undergoes chemical changes when exposed to light. In this case, a negative photoresist with a thickness of 300 nm is used, and after application, the wafer is heated for 1 minute at 90 °C.



Figure 3.5: *Plasma Surface Technology by Diener Electronic.*

3. Resist Exposure – e-beam lithography

Following this, a focused beam of electrons is used to selectively expose the resist-coated substrate according to the desired pattern, defining the layout.



Figure 3.6: *E-beam lithography system (JBX-8100FS) by Jeol.*

4. Resist Development

After exposure, the substrate undergoes a development process where the exposed regions of the negative photoresist become insoluble and remain on the substrate, forming the pattern.



Figure 3.7: *CEE100 Resist Developer by Equip X.*

5. Reactive Ion Etching (RIE)

The pattern is then transferred onto the underlying layers of the substrate using Reactive Ion-Etching (RIE). During this step, the substrate is placed in a vacuum chamber filled with a reactive gas like trifluoromethane (CHF_3) and subjected to an electric field, creating chemically reactive ions that selectively etch away the unprotected areas.

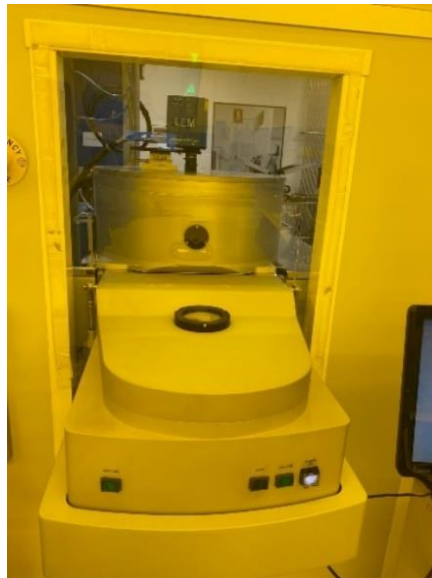


Figure 3.8: *210IL ICP-RIE etch system by Corial.*

6. Resist Removal

Once the pattern is transferred, the remaining photoresist is removed using plasma ashing, ensuring that only the patterned features remain on the substrate, ready for the characterization process.



Figure 3.9: *Plasma Asher by PVA TePla AG.*

7. Thickness Measurement

Finally, the thickness of the silicon thermal oxide is analyzed using a microscope, verifying it to be approximately 40 nm.

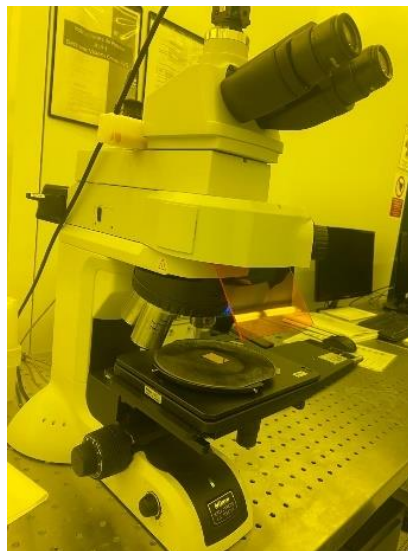


Figure 3.10: *Microscope-Nikon ECLIPSE LV150N.*

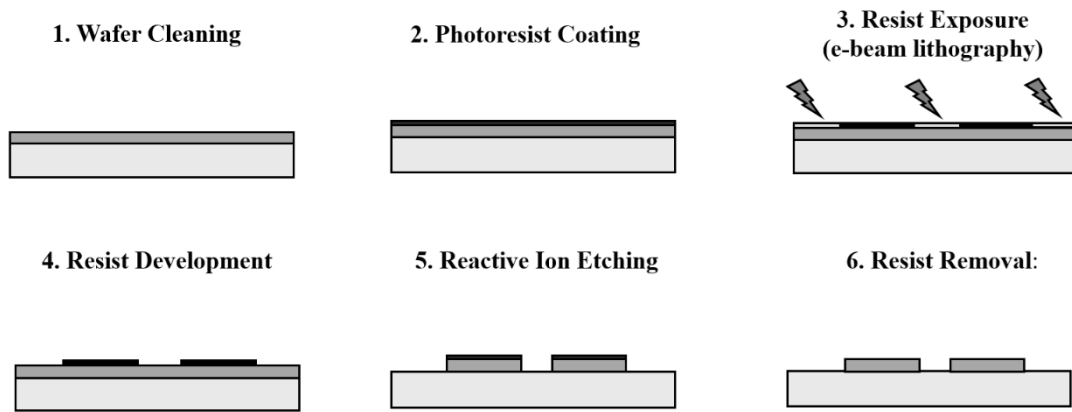


Figure 3.11: *Summary of Si_3N_4 ring resonators' fabrication process.*

Each step in the fabrication process depicted in Fig. 3.11 plays a critical role in determining the quality of the final ring resonator. Initially, wafer cleaning is essential to remove any contaminants or particles that could cause defects. Residual contamination can lead to scattering losses and structural irregularities, adversely affecting the resonator's performance. Following this, the photoresist coating step requires a uniformly applied layer to ensure consistent patterning. An uneven photoresist layer can result in non-uniform etching, which compromises the resonator's dimensions and functionality.

During resist exposure using e-beam lithography, precise control over the electron beam is paramount. Any inaccuracies in this step can lead to deviations in the pattern, introducing imperfections that degrade the resonator's optical properties. The resist development step, where the exposed photoresist is developed to reveal the pattern, must be carefully monitored. Overdevelopment or underdevelopment can alter the pattern dimensions, impacting the resonator's efficiency and performance.

The reactive ion etching step then transfers the pattern onto the substrate. The etch rate and uniformity are crucial here, as non-uniform etching can lead to dimensional variations that affect the resonator's optical characteristics. Finally, resist removal must be thorough and complete to prevent any remaining residues from introducing scattering centers or other defects that could impair the resonator's quality.

Overall, meticulous control and precision at each step—from wafer cleaning to resist removal—are vital to ensure the fabrication of a high-quality ring resonator with optimal performance.

Experiments

The functionality of the fabricated devices is assessed by analyzing the transmission spectrum of 6 mm long bus waveguides evanescently coupled to ring resonators with air as the top cladding. First, the sample is placed on a holder using air suction. Then, input and output fibers are positioned at a standard 10° angle for TE-mode using 3D-printed wedges. The fibers' inclination allows for varying coupling distances, which are adjusted using automated 3-axis positioners. This iterative refinement process continues until no further increase in output power is observed. Throughout the alignment process, a camera and light source are employed to visualize the sample and optical fibers. In addition, a tunable continuous wave (CW) laser is used to perform a wavelength sweep, and the transmission spectrum is recorded by measuring the received power in dBm units with an optical power meter. A detailed image of the setup used for the characterization at a wavelength of 1310 nm is presented in Fig. 3.12.

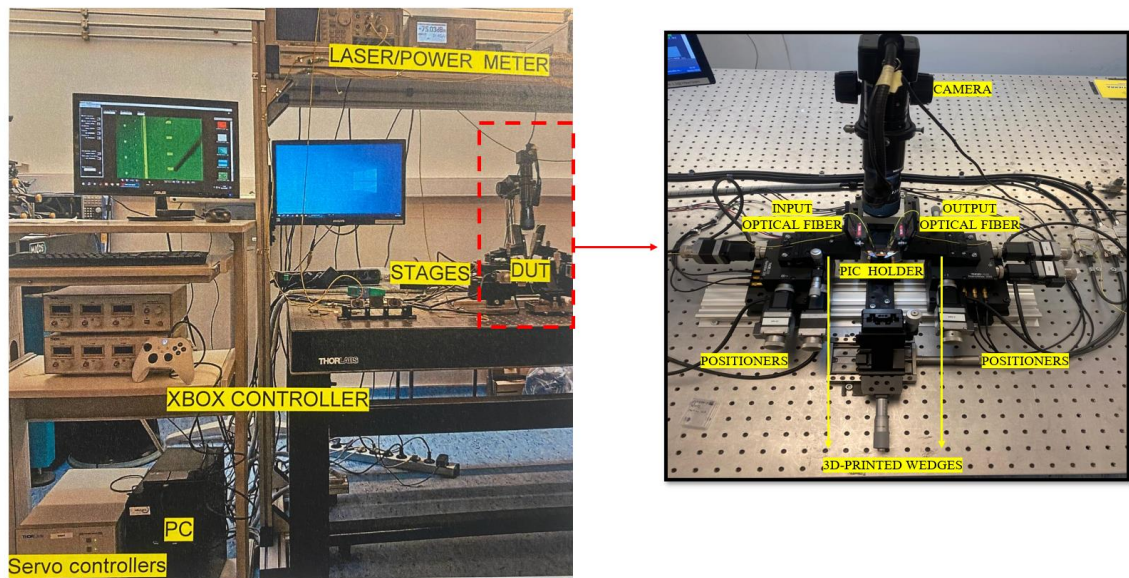
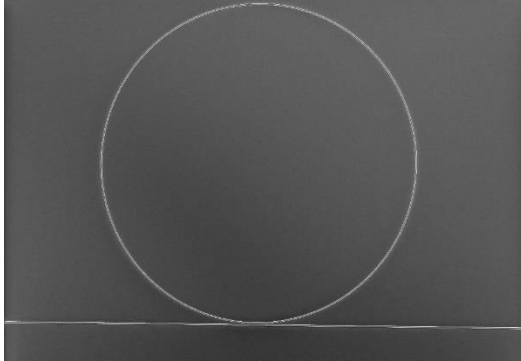
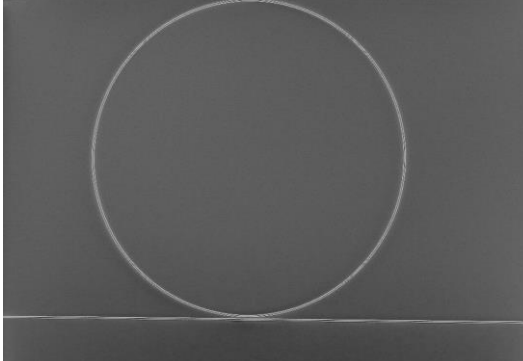
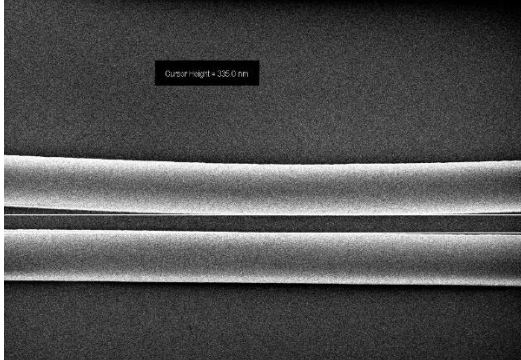
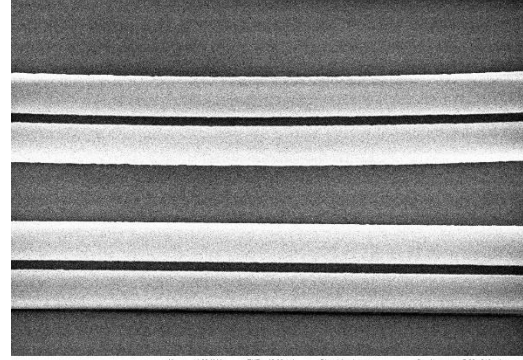


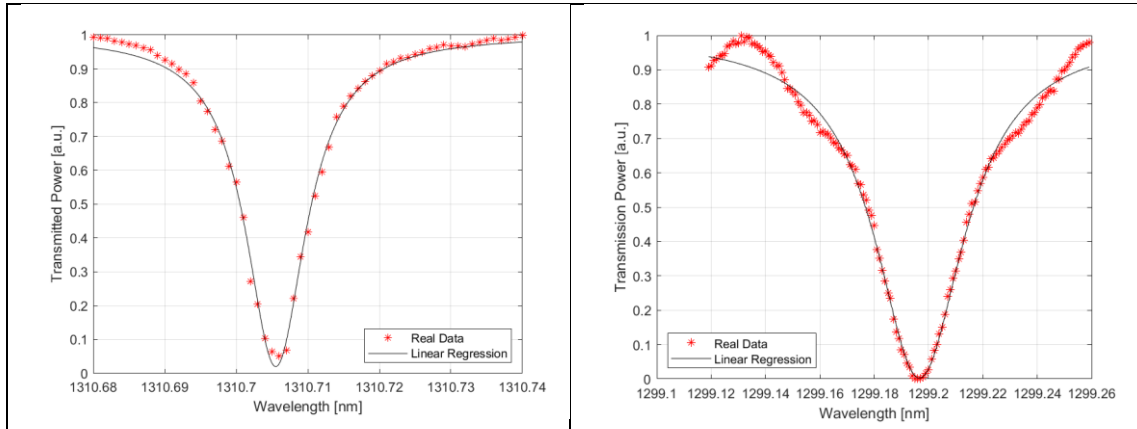
Figure 3.12: Details of the components of the vertical coupling setup used for characterization at a wavelength of 1310 nm and an angle of 10° .

From a preliminary analysis, values of approximately 1.3 nm and 1.5 nm are estimated for the free spectral range (*FSR*) in the case of RRs with strip waveguides and RRs with

slot waveguides, respectively. As already mentioned, the coupling efficiency between the rings and the bus waveguides is evaluated across various gap distances. The optimal gap value based on the characterization process in air is selected. The devices with the highest Q-factor values among those exhibiting an extinction ratio (ER) greater than 10 dB are chosen. Specifically, ring resonator with strip waveguides characterized by a gap = 450 nm and ring resonator with slot waveguides characterized by a gap = 500 nm are considered as the ones performing better in this sense. The spectral response is fitted with a Lorentzian function, resulting in a Q-factor of approximately 129.000 for the ring resonator with strip waveguides and 66.300 for the ring resonator with slot waveguides. Scanning electron microscope (SEM) images depicting the fabricated ring resonators are provided in Table 3.2, along with experimental results obtained from testing the devices in air.

Table 3.2: SEM images and results of the characterization in air of ring resonators designed with strip and slot waveguides.

RING WITH STRIP WAVEGUIDES	RING WITH SLOT WAVEGUIDES
 Mag = 347 X 20 μm EHT = 10.00 kV WD = 7.7 mm Signal A = InLens Aperture Size = 30.00 μm Gun Vacuum = 8.21e-09 mbar System Vacuum = 2.50e-05 mbar	 Mag = 339 X 20 μm EHT = 10.00 kV WD = 7.7 mm Signal A = InLens Aperture Size = 30.00 μm Gun Vacuum = 7.87e-09 mbar System Vacuum = 3.30e-05 mbar
 Gap height = 355.0 nm Mag = 31.00 K X 2 μm EHT = 10.00 kV WD = 7.7 mm Signal A = InLens Aperture Size = 30.00 μm Gun Vacuum = 8.74e-09 mbar System Vacuum = 2.50e-05 mbar	 Mag = 34.50 K X 2 μm EHT = 10.00 kV WD = 7.7 mm Signal A = InLens Aperture Size = 30.00 μm Gun Vacuum = 7.15e-09 mbar System Vacuum = 3.15e-05 mbar



Sensors are exposed to ethanol solutions at various concentrations as well as to BSA and antiBSA solutions in order to characterise their performance in fluid conditions and determine their bulk and surface sensitivity. For this reason, a flow-cell made of methacrylate, with two transversal holes (an inlet and an outlet) that align with the spacing between the ends of the central channel, is positioned on the PIC using a double-sided adhesive. Silicone elastomer tubing is properly inserted through the inlet and the outlet of the flow-cell in order to connect the microfluidic channel with the pump and the analyte container to handle the fluidics. The double-sided adhesive tape is first applied to the chip, centering the RRs at the channel, and then the other side is attached to the methacrylate piece that contain the tubing to complete the assembly of the fluidic system (see Fig. 3.13).

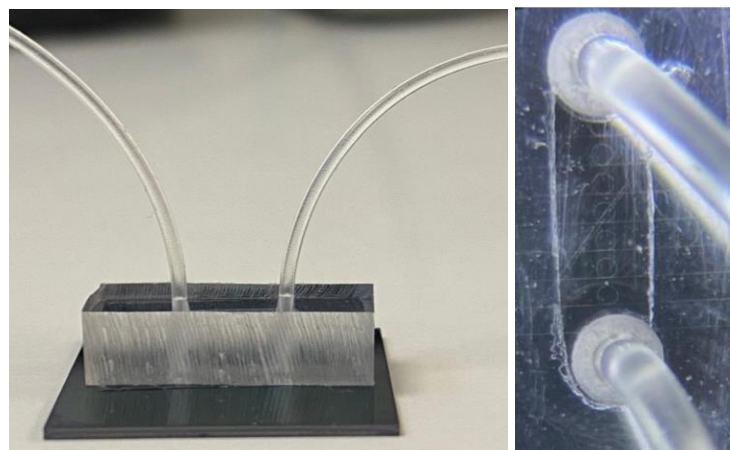


Figure 3.13: *Adhesive and flow-cell mounting on the chip (left) and an optical microscope view of the fluidic channel with the ring resonators at the centre (right).*

A syringe pump is used in withdrawal mode to draw solutions across the sensors at a controlled flow rate (ranging between 10 and 20 $\mu\text{L}/\text{min}$). To switch between solutions during assays, the tubing is manually compressed with a tweezer at the container end and quickly introduced into the next analyte container.

The setup used to perform the measurements is schematically shown in Fig. 3.14.

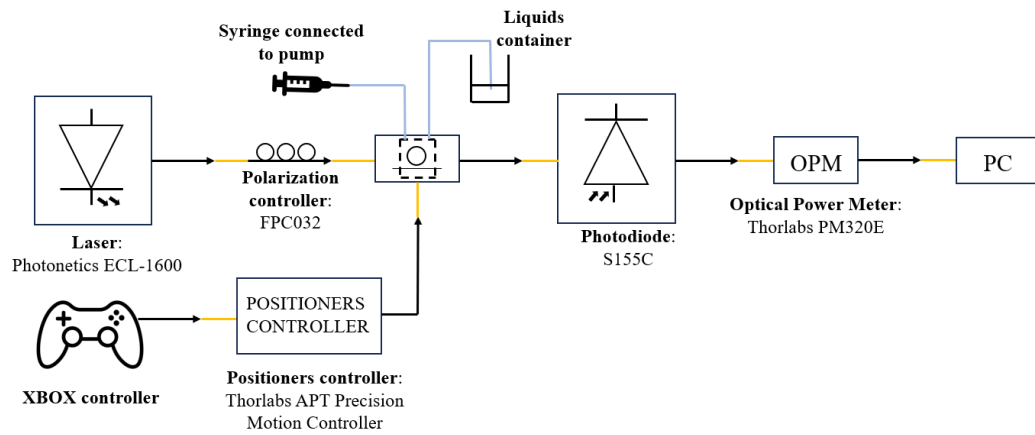


Figure 3.14: Schematic of the characterization setup for testing the sensitivity of the chip to changes in the refractive index of the cladding.

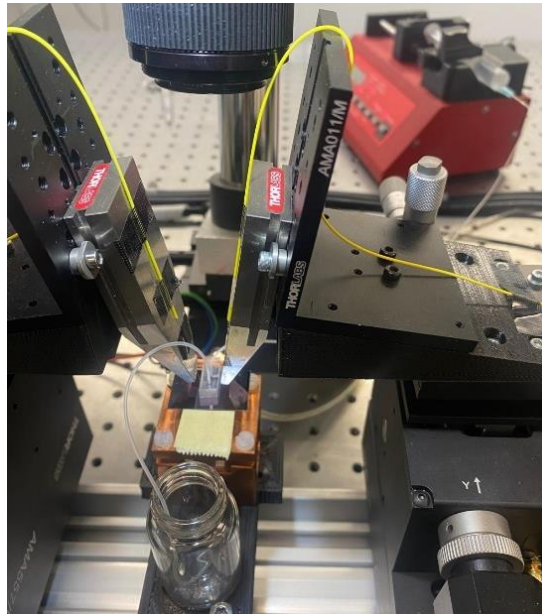


Figure 3.15: Details of the setup components used for the sensing experiments. A syringe pump is connected to the flow-cell in order to draw the solutions across the sensors.

Experimental Bulk Sensitivity

As previously mentioned, to evaluate the bulk sensitivity to changes in the refractive index of the cladding, the sensors are exposed to a flow of ethanol solutions prepared in increasing concentrations, ranging from 0% to 32% in volume. For these experiments, the flow rate set by the syringe pump is 20 $\mu\text{L}/\text{min}$. It is crucial to conduct the experiment within a reasonable time frame and with high precision to minimize errors when evaluating the resonance peak shift. Therefore, a wavelength range of approximately 4 nm is selected to follow the displacement of a specific resonance peak, and a resolution of 1 pm (the maximum possible) is used. For each ethanol solution, about ten experiments are realized under the same conditions in order to calculate the average transmitted power during the post-processing.

The full width at half maximum (FWHM) of resonant peaks in distilled water is measured and it appears to be of about 0.1 nm, corresponding to a Q-factor of 32.000, in the case of RR with strip waveguides; similarly, values of about 0.04 nm and 30.000 are found for the FWHM and the Q-factor in the case of RR with slot waveguides.

As shown in Fig. 3.16, the shifts in the resonance peak wavelength are reported as a function of the refractive index of the solution used and the corresponding percentage of ethanol concentration. The refractive index of distilled water is 1.3223 [24], whereas the refractive indices of ethanol solutions are calculated at 1310 nm and summarised in Table 3.3 [19]. The slope of the linear fit is the criterion by which the sensors' sensitivity to refractive index is determined and it is equal to 150 nm/RIU for the ring resonator with strip waveguides and 275 nm/RIU for the ring resonator with slot waveguides.

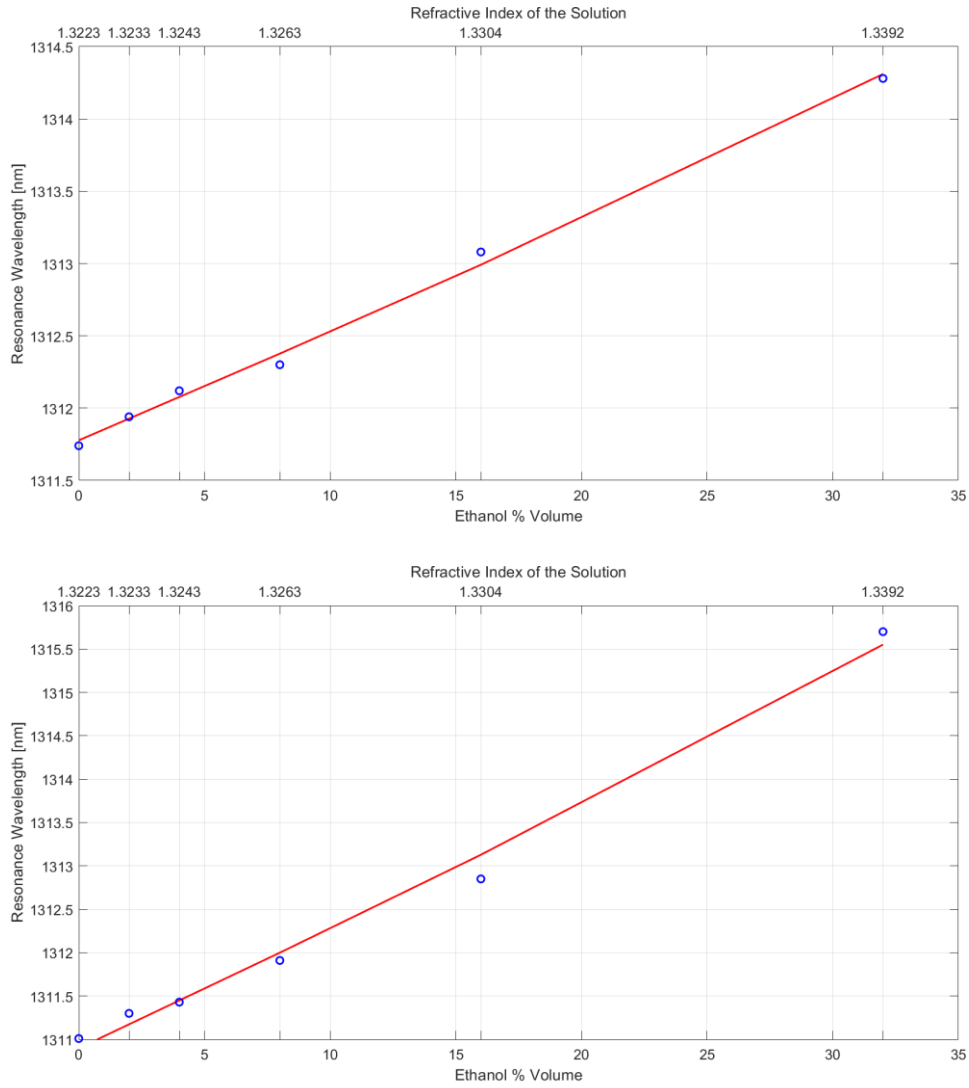


Figure 3.16: Resonance peak wavelength shifts against refractive index of each solution used for the experiments and the corresponding (%) concentration in the case of ring resonator with strip waveguides (on the top) and slot waveguides (on the bottom).

Table 3.3: Refractive indices of ethanol solutions at 1310 nm wavelength.

Ethanol % volume	RI Solution
2	1.3233
4	1.3243
8	1.3263
16	1.3304
32	1.3392

Considering the influence of Q-factor and bulk sensitivity, S_{bulk} , on sensing performances, the inherent limit-of-detection ($ILOD$) of ring resonators can be defined as follow:

$$ILOD = \frac{\lambda_{res}}{Q - factor \cdot S_{bulk}} \quad (3.6)$$

By means this definition, $ILOD$ values of about 6.6×10^{-4} RIU and 1.5×10^{-4} RIU are found in the case of RR with strip and slot waveguides, respectively.

A common figure-of-merit (FoM) to evaluate the sensing performances of the devices is given by the experimental bulk sensitivity divided by the resonance width. Both for ring resonator with strip and slot waveguides, the width of the resonance peak obtained while testing in distilled water is considered. The results confirm that the ring resonator with slot waveguides is the most sensitive device, with $FoM \approx 8000 \text{ RIU}^{-1}$, with respect to ring resonator with strip waveguides having $FoM \approx 5000 \text{ RIU}^{-1}$.

Experimental results about FoM are close to the calculated ones. Considering $FWHM = \delta\lambda$ and λ_0 the central resonance wavelength, it is possible to approximate the definition of the FoM as follows:

$$\begin{aligned} FoM &= \frac{S}{\delta\lambda} = \left(\frac{Q - factor}{\lambda_0} \right) \left(\frac{\partial\lambda_0}{\partial n_c} \right) = \left(\frac{Q - factor}{\lambda_0} \right) \left(\frac{\partial\lambda_0}{\partial n_{eff}} \right) \left(\frac{\partial n_{eff}}{\partial n_c} \right) \\ &\rightarrow FoM = \left(\frac{Q - factor}{\lambda_0} \right) S_w \left(\frac{\partial\lambda_0}{\partial n_{eff}} \right) \end{aligned} \quad (3.7)$$

where S is the sensitivity of the device, n_{eff} is the effective refractive index, n_c is the cladding refractive index, and S_w is the waveguide sensitivity.

For ring resonators, it is possible to assume that $\frac{\partial\lambda_0}{\partial n_{eff}} = \frac{\lambda_0}{n_g}$, so:

$$FoM = \left(\frac{Q - factor}{\lambda_0} \right) S_w \left(\frac{\lambda_0}{n_g} \right) = Q - factor \left(\frac{S_w}{n_g} \right) \quad (3.8)$$

where n_g is the group index.

For both strip and slot waveguides, considering the experimental Q-factor values in distilled water, and the calculated S_w and n_g values reported in Table 3.4, it is possible to confirm the accuracy in the evaluation of experimental FoM values and the dependency of this parameter on the Q-factor.

Table 3.4: *Calculated values for the waveguide sensitivity S_w , the group index n_g , and the FoM in the case of strip and slot waveguides.*

	S_w	n_g	FoM
<i>Strip Waveguide</i>	0.188	1.179	5086 [RIU ⁻¹]
<i>Slot Waveguide</i>	0.321	1.222	7892 [RIU ⁻¹]

FoM values achieved by the ring resonators discussed in this work high light their superior performance in sensing applications when compared to those reported in the literature and competitive technologies, i.e. photonic crystal devices, metasurfaces, and others. Only using PhC nanolasers or optofluidic RRs, which are not planar devices, FoM values exceeding 10^5 RIU⁻¹ are demonstrated [25][26].

For ring resonators in SOI technology, the state-of-the-art experimental FoM is typically 1000 RIU⁻¹ [27][28][29][30]. As already anticipated, SOI ring resonators are considered the gold standard technology for biosensing applications, in fact they are characterized by higher values of Q-factor, sensitivity, and FoM with respect to silicon nitride ring resonators. However, the use of silicon nitride combined to specific device configurations could be beneficial due to the absence of nonlinear absorption effects and, in certain scenarios, can be associated to acceptable values of FoM , as presented in [18][19][20][31].

Moreover, recent studies indicate that PhC devices typically achieve FoM values in the range of 1000 to 9000 RIU⁻¹ [32][33][34], while metasurfaces often fall within 300 to 600 RIU⁻¹ [35][36][37].

Experimental Surface Sensitivity

After conducting sensing experiments with ethanol solutions, a more practical test is performed to assess the sensors surface sensitivity to biomolecules, showcasing their capability to examine biomolecular interactions.

The reagents used for the experiments are 1 mg/mL bovine serum albumin (BSA) and anti-bovine serum albumin (antiBSA) at different concentrations, as well as a PBS 1X buffer. BSA is a globular protein, with molecular weight 66.5 kDa, that is soluble in water and only slightly soluble in strong salt solutions. Specifically acting as an antibody against BSA, antiBSA is an immunoglobulin type IgG with a molecular weight of 160 kDa [38]. BSA used in the experiments is supplied by Fisher Chemical and produced by a proprietary heat shock process (catalog number: BPE9702-100), whereas antiBSA is provided by Bethyl Laboratories, Inc (catalog number: A10-113).

Preliminary measurements with Phosphate Buffered Saline (PBS) 1X buffer are carried out in order to choose a trade-off between timing accuracy and proper resonant peak tracking. In the end, always considering a 4-nm wavelengths window, consecutive measurements are performed with a wavelength step resolution of 0.001 nm. A good approximation for real-time monitoring is obtained by flowing the reagents and buffer solutions through the microfluidic delivery system at a rate of 10 $\mu\text{L}/\text{min}$, as each measurement takes around 8 minutes to finish.

AntiBSA stock solutions are prepared with concentration of 0.25 $\mu\text{g}/\text{mL}$, 0.5 $\mu\text{g}/\text{mL}$, 1.25 $\mu\text{g}/\text{mL}$, 2.5 $\mu\text{g}/\text{mL}$, and 5 $\mu\text{g}/\text{mL}$ for experiments on ring resonator with strip waveguides; whereas, in the case of ring resonator with slot waveguides, being this one more sensitive, the efficiency of the device in detecting lower values of concentration is tested, preparing antiBSA solution with concentration of 0.0075 $\mu\text{g}/\text{mL}$, 0.023 $\mu\text{g}/\text{mL}$, 0.075 $\mu\text{g}/\text{mL}$, 0.225 $\mu\text{g}/\text{mL}$, and 0.5 $\mu\text{g}/\text{mL}$.

The sensorgrams depicted in Fig. 3.17 represent the end result of a sequence of stages in the biosensing experiment. It should be noticed that concentration values of antiBSA are reported in nanomolar (nM) unit. There is no need for previous surface treatments since the biomolecules are physically adsorbed onto the surface without any covalent immobilization. The first stage involves equilibrating the sensor with PBS 1X buffer for 10 minutes to establish a signal baseline. Next, BSA is introduced for approximately 15

minutes, resulting in a shift in the resonance wavelength, indicating successful detection. This is followed by a 20-minute PBS 1X rinse to remove any unbound protein and re-establish the signal baseline in the sensorgram before introducing the next reagent. Then, antiBSA at different concentrations is passed over the BSA-functionalized sensor for about 20 minutes per step, with the selective binding to BSA causing irreversible and progressively larger shifts in the resonance wavelength. Finally, PBS 1X is introduced for about 20 minutes to remove any unbound antiBSA molecules from the fluidic channel.

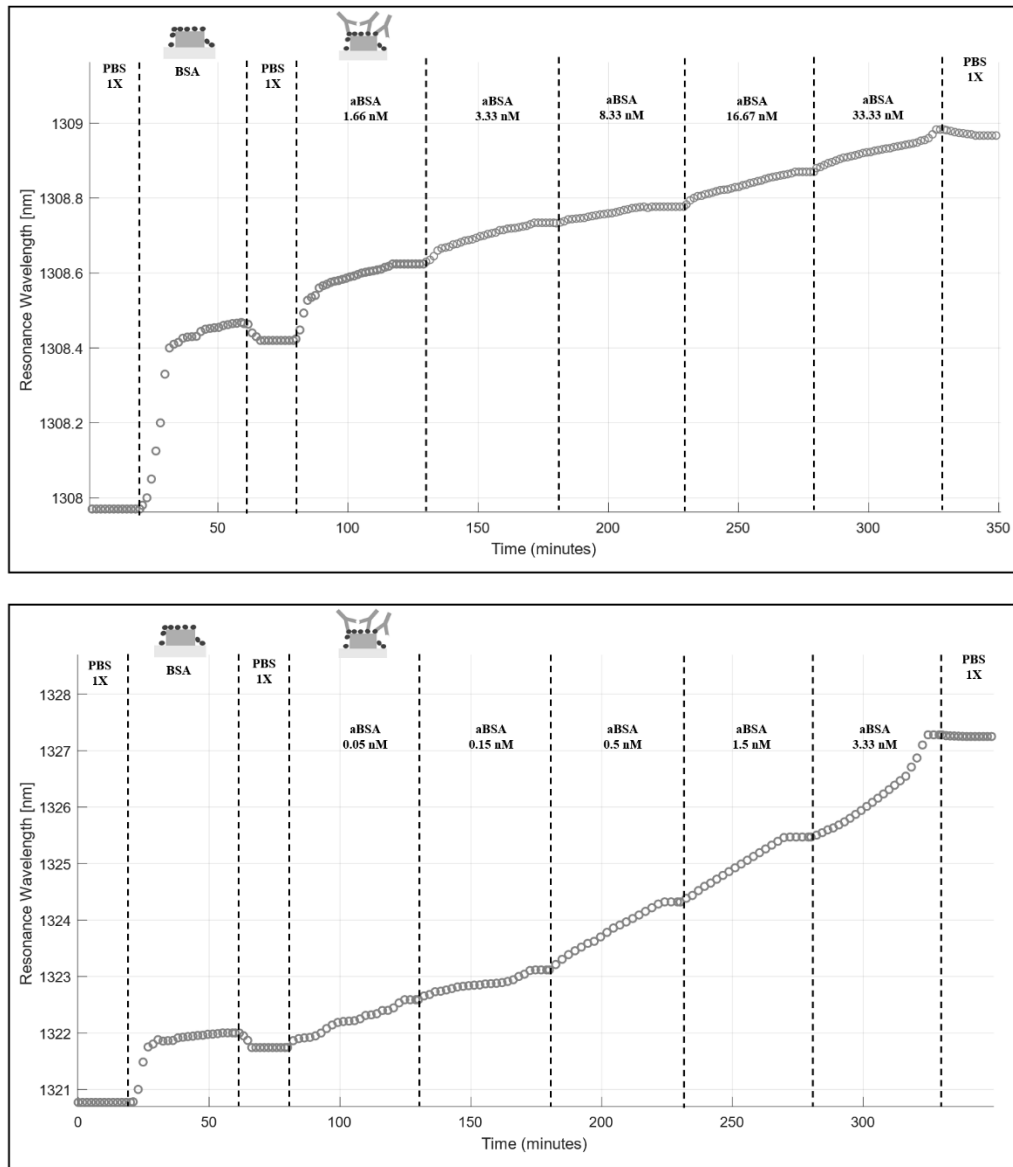


Figure 3.17: Sensorgrams for the TE mode at 1310 nm acquired from BSA-antiBSA studies in the case of RR with strip waveguides (on the top) and RR with slot waveguides (on the bottom). The dashed vertical lines show the region boundaries involving a change in the flowing solution, and it takes around 8 minutes for the new solution to reach the sensor.

The resonance shift as a function of antiBSA concentration, shown in Fig. 3.18, fits well to Langmuir's equation, describing the adsorption of antibodies onto a surface [39][40]:

$$\Delta\lambda = \Delta\lambda_{max} \frac{KC}{1 + KC} \quad (3.9)$$

where $\Delta\lambda_{max}$ is the maximum resonance shift corresponding to the saturation point, K is the Langmuir adsorption constant, and C is the adsorbed species concentration. From the curve, considering the resonance wavelength at which a condition of stability is achieved during the third step (PBS 1X), it is possible to estimate a resonance shift at saturation of about 0.56 nm and 5.54 nm in the case of ring resonator with strip waveguides and slot waveguides, respectively.

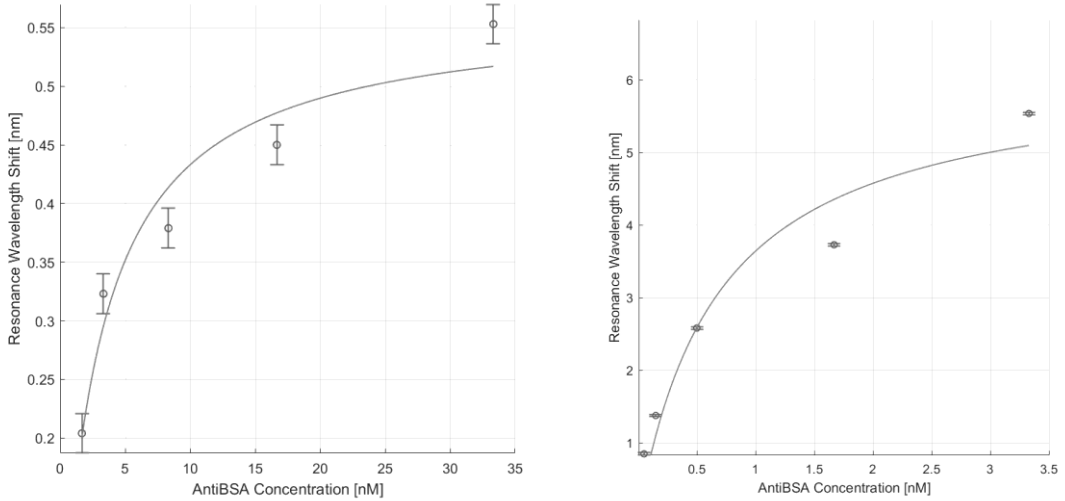


Figure 3.18: Evaluation of the resonance wavelength shift against the antiBSA concentration in the case of ring resonator with strip waveguides (on the left) and slot waveguides (on the right). The error bars are evaluated by considering 3.3 times the standard deviation of the measurements done while flowing PBS 1X in the first step of the assay.

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CHAPTER 4

Virus Detection

Silicon Nitride Platforms for Virus Detection

The demand for high-performance diagnostic systems has significantly increased following the onset of the coronavirus disease 2019 (COVID-19) and the continuous emergence of different variants. The primary interest lies in reducing the diagnosis time compared to that required by existing commercial devices based on reverse transcription polymerase chain reaction (RT-PCR), lateral flow immunoassays, and enzyme-linked immunosorbent assay (ELISA) [1][2][3].

In this context, it would be beneficial not only to detect the presence of SARS-CoV-2 in individuals previously infected with the virus but also to verify the actual presence of antibodies in individuals who have been vaccinated. This is highlighted in [4] where the fabrication of an immunosensor capable of performing multiplex electrochemical analysis is reported. This immunosensor can detect the presence of SARS-CoV-2 RNA in saliva as well as anti-SARS-CoV-2 immunoglobulins in plasma samples

The possibility of combining plasmonic photothermal (PPT) effects and localized surface plasmon resonance (LSPR) in a single biosensor is proved in [5]. The basic concept involves functionalizing gold nanoislands (AuNIs) with complementary DNA receptors to detect specific SARS-CoV-2 sequences through nucleic acid hybridization. Notably, the biosensor exhibits high sensitivity, with a limit-of-detection as low as 0.22 pM, and the capability to identify specific targets within a mixture of multiple genes.

A chip-scale biosensor for the detection of SARS-CoV-2, featuring two cascaded silicon nitride ring resonators, is reported in [6]. Specifically, one device is used for actual sensing while the second serves as a reference. The sensor is functionalized with DNA primers, and its performance is assessed by flowing varying amounts of complementary SARS-CoV-2 RNA contained in reference samples such as nasopharyngeal, nasal, and saliva. Experimental results demonstrate the capability to detect very low target concentrations, below 10 cp/ μ L, with a sensitivity of 743 nm/RIU.

A disposable photonic sensor platform in which rice-sized silicon nitride ring resonator sensor chips are paired with plastic micropillar fluidic cards for sample handling and optical detection is presented in [7]. The Authors demonstrate the utility of the platform in the context of detecting human antibodies to SARS-CoV-2, both in convalescent COVID-19 patients and for subjects undergoing vaccination, with a limit-of-detection of 1 $\mu\text{g/mL}$.

A multiplexing analysis for the simultaneous detection of COVID-19 and influenza A is proved in [8], utilizing subwavelength grating (SWG) ring resonators in Si_3N_4 integrated with a Y-shaped microfluidic structure. Such an advanced microfluidic system allows the contemporary flow of two fluids containing the target analytes. The results of the study demonstrate the capability to achieve a limit-of-detection of 1.31 fM and a sensitivity of approximately 437.2 nm/RIU, in just 15 minutes, while maintaining specificity during the test.

Silicon Nitride Ring Resonators for SARS-CoV-2 Detection

The focus of the work is to implement the use of the more performing device for an accurate bio-application, that is virus detection. For this aim, the ring resonator with slot waveguides is functionalized first *in-situ* and then, by using an automated piezo driven, non-contact dispensing system (SciFLEXARRAYER S3 produced by SCIENION) for the immobilization of antibodies (see Fig 4.1). In our case, the aim is the detection of the spike protein of SARS-CoV-2.

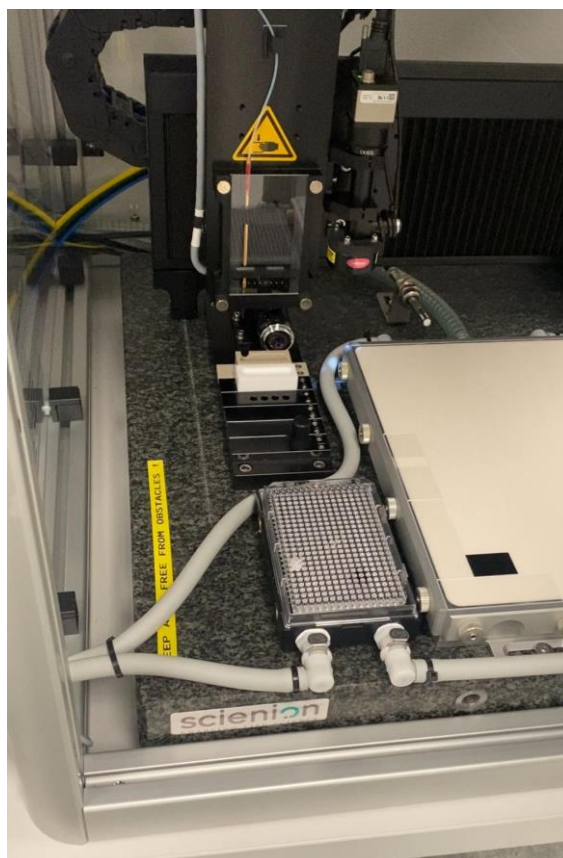


Figure 4.1: Preparation of the dispensing system, SciFLEXARRAYER S3. In the photo, it is possible to see: a) at the top left, the point used to take the drop of antibodies' solution to be printed on the sensor, b) at the bottom left, the container containing the antibodies' solution prepared, and c) on the bottom right, the chip.

The *in-situ* immobilization of the anti-spike protein (rabbit polyclonal antibody, catalog number: IT-002-030-200UG, CliniScience), and the subsequent detection of the target analyte, is done by following a specific protocol, setting a flow rate of 10 $\mu\text{L}/\text{min}$ and a step resolution of 0.001 nm (see Fig. 4.2):

- i) Surface pretreatment: cleaning of the sensor surface with acetone, iso propyl alcohol, and MilliQ Water;
- ii) Flow of PBS 1X buffer to establish a stable baseline;
- iii) Fixation of protein A from Staphylococcus Aureus (0.1 mg/mL protein A in PBS 1X, catalog number: P6031, Merck- Sigma Aldrich) to obtain an oriented immobilization of antibodies;
- iv) Washing with PBS 1X buffer to remove any unbound molecule of protein A;

- v) Immobilization of anti-spike protein of SARS-CoV-2 (0.02 mg/mL in PBS 1X);
- vi) Washing with PBS 1X buffer to remove any unbound antibody;
- vii) Surface blocking with BSA (10 mg/mL BSA in PBS 1x, catalog number: BPE9702-100, Fisher Chemical);
- viii) Washing with PBS 1X buffer to remove any unbound molecule of BSA;
- ix) Spike protein of SARS-CoV-2 detection (molar concentrations = 0.5 nM, 1.5 nM, 3.5 nM);
- x) Washing with PBS 1X buffer to remove any unbound target analyte.

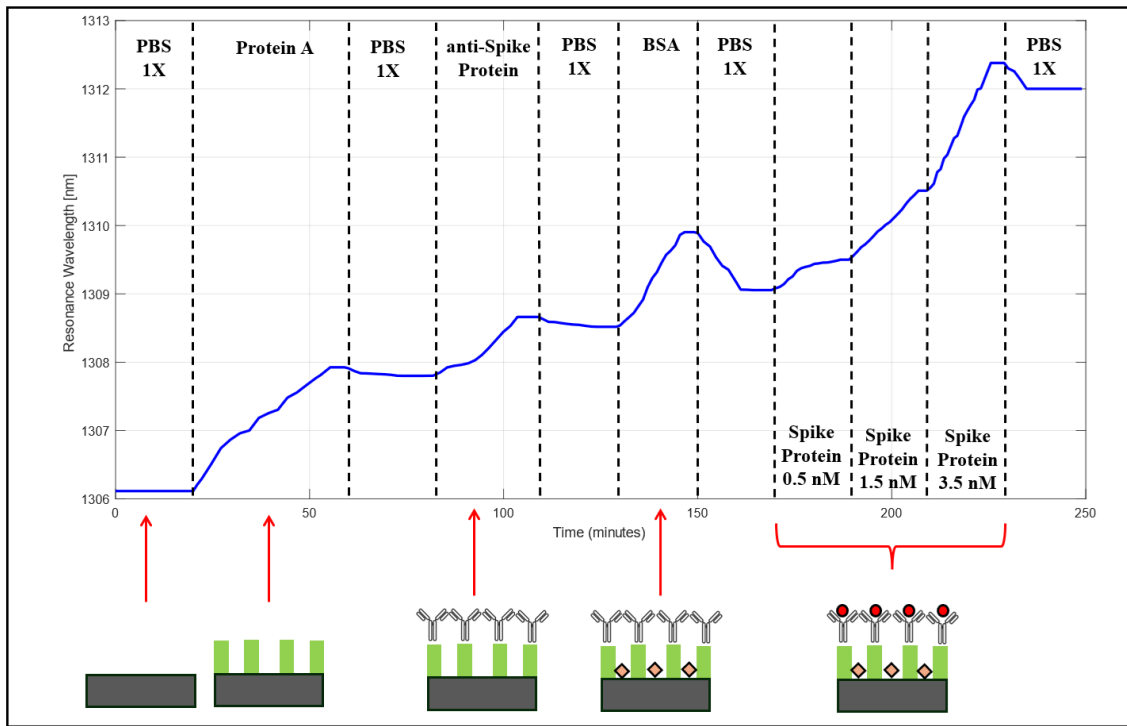


Figure 4.2: *Functionalization in situ: sensorgram for the TE mode at 1310 nm acquired for the detection of the spike protein of SARS-CoV-2 virus studies in the case of RR with slot waveguides.*

Since the assay takes around 4 hours to complete and thinking about a sensing device that could be potentially sold on the market, it is useful to search a good compromise between temporal precision and good sensitivity. For this reason, a faster functionalization method where the preparation of the chip follows what done in the previous procedure is implemented, with the difference that 1000 pL drops of the anti-spike protein of SARS-

CoV 2 solution in PBS 1X (0.02 mg/mL, catalog number: IT-002-030-200UG, CliniSciences) are printed with SciFLEXARRAYER S3. Then, the antibody is incubated for 2 hours under controlled temperature and humidity (10°C and 55% H). Finally, the chip is immersed in a 1% BSA solution (10 mg/mL) in PBS 1x at 4 °C overnight.

In this perspective, the first step is to demonstrate that the functionalization process has been successful. To this end, the capability to detect the presence of a secondary antibody (goat anti-rabbit IgG H&L, catalog number: ab150079, Abcam), prepared at a concentration of 0.02 mg/mL in 1X PBS, is demonstrated. As shown in Fig. 4.3, the signal rising indicates the effectiveness in detecting the presence of the target under consideration.

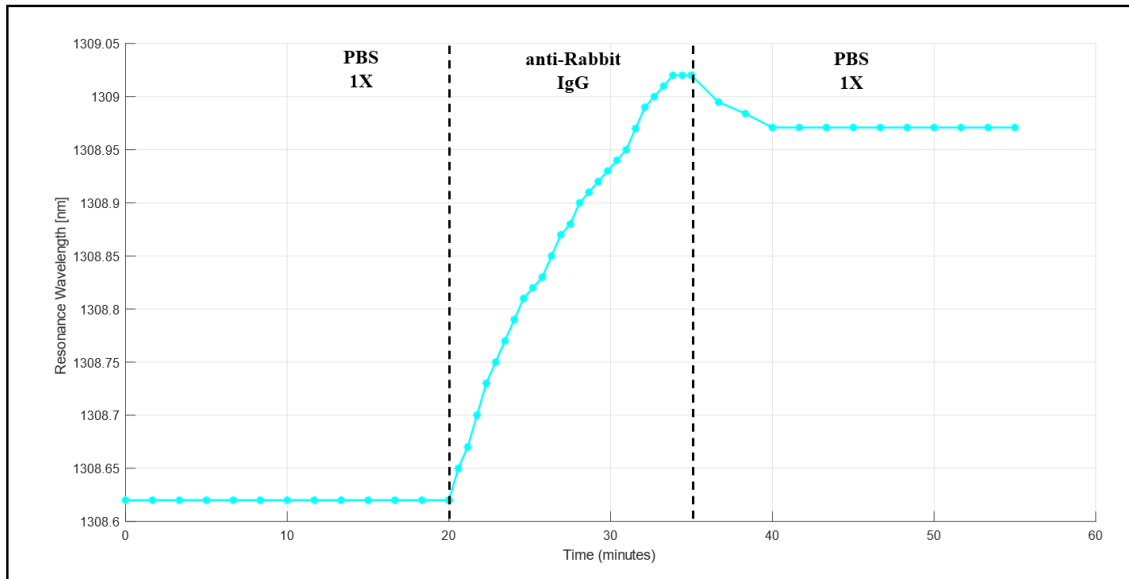


Figure 4.3: *Functionalization with SciFLEXARRAYER S3: sensorgram for the TE mode at 1310 nm acquired to prove the effectiveness of the functionalization with the printer.*

Then, the experiments to detect certain concentrations of the spike protein of SARS-CoV-2 are repeated (see Fig. 4.4). Doing a comparison with the results obtained previously, it is possible to underline that the lowest concentration value the sensor is able to detect is 1.5 nM. Moreover, the resonance wavelength shift obtained is reduced, and this is related to the fact that the amount of antibodies immobilized on the surface is certainly lower.

It should be noticed that both approaches are based on the use of an intermediate layer of protein A able to properly orient the antibody receptors, which is translated into a better sensitivity of the photonic structure. Furthermore, since protein A provides four binding sites, it does not need a specific orientation to allow the oriented antibody immobilization [9].

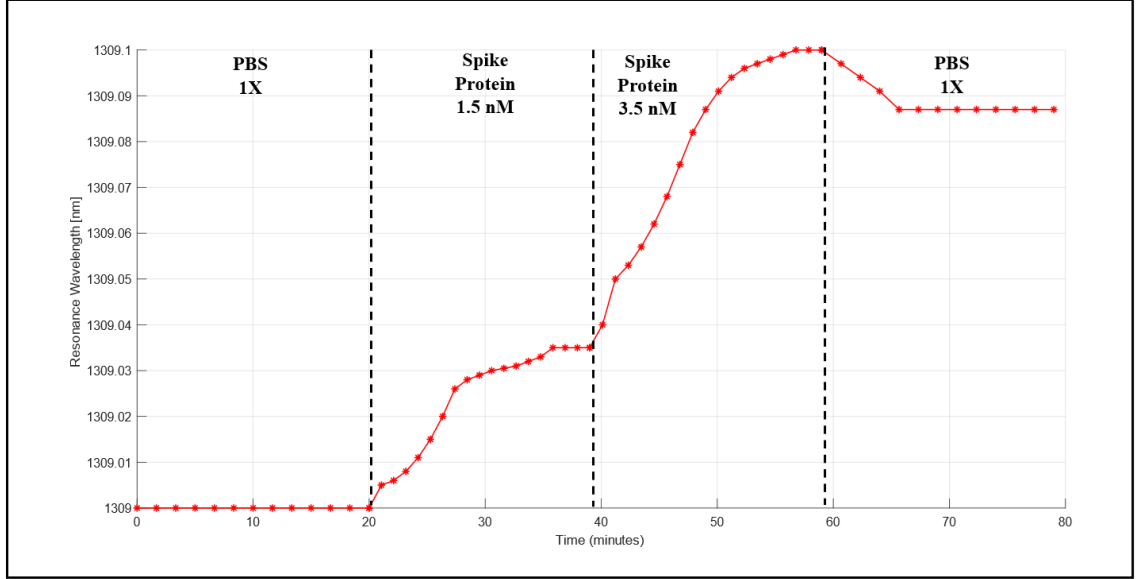


Figure 4.4: *Functionalization with SciFLEXARRAYER S3: sensorgram for the TE mode at 1310 nm acquired for the detection of the spike protein of SARS-CoV-2 virus studies in the case of RR with slot waveguides.*

The approach based on the standard deviation of the response of the blank (not containing the analyte of interest) is the simplest currently used method to estimate the limit-of-detection in analytical systems, and it requires performing N independent measurements of the blank, represented in this case by PBS 1X buffer solution. After estimating the standard deviation of the response of the blank, σ , LoD is defined as the minimum input quantity that can be distinguished with more than 99% fidelity, and can be calculated as [10]:

$$LoD = 3.3 \times \left(\frac{\sigma}{S} \right) \quad (80)$$

where S represents the sensitivity of the device determined by evaluating the slope of the regression line in Fig. 4.5. In this work, LoD values of 36 pM and 112 pM are measured

in the case of *in-situ* functionalization and functionalization with SciFLEXARRAYER S3, respectively.

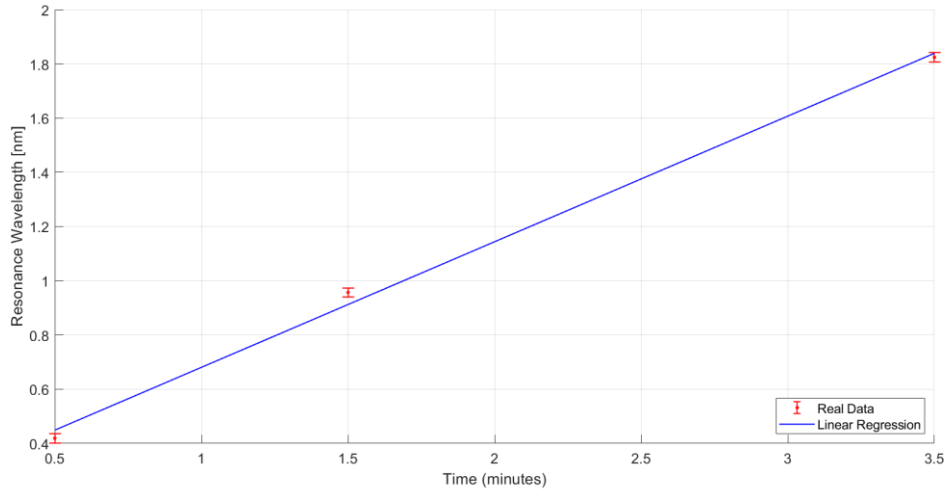


Figure 4.5: *Resonance wavelength shift against the spike protein of SARS-CoV-2 concentrations. The error bars are evaluated by considering 3.3 times the standard deviation of the blank.*

The achieved performance in terms of *LoD* is appropriate for the specific medical application, i.e., early detection of the virus infection, and can be further improved by using a more sophisticated functionalization technique and microfluidics system at the expense of an increase of the fabrication cost. As demonstrated in [8], the integration of sensors with a meticulous microfluidic chip with an anti-backflow Y-shaped structure could improve the specificity of the optical diagnostic assay and enable the concurrent detection of two analytes. A *LoD* on the order of 1 fM, as reported in this last work, or better is realistically achievable by refining the overall packaging process and improving system reliability, but the actual aim of this research is the demonstration of a technology that is compliant to the point-of-care testing (PoCT) paradigm also in term of cost and fabrication complexity

Use of the platform for detecting other virus and pathogens

The versatility of the fabricated and tested silicon nitride ring resonators as a detection platform extends beyond the identification of SARS-CoV-2, offering promising potential for the detection of other respiratory viruses such as Influenza A and B, as well as respiratory syncytial virus (RSV). This adaptability is particularly crucial in the context

of pandemics and seasonal outbreaks, where rapid and accurate detection of various pathogens is essential for effective public health responses. In this context, protocols for surface functionalization for diagnostic assays can be readily developed, building upon the methodologies used in SARS-CoV-2 detection. For example, in [8], a functionalization protocol is developed for the detection of Influenza A H1N1 Nucleoprotein using Pan Influenza A Nucleoprotein antibodies at a concentration of 10 µg/mL.

Moreover, the application of this technology is not limited to virology; it can also be effectively employed in other fields, such as food safety monitoring. For instance, detecting foodborne pathogens like *Salmonella* and *Listeria* is critical for preventing contamination that can lead to significant disruptions in the human microbiota, with serious health implications. In [11], a flow-based protocol is presented to detect and quantify Lipopolysaccharides (LPS) of *Salmonella* spp., achieving a limit-of-detection of approximately 10 CFU/mL. This study uses reference strains such as *Salmonella enterica* serotype Typhimurium CECT4266 and *Salmonella enterica* serotype Enteritidis CECT 7236, inoculating meat and vegetable samples for analysis. For this application, both polyclonal and monoclonal antibodies are viable options; polyclonal antibodies generally offer superior antigen-binding capacity across a wide range of concentrations, while monoclonal antibodies are effective at lower concentrations. Specifically, a polyclonal (rabbit) anti-*Salmonella* antibody and a monoclonal (mouse) anti-*Salmonella* LPS core antibody is identified as suitable for immobilization on silicon nitride surfaces.

Similarly, in [12], a functionalization approach is developed to detect the presence of *Listeria monocytogenes*, achieving a LoD of approximately 5 CFU/mL. The reference strains used in this study include *Listeria monocytogenes* CECT936, *Listeria innocua* CECT910, and *Listeria monocytogenes* M4. For this purpose, a rabbit polyclonal anti-*Listeria* antibody and a mouse monoclonal anti-*Listeria* antibody are successfully immobilized on silicon nitride surfaces, demonstrating the potential of this platform in food safety applications.

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Conclusions

The doctoral thesis has explored the significant advancements in ring resonator-based devices for biosensing applications, particularly focusing on silicon and silicon nitride platforms. By means of a comprehensive investigation organized in four chapters, the potential and efficacy of such a technology has been thoroughly examined, providing valuable insights into their practical applications in the field of biosensing.

In the first chapter, an extensive overview of biosensors, particularly focused on the operational principles of ring resonators, is presented. By highlighting the mechanisms behind their functionality, the critical role of functionalization techniques that enhance the sensitivity and specificity of these devices is presented. The discussion included case studies of established companies, such as SiPhox and Genalyte, whose innovative biosensing technologies based on ring resonators have already been commercialized. This context underscores the relevance of this research, linking theoretical advancements to real-world applications that demonstrate the transformative potential of biosensing technologies.

The second chapter focused on the fabrication and characterization of ring resonators fabricated in Silicon-on-Insulator (SOI) technology at SiPhotonIC in Copenhagen, Denmark. Four distinct configurations—single ring, slotted ring, panda ring, and ring with “S” junction—have been explored, evaluating their performance through bulk sensitivity experiments measured in terms of figure-of-merit (FoM). The findings revealed that the slotted ring configuration exhibits superior sensitivity values, a crucial aspect for future biosensing applications. This sensitivity enhancement can be attributed to the unique propagation characteristics of the guided modes within the slotted structure, presenting a promising avenue for further research and development.

In the third chapter, the focus is shifted to silicon nitride ring resonators fabricated at Polytechnic University of Valencia, Spain. Here, two configurations of ring resonators obtained using strip and slot waveguides are examined, by means of bulk sensitivity measurements using progressively concentrated ethanol solutions. Additionally, surface sensitivity experiments employing the BSA-antiBSA pair are conducted. The results

indicated that the device demonstrating the best performance in these assessments would serve as a suitable platform for subsequent viral detection applications.

The fourth chapter focuses on the practical implementation of the most promising resonator configuration for the detection of viruses, specifically the SARS-CoV-2, comparing the ability in detecting its spike protein while functionalizing the sensor with two different methods (*in-situ* functionalization and functionalization through the microprinter). The experiments yield estimations of the limit-of-detection, affirming the potential of the developed platform in addressing critical public health challenges. The results not only highlight the efficacy of the ring resonator design in achieving high sensitivity but also demonstrate its applicability in rapid diagnostics, which is especially vital in the context of global health crises.

In comparison to other biosensing approaches (Surface Plasmon Resonance, optical-fibers, interferometers, Photonic Crystals), ring resonator-based devices offer several distinct advantages. Surface Plasmon Resonance (SPR) is known for its high sensitivity and real-time, label-free detection capabilities. However, SPR systems tend to be bulky and expensive, making them less suitable for portable or point-of-care applications. The complexity and size of the required instrumentation can hinder their integration into compact diagnostic platforms.

Optical fiber-based biosensors provide flexibility and are useful for remote sensing applications due to their ability to transmit light over long distances. However, they often lack the compactness and ease of integration that ring resonators offer. The challenge of miniaturizing optical fiber systems can limit their application in highly integrated lab-on-chip devices.

Photonic crystal (PhC) biosensors are highly sensitive due to their ability to manipulate light at sub-wavelength scales, making them effective for detecting minute changes in refractive index. Despite their sensitivity, PhC biosensors can be complex to fabricate and integrate, which can increase costs and complicate their use in practical applications.

Interferometric biosensors, another alternative, provide high sensitivity and accuracy in detecting biomolecular interactions by measuring changes in optical path length. However, interferometric systems often require precise alignment and can be sensitive to environmental perturbations, which can affect their robustness and practicality.

In contrast, ring resonator-based devices excel in several key areas. They offer exceptional miniaturization, allowing for the integration of multiple sensors on a single chip, which is crucial for developing compact and portable diagnostic tools. Their high sensitivity is achieved through enhanced light-matter interactions within the resonator structure, enabling the detection of low concentrations of analytes with high precision. Additionally, ring resonators have versatile functionalization capabilities, allowing for the detection of a wide range of biomolecules by simply changing the surface chemistry.

Furthermore, the fabrication techniques for ring resonators are compatible with standard semiconductor manufacturing processes, facilitating mass production and scalability. This compatibility also allows for seamless integration with electronic and microfluidic components, paving the way for advanced lab-on-chip systems.

While SPR, optical fibers, PhC biosensors, and interferometric systems each have their strengths, ring resonator-based devices combine the advantages of high sensitivity, compactness, and versatile functionalization. These attributes make them highly competitive and suitable for a wide range of biosensing applications, particularly in environments where space, integration, and sensitivity are critical.

In summary, this thesis establishes a foundational understanding of ring resonators as powerful biosensing tools in silicon and silicon nitride platforms. The comparative analyses across different configurations, combined with practical testing for viral detection, affirm the versatility and effectiveness of these devices in real-world applications. The insights gained from this research lay the groundwork for future innovations in biosensing technology, potentially leading to the development of more sensitive, specific, and rapid diagnostic tools.

Looking ahead, further exploration is justified to optimize the fabrication processes and functionalization strategies of these devices. The integration of advanced materials and innovative sensing techniques could yield even greater performance enhancements. Additionally, expanding the range of applications beyond viral detection to include a wider range of biomarkers could significantly enhance the impact of ring resonators in clinical and environmental monitoring.

List of Publications

Journal Articles

[j1] A. la Grasta, M. De Carlo, A. Di Nisio, F. Dell'Olio, V. M. N. Passaro, "Potentiometric Chloride Ion Biosensor for Cystic Fibrosis Diagnosis and Management: Modeling and Design", *Sensors*, 2023, doi: [10.3390/s23052491](https://doi.org/10.3390/s23052491) (**published**)

[j2] A. la Grasta, M. De Carlo, N. Ardoino, R. Favaretto, F. Labbé, Y. Ding, V. M. N. Passaro, F. Dell'Olio, "Silicon-on-insulator microphotonic resonators for label-free biosensing: an experiment-based comparison between the different configurations", *IEEE Sensors Journal*, 2024, doi: [10.1109/jsen.2024.3406945](https://doi.org/10.1109/jsen.2024.3406945) (**published**)

[j3] A. la Grasta, M. I. Gómez-Gómez, A. Griol, E. Gómez, M. De Carlo, V.M.N. Passaro, A. Martínez, F. Dell'Olio, "Integrated Microphotonic Silicon Nitride Platform for Highly Sensitive Virus Detection", *Sensors and Actuators B: Chemical* (**submitted**)

[j4] A. la Grasta, R. Marani, A.G. Perri, "A review on biomedical applications of CNTs" *International Journal of Advances in Engineering & Technology (IJAET)*, ISSN: 2231-1963 (**published**)

[j5] G. Volpe, M. Fiore, A. la Grasta, F. Albano, S. Stefanizzi, M. Mongiello, A. M. Mangini, "A Petri Net and LSTM Hybrid Approach for Intrusion Detection Systems in Enterprise Networks", *Sensors*, 2024, doi: [10.3390/s24247924](https://doi.org/10.3390/s24247924) (**published**)

Conference Proceedings

[c1] A. la Grasta, M. De Carlo, F. Dell'Olio, V.M.N. Passaro, "Modelling and design of an ISFET based NaCl sensor for cystic fibrosis diagnosis and management", *Proceedings of SIE 2022, Lecture Notes in Electrical Engineering–Springer*, doi: [10.1007/978-3-031-26066-7_18](https://doi.org/10.1007/978-3-031-26066-7_18) (**published**)

[c2] A. la Grasta, M. De Carlo, A. Di Nisio, F. Dell'Olio, V.M.N. Passaro, "Modeling and Design of an Ion-Sensitive Field-Effect Transistor for Chloride Ion Sensing", *9th International Workshop on Advances in Sensors and Interfaces (IWASI) 2023*, doi: [10.1109/IWASI58316.2023.10164492](https://doi.org/10.1109/IWASI58316.2023.10164492) (**published**)

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