

Highly sensitive detection using microring resonator and nanopores

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Abstract

One of the most significant challenges facing physical and biological scientists is the accurate detection and identification of single molecules in free-solution environments. The ability to perform such sensitive and selective measurements opens new avenues for a large number of applications in biological, medical and chemical analysis, where small sample volumes and low analyte concentrations are the norm. Access to information at the single or few molecules scale is rendered possible by a fine combination of recent advances in technologies. We propose a novel detection method that combines highly sensitive label-free resonant sensing obtained with high-Q microcavities and position control in nanoscale pores (nanopores). In addition to be label-free and highly sensitive, our technique is immobilization free and does not rely on surface biochemistry to bind probes on a chip. This is a significant advantage, both in term of biology uncertainties and fewer biological preparation steps. Through combination of high-Q photonic structures with translocation through nanopore at the end of a pipette, or through a solid-state membrane, we believe significant advances can be achieved in the field of biosensing. Silicon microrings are highly advantageous in term of sensitivity, multiplexing, and microfabrication and are chosen for this study. In term of nanopores, we both consider nanopore at the end of a nanopipette, with the pore being approach from the pipette with nanoprecise mechanical control. Alternatively, solid state nanopores can be fabricated through a membrane, supporting the ring. Both configuration are discussed in this paper, in term of implementation and sensitivity.

Keywords: microring resonator, nanopore, biosensing, particles

1. INTRODUCTION

Sensitive label-free sensing is very attractive in analytical science. It has applications in the field of diagnosis, drug screening, biochemical attacks, food safety, etc. Miniaturization of sensors and their microfluidic integration gave rise to highly sensitive sensing, using low amount of analyte. Decreasing the dimensions of sensors also allows faster analysis. Such fast and sensitive sensing can be obtained thanks to the recent advances in micro/nanotechnologies [1], opening new applications in the field of biosensing. There is a large interest in label-free technologies and multiplex sensing. Nanopores sensing has enabled sensing of a large variety of single molecules. Positioning control in and through nanopores can be implemented with electrophoretic force, to allow for precise control of translocation time and type of molecules being translocated. With a dielectrophoretic trap, molecules can be easily repelled or attracted from the zone of interest, near the microcavity area. The most popular sensing technique in that field is the electric probing of ionic current. However, noise contribution remain an important issue [2]. New strategies combining sensitivity and multiplex sensing can be considered by label-free optical resonant sensing. Change of refractive index induced by biomolecules in the close vicinity of an optical resonator results in a modification of guiding properties and consequently of resonant conditions. The resonant condition can be assessed through spectral measurement, and the shift resulting from the change of refractive index can be exploited for quantitative sensing [3].

2. RESONANT SENSING THROUGH NANOPORES WITH SOI MICRORINGS

2.1 Nanopores

In nanopore sensing, sub-100 nm holes can be used to separate 2 chambers and act as a conduit between 2 different reservoir containing both electrolyte and analyte. They can be made through a membrane in a chip or at the end of a nanocapillary. Each reservoir contain a non-polarisable electrode. Upon application of an electrical potential, charged molecules are driven or translocated through the nanopore by dielectrophoretic forces.

There are numerous detection strategies to measure translocation through nanopores. The ionic current measurement is the most widely used technique. However, several alternative have been demonstrated. Optical detection demonstrated so far involves fluorescence. This has been demonstrated with single molecule fluorescence spectroscopy [4] and total internal reflection fluorescence (TIRF) spectroscopy [5]. Strategies with Ca^{2+} ions using Ca^{2+} sensitive dyes have also been developed [6]. The advantage of TIRF microscopy compared to fluorescence imaging is that it allows to confine the excitation in the pore area. This intrinsically limits the fluorescence background and allow to use simple SiNx membrane, while an additional metal mirror coverage is usually needed to reduce the background in for non-confined excitation. In addition to being an additional microfabrication steps, this can induce unspecific binding, as well as stability issues. Therefore, there is a large interest in label-free resonant sensing of translocation events through nanopores.

2.2 Resonant sensing with microring resonators

Label-free optical sensing can be realized exploiting optically resonant structures. By locating nanopores close from the resonant structure, the translocation of molecules through the nanopores induce a change of refractive index and therefore modification of guiding properties. This results in a change of the resonant response which can be used for sensing.

Optical microcavities that confine light in high-Q resonance are promising as they allow down to single/few biomolecule(s) [7]. Although the most promising in term of sensitivity and quality factors ($Q \sim 10^8$ - 10^9), optical microsphere resonators [3] and microtoroids [8] are limited in term of integration and multiplexing. Microrings are a good compromise in term of high-quality factor ($Q \sim 10^5$) and integration possibilities.

Silicon microring resonators demonstrated high sensitivity in the field of biosensing, with probes immobilized on their surface [9], achieving a sensitivity down to few hundreds of molecules on the ring surface [10].

In practice, light is coupled into a waveguide and can be used for the sensing of multiple microring placed on the chip surface. At resonance, light couple into a resonator. This can be measured through the outcoupled light, by scanning the source wavelength and further measured by a photodetector. Thanks to the integration of the microring structures inside the chip, parallel sensing becomes possible, thus allowing high-throughput sensing [9].

SOI microring resonators benefit from well-established knowledge, and optimized fabrication process [11]. Using 2 polarizations, conformation changes might also be assessed [12]. Their multiplex capability and on-chip configuration make them optimal structures for resonant sensing with nanopores. Depending on the pore(s) position, the field spatial distribution and enhancement can be optimized. As will be detailed further, slot waveguide based ring resonator in silicon on insulator can be considered to increase interaction inside the pores [13].

2.3 Translocation sensing with SOI microrings

In term of having nanopores close from the resonant structure, two types of implementation can be considered:

- (i) nanopore at the end of a nanocapillary (see Fig. 1(a)).
- (ii) solid-state nanopores through a thin insulated membrane (see Fig. 1(b))

Typical resonant signal are presented in Fig. 1(c). The light is coupled into the waveguide and propagates.

At resonance condition, the light couples into the microring. This results in a peak in the transmitted spectrum. Molecules in the near vicinity of the resonator induce a variation of the refractive index locally, resulting in a change of the mode effective index, and hence a resonant shift which can be used for sensing, as illustrated in Fig. 1(c).

Therefore, with pores located in close vicinity from the resonant cavity, optical resonant sensing can be used to sense translocations of molecules though the pore (see Fig. 1(d)).

Both types of nanopores can be implemented for sensing with SOI microring resonators structures. In this paper, we present the design and electromagnetic modelling of the different configurations, with single nanopore approached from the side of the ring and for nanopores made through a membrane.

Sensitivity down to single/few molecules level depends on the size of the particle and localisation of the pore. In term of implementation using a single nanopore at the end of a pipette, precise positioning of the pipette is controlled by nanopositioning of the pipette with parallel imaging. In the case of solid state nanopores close from the ring, slotted microring structures can further enhance the sensitivity, since the field can be enhanced in the pores area. Experimental consideration for chip fabrication and measurements are introduced.

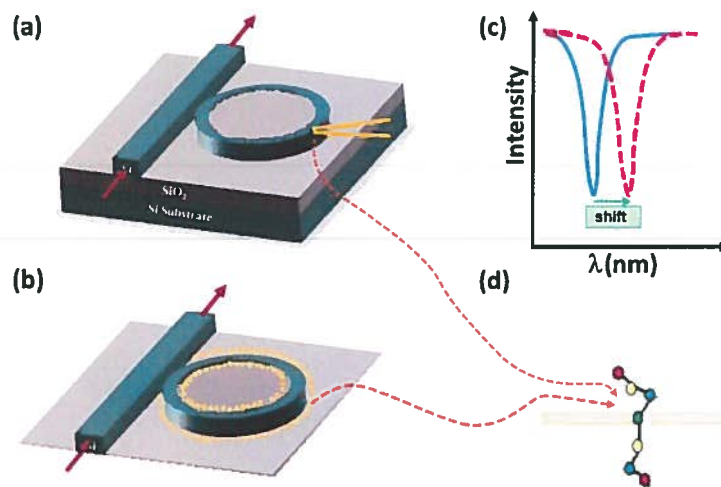


Figure 1: (a) Nanopipette approach to microring resonator, with a nanopore hole at the end of the pipette (b) Microring resonators with solid state nanopores through a membrane (c) Resonant profiles (d) Translocation of biomolecules through a pore

3. STRUCTURES AND IMPLEMENTATION

2.1 Microring resonators

The silicon microring resonators are fabricated on SOI wafers, with oxide thickness of 2 microns, on top Si thickness of 220 nm. The pattern is realized using deep UV lithography at 193 nm using well-established process for photonics integrated structure. Silicon etching is carried out using inductively coupled plasma reactive ion etching (ICP-RIE) [14].

2.2 Nanopores

Nanopores structures allow nanoparticles to be transported directly through the detection zone. They consist in nanoscale holes that separates aqueous reservoir containing electrolyte and analyte. Upon application of an electrical potential, charged molecules are driven or translocated through the nanopore [2]. Two types of nanopores are considered, with different fabrication processes.

Pore at the end of a nanopipette

Nanopore can be obtained at the end of capillary (typically a quartz capillary, with inside diameter of ~ 0.5 mm and outside diameter ~ 1 mm). The capillary is fixed into a pipette puller and heated by a high power laser and pulled mechanically. Pipette pulling typically involves two steps: first, the capillary is pulled and heated to obtain a taper of ~ 1.5 mm length, then with increased pulling and heating, it is pulled till breaking, which results to a pore at its end. The heating/pulling program can be optimized to obtain a given size of pore.

Solid-state nanopores

Solid state nanopores are typically fabricated by making a nanoscale hole in a thin insulating membrane. Low-stress silicon nitride is usually chosen for its good mechanical properties and resistance to stress. Typically, the membrane has a thickness in the range of 20-30 nm, and pores a diameter of less than 100 nm. With optimized deposition conditions [2], this results in a thin membrane with typical stress of 50 to 150 MPa. This stress is low enough to allow the formation of free standing membranes. A $50\mu\text{m} \times 50\mu\text{m}$ window can then be fabricated on the silicon substrate wafer by backside photolithography and standard KOH wet-etching. Solid-state nanopores are usually realized by focused ion beam milling or electron beam lithography, and their position can be chosen to enhance the sensitivity.

Configuration comparison

Nanopore at the end of a pipette have simple fabrication procedure and allow to sense translocation through the pipette pore (Fig. 1(a)). They allow sensing of successive single events and have a wide range of application in analytical science. While multiplexity and referencing is possible with pores at the end of a capillary, this remains practically limited by the number of pores which can be approached from rings with nanopositioning precision.

Solid state nanopores through a membrane allow on-chip configuration and simplified experimental set-up. Solid-state nanopores on a membrane are more challenging in term of fabrication, but can benefit from well-established processes [4,11,14]. They also allow simpler multiplexing of nanopores (see Fig. 1(b)).

This second configuration is therefore more advantageous in term of multiplex sensing. In what follows, we discuss the fluidic integration involved by each of the configurations.

2.3 Translocation control

In order to perform translocations through pores, an electric potential is applied on both sides of the membrane. This is obtained by placing two electrodes, one on each side of the pore. Electrodes usually consist in Ag/AgCl electrodes, with one electrode introduced on each side of the pore.

Using a pore at the end of a capillary, the electrode can be introduced inside the capillary, while the other one is placed in an external reservoir and grounded [2] (see Fig. 2(a,b)). In that configuration, controlling accurately the position of the pipette is critical. In term of fluidic, it should be compatible with this nanopositioning. A top-view camera can be used for the approach. It might be inclined for a better view of the distance of the pipette from the chip. Moreover, in the case of grating couplers to couple light into the waveguide, due to the small 10 degree incidence angle, inclination allows a smaller working distance.

Alternatively, in the case of solid-state nanopores through a membrane, the chambers are on each side of the chip. In that case, one electrode is placed into each chamber [15] (see Fig. 2(b,c)). Bottom-view imaging is there the most suitable for parallel membrane imaging, as this is compatible with a short working distance with the fluidic and fibers on the other side, and allows convenient imaging configuration.

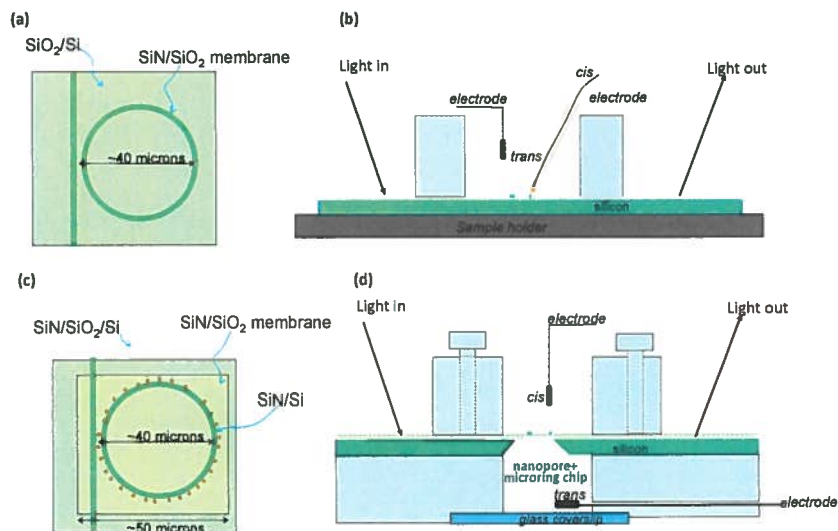


Figure 2: (a) Microring resonator on a silicon substrate (b) Approach from the pore at end of a capillary, with nanocontrol for the positioning of the pore close from the ring. Top-view imaging is an indication of the pipette position. (c) Free standing silicon microring on a membrane, with back-side etching (d) Fluidic integration of a chip with nanopores. This configuration allows parallel imaging from bottom view and measurement of a larger number of events.

4. SENSING THROUGH NANOPORES

3.1 Sensitivity

With optimized microring resonator of diameter 10 microns, and a theoretical sensitivity of 0.7 fg molecular mass on the surface of the ring has been estimated [9]. This was evaluated considering a spectral resolution of 5 pm. An increase by a factor of 3.5 has also been demonstrated for slot waveguide microrings, in comparison to standard SOI microrings [13].

By fine correction using on-chip referencing for drift cancellation, using 2 rings of diameter 40 and 56 microns excited by the same waveguide, and with a spectral resolution of 2 pm and a resonance resolution <0.3 pm, a sensitivity down to 40 ag on the ring (0.3 pg/mm^2) was latter demonstrated [10]).

Taking the example of the widely studied BSA molecule of 66.463 Da (~ 0.110 ag), this corresponds to a sensitivity of few hundreds of molecules on the ring. The solvated size of the BSA is considered to be $4 \times 4 \times 14 \text{ nm}^3$, with a refractive index $n=1.45$. With these numbers in mind, it sounds relevant to use to start our studies with elements in the ~ 100 nm range.

3.2 Pore position

As an initial study, we performed finite element simulations using comsol software. In order to reduce computation demand, a 2D model is chosen for this modeling and we choose a silicon microring of 5 microns radius ($n=3.46$). The width of the ring is of 450 nm, and the distance between the ring and the waveguide is 100 nm. The core is silica, with refractive index $n=1.46$. The pore is modeled as a high index rectangle area, of dimensions $100 \text{ nm} \times 75 \text{ nm}$, and index of $n=2$. Its index is chosen as an upper limit of what would be the analyte/particle index, and thus corresponds to the maximal perturbation which can be induced on the propagation and coupling properties. The structure is schemed in Figure 3(a). We study the shift and field distribution in the absence and presence of pore(s) as well as the dependence in position.

Specifically, the pore is either (1) in the coupling area, or (2) at the opposite, or (3) with one pore in both sites. In order to take into account the discretization of the numerical simulation, in the absence of pore in term of mesh, the geometrical structure is always considered the same. As such, in the absence of pore, we use the index of silica $n=1.46$. The calculated spectra for the different configuration are given in Figure 3(b). Note that their quality factor ($Q \sim 5000$) are not representative of what would get with 3D structures, with the field also constrained in the vertical direction. The induced spectral shift here is of $\Delta\lambda=0.03$ nm for one pore, also not fully representative of what we would get in a 3D structure. Nevertheless, this simple modeling shows that the spectral shift is independent of the position of the pore. This means that the shift will be proportional to the number of events, which is of significant interest for our application, as the shift will depend on the number of event / size of the molecules, on not on the position of the pore it went through.

In term of electric field distribution, we calculated the field intensity. This is illustrated in Figure 3(c-f), with (c) the electric field distribution of the reference structure (ring only), (d) with a pore outside of the coupling area (opposite), (e) with a pore in the coupling area and (f) with 2 pores, one in the coupling area and the other opposite to the coupling area. The obtained field distribution confirms the low influence of the pore position on the electromagnetic properties.

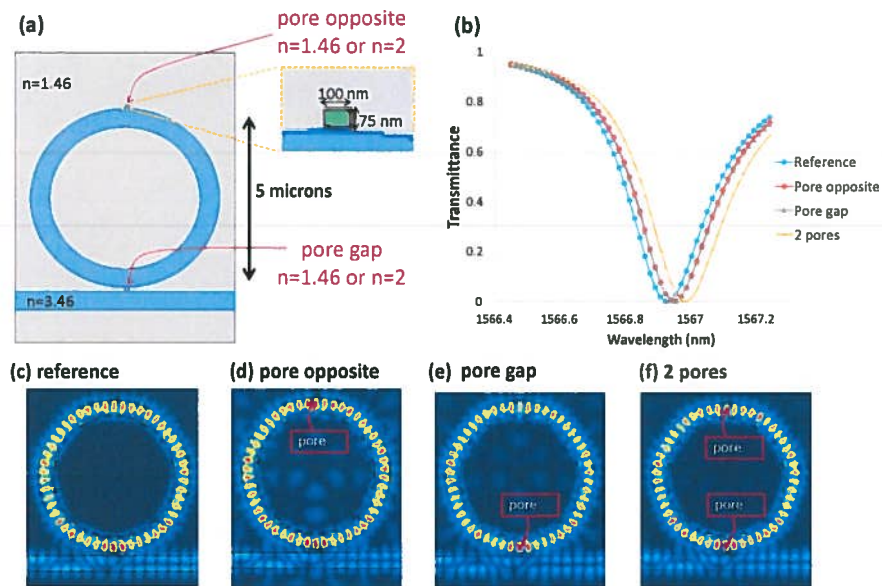


Figure 3: (a) Microring resonator with high index nanopores, modeled in 2D dimension (b) Resonant sensing signal for the reference (no pore), 1 pore placed at the opposite of the coupling section, 1 pore placed in the coupling region, and 2 pores (c-f) Normalized electric field (V/m) on a scale $[0-3.5 \times 10^5]$ for (c) the reference ring (d,e,f) the same structure with (d) a pore placed at the opposite of the coupling section (e) a pore placed at the opposite (f) 2 pores, 1 in the coupling region and one at the opposite

3.3 Increased field enhancement for nanopores in SiN membrane with slot microrings

We now turn our attention to solid state nanopores on a membrane. We are looking for a high field enhancement into the nanopore to obtain a high sensing sensitivity, and expect a higher field enhancement in the pore area for slot waveguide structures [13].

We consider both single waveguide microring (Fig. 4(a)) and slot waveguide microring (Fig. 4(b)), and compare the field enhancement of a waveguide into the pore. In terms of pore size, we choose a similar dimensions than in the previous study, with a pore diameter of 75 nm. The microring guiding structures are located onto a free standing membrane of SiN/SiO₂. Indeed, while approaching a pipette into the slot might be possible, the nanopositioning of the capillary would be critical and not relevant for this study.

The membrane consists in a SiN thickness of 30 nm. The SiN layer is obtained by SiN deposition onto a silicon microring structure. Due to the unselective etching of the SiO₂ compared to the SiN (in the step of backside etching to fabricate the membrane), we also consider a 50 nm SiO₂ residual layer.

In terms of dimensions, for the single waveguide microring, the silicon waveguide is 450 nm wide, with a thickness of 220 nm. In terms of slot waveguide, considering a pore diameter of 75 nm, we choose a slot of 100 nm width. Based on previous optimization [13], we choose a rib width of 210 nm. The waveguide height is also of 220 nm.

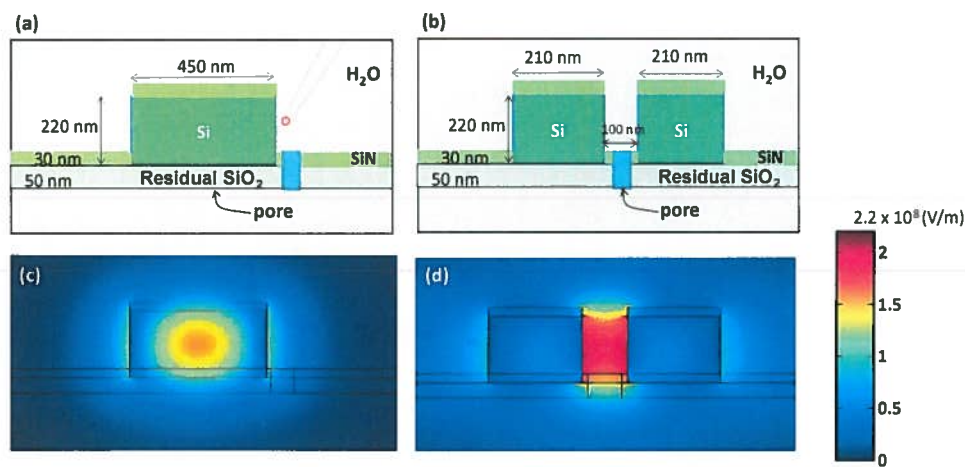


Figure 4: (a) Geometry of the silicon waveguide onto a SiN on SiO₂ membrane (b) Geometry of the slot waveguide onto a SiN/SiO₂ membrane. (c) Electric field distribution for TE polarized light in a silicon waveguide (d) Electric field distribution for TE polarized light in a silicon slot waveguide.

The field distribution for the TE component is presented in Fig. 4 (c,d) respectively for the normal waveguide and the slot waveguide. We use a scale $[0 - 2.2 \times 10^8]$ V/m for both geometry. The maximum intensity is larger in case of the slot waveguide on membrane (2.2×10^8 V/m than in the case of the simple waveguide). Similarly, in the pore area, a larger enhancement is observed in the case of the slot waveguide, and consequently a larger interaction with the translocating particle/biomolecule. For this reference structure (no pore), the effective index are respectively of $n=2.3405$ for the silicon waveguide, and of $n=1.6540$ for the slot waveguide. This is very similar to effective index in similar structures on a SOI substrate.

In term of sensing, the field distribution and the influence of the analyte can also be studied. We thus consider the influence of a particle into the pore. We consider a particle passing through. As such, the configuration to compare are with the buffer index (here water, with $n=1.31$ at $\lambda=1550$ nm). Again, we consider the extreme refractive index for the particle, with $n=2$. Electric field distribution are given in Figure 5. The field enhancement being lower for the simple waveguide, we adapt the color scale to $[0-1.6 \times 10^8]$ in that configuration, while a scale $[0-2.2 \times 10^8]$ is used for the slot waveguide.

For the normal silicon waveguide, the effective index of the mode propagating in the silicon is of (a) $n=2.3405$ for the reference without particle. It is slightly decreased to $n=2.3366$ ($\Delta n/n=0.17\%$) in the case of a pore filled with water, and increased to $n=2.3427$ ($\Delta n/n=0.22\%$) in the case of a high index particle filling the pore.

In the case of the slot waveguide, from this field distribution, we also observe that the presence of the SiN layer results in an intensification of the field in the pore area (vertical asymmetry of the mode, with water on the top side of the slot and SiN on the bottom side of the slot), which is favorable in term of increasing the sensitivity during translocation. The effective index of the mode without pore is of $n=1.6540$. It is decreased to $n=1.6201$ in the case of the pore filled with water ($\Delta n/n = 2.1\%$) and increased to $n=1.669$ ($\Delta n/n=0.9\%$) in the case of a particle of index $n=2$. These significantly larger variations confirm the larger interaction with the guided mode.

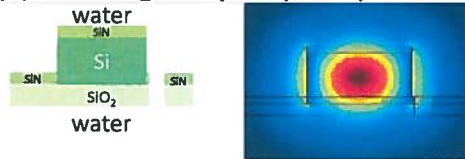
(a) Microring on membrane



(d) Slot waveguide on membrane



(b) Microring with pore (water)



(e) Slot waveguide on membrane with pore (water)



(c) Microring with pore (n=2)



(f) Slot waveguide on membrane with pore (n=2)



Figure 6: Normalized electric field distribution for TE polarized light (a,b,c) for a silicon waveguide on a SiN/SiO₂ membrane, without pore, with a pore filled with water, and with a pore filled with a high index particle (d,e,f) for a silicon slot waveguide on a SiN/SiO₂ membrane without pore, with a pore filled with water, and with a pore filled with a particle of index n=2.

4 CONCLUSION

In this paper, we presented configurations to combine resonant sensing and translocation through nanopores. While ionic current measurement is the most usual technique for translocation measurements, it suffers from noise issues and is limited in term of multiplex sensing. Therefore, there is a large interest for multiplex and label-free optical sensing. High-Q microcavities allow highly sensitive sensing, and SOI microring resonators have high potential to combine sensitivity and multiplex sensing. While demonstrations of optical sensing through nanopores so far involve fluorescence, label-free resonant sensing can serve to sense translocation through nanopores. This combination is possible by combining either a nanopore at the end of a capillary, and approaching it from the ring using nanopositioner. Alternatively, pores might be realized into a membrane, with back-side etching of the microring structure. Corresponding imaging and fluidic implementation have also been discussed. While pores at the end of a pipette are easier to fabricate, they are more limited in term of multiplex sensing. Moreover, the precise nanopositioning is critical in term of sensing in the close vicinity of the guided wave. In term of enhancement of the interaction, slot waveguide microrings allow larger field and interaction enhancement. Therefore, although more challenging in term of microfabrication, free-standing slot waveguide microrings onto a membrane with solid-state nanopores into the slot seem to be the best configuration for multiplex and sensitive sensing. Such platform might also open possibilities for study of modified nanopores having biochemical selectivity [16]. Rescaling the device with materials compatible for visible/near infrared wavelength (for instance silicon nitride on glass), there are also some possibilities with parallel fluorescence imaging [12] or SERS enhancement [17,18] which can guide and enhance coupling in the groove both the coupling both for excitation and emission. Above being a significant advantage in the field of nanopores sensing, we expect our platform to open new avenues to combine elements positioning and field/sensitivity enhancement.

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Abstract

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Keywords

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KeyWords Plus: [SILICON-ON-INSULATOR](#); [SOLID-STATE NANOPORES](#); [LABEL-FREE DETECTION](#); [MICROCAVITIES](#); [CIRCUITS](#); [PROTEINS](#)

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