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On-Chip Nanoplasmonic Biosensors with Actively Controlled Nanofluidic Surface Delivery

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ABSTRACT

Performances of surface biosensors are often controlled by the analyte delivery rate to the sensing surface instead of sensors intrinsic detection capabilities. In a microfluidic channel, analyte transports diffusively to the biosensor surface severely limiting its performance. At low concentrations, this limitation, commonly known as mass transport problem, causes impractically long detection times extending from days to months. In this proceeding, we propose and demonstrate a hybrid biosensing platform merging nanoplasmonics and nanofluidics. Unlike conventional approaches where the analytes simply stream pass over the sensing surface, our platform enables targeted delivery of analytes to the sensing surface. Our detection platform is based on extraordinary light transmission effect (EOT) in suspended plasmonic nanohole arrays. The subwavelength size nanoholes here act as nanofluidic channels connecting the microfluidic chambers on both sides of the sensors. In order to materialize our detection platform, we also introduce a novel multilayered micro/nanofluidics scheme allowing three dimensional control of the fluidic flow. Using our platform, we show 14-fold improvement in mass transport rate constant appearing in the exponential term. To fabricate these biosensors, we also introduce a lift-off free plasmonic device fabrication technique based on positive resist electron beam lithography. Simplicity of this fabrication technique allows us to fabricate nanostructures with ease, high yield/reproducibility and minimal surface roughness. As a result, we achieve higher refractive index sensitivities. This fabrication technique can find wide range of applications in nanoplasmonics field by eliminating the need for operationally slow and expensive focused ion beam lithography.

Keywords: Plasmonics, Nanohole, Biosensors, Mass Transport, Extraordinary Light Transmission

1. INTRODUCTION

Label free biosensors, offering a rapid way to obtain equilibrium and rate constants of the biomolecular interaction, have taken much interest recently. In particular, nanoscale optical biosensors with high multiplexing capabilities and signal to noise ratios are promising for detection of low concentrations of analytes [1]. However, performances of surface biosensors are often limited in a fluidic environment by the inefficient analyte (mass) transport instead of their intrinsic detection capabilities [2]. As the analytes are collected by the functionalized surface, a depletion zone forms around the sensing area where the analyte transport is diffusive (Fig.1) [3]. Depletion zone expands with time until the convective flow ceases its further growth. Randomized nature of the mass transport in the depletion zone severely limits the delivery of the analytes from the convective flow to the sensor surface. At low concentrations, this limitation causes unpractically long detection times [2,3]. One can compress the extent of these depletion zones by increasing the convective flow rate [3]. However, such a passive control scheme often results in moderate improvements of the device performances due to the shorter times required for analytes to stream pass the sensing surface. Stirring of the depletion zone using various mixing strategies also seem to result in moderate enhancements in performances [3]. Innovative approaches are needed to overcome the mass transport limitations. One of the main conceptual constraints in previous approaches is that microfluidics and biosensing are always considered as different parts of a sensor platform completing each other but not a fully merged single entity.

In this article, we propose and demonstrate a hybrid biosensing system merging nanoplasmonics and nanofluidics in a single platform. Unlike convectional approaches where the analytes simply stream pass over the surface, our platform enables targeted delivery of the analytes. Using our platform, we show 14-fold improvement in the mass transport rate constants. Considering that this rate constant appears in the exponential term, such an improvement means superior analyte delivery to the biosensor surface at low concentrations. Our detection platform is based on extraordinary light

transmission effect (EOT) in suspended plasmonic nanohole arrays [4]. The nanoholes here act as nanofluidic channels connecting the fluidic chambers on both sides of the sensors. To fabricate these nanostructures, we introduce a lift-off free plasmonic device fabrication technique based on positive resist electron beam lithography (EBL). The simplicity of this fabrication technique allows us to fabricate nanostructures with extremely high yield/reproducibility and minimal surface roughness. As a result, we achieve higher refractive index sensitivities ($\Delta\lambda/\Delta n = 630 \text{ nm} / RIU$) with respect to the previous studies based on simple nanohole arrays [4]. We believe this fabrication technique can find wide range of applications in nanoplasmonics field by eliminating the need for operationally slow and expensive focused ion beam (FIB) lithography. A unique property of our sensing platform is that it also offers an extra degree of freedom in microfluidic circuit engineering by connecting separate layers of microfluidic circuits through biosensors. Through this platform, it is possible to create “multilayered lab-on-chip systems” allowing three dimensional control of the fluidic flow.

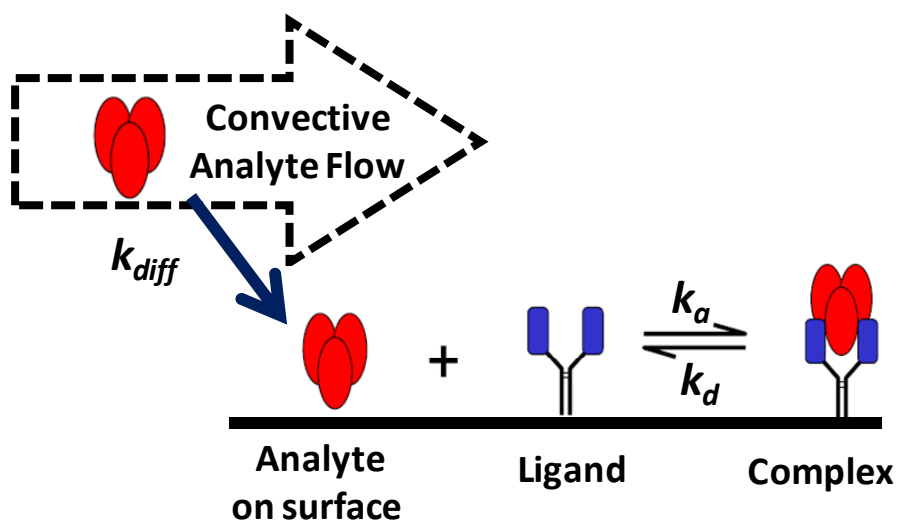


Fig. 1. Analyte delivery can be extremely limiting due to the diffusion limited transport of analytes to the sensing surface (adapted from .

2. EXPERIMENTAL RESULTS

2.1 Lift-off Free Fabrication of Plasmonic Nanoholes

Lift-off free fabrication scheme summarized in Fig. 1(a-f), consists of three stages: (i) fabrication of the free standing membrane, (ii) patterning on the membrane and (iii) direct deposition of metallic plasmonic devices [4].

Free standing membranes: An important consideration here is the mechanical strength of the membranes as a result highly robust Low Pressure Chemical Vapor Deposition (LPCVD) SiN_x films are used. Starting with a $550 \mu\text{m}$ thick silicon wafer coated with 400 nm thick LPCVD SiN_x on double sides, we can create standing SiN_x membranes using photolithographic and a wet etching processes. Initially, $2 \mu\text{m}$ thick MICROPOSIT™ S1818™ positive photoresist is spin coated, and $800 \mu\text{m} \times 800 \mu\text{m}$ apertures on the SiN_x layer are defined by photolithography with SUSS MicroTec MA/BA6 Mask Aligner. Photolithographic pattern is transferred to the backside of the wafer using a reactive ion etching (RIE) process with Plasma Therm 790 RIE/PECVD System. Later, the chips are immersed in KOH solution to create free standing membranes. $\sim 200 \mu\text{m} \times 200 \mu\text{m}$ and 400 nm thick free standing SiN_x membranes are obtained once the etching stops at the SiN_x layer.

Patterning of the membrane: Initially, the SiN_x membrane is thinned down to 50 nm and a positive e-beam resist, poly (methylmethacrylate) (PMMA), is spin coated. After e-beam writing in a Zeiss Supra 40VP system with GEMINI electron-optics column, nanohole pattern is defined in the PMMA resist (Fig. 2(b)). Nanohole pattern (with hole diameters of 220 nm and a periodicity of 600 nm) is transferred to the suspended SiN_x film through a dry

2.2 Subwavelength Nanofluidics in 3-D

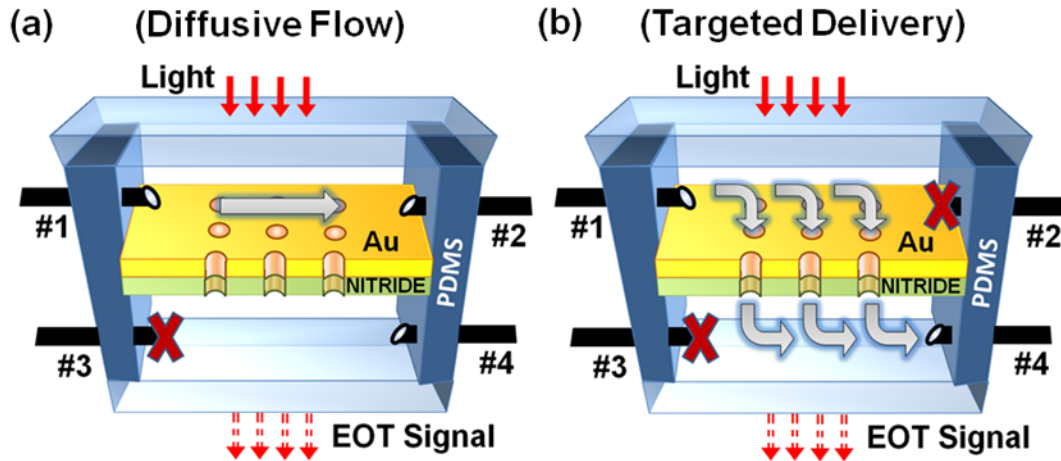


Fig. 3. Multilayered microfluidic scheme allows 3-D control of the convective flow enabling (a) passive (diffusive) and (b) active (targeted delivery) transport of the analytes to the sensing surface. Perpendicular steering of the convective flow is achieved by allowing flow only through one of the inlet/outlets of the top/bottom channels (b).

Fabricated arrays are mounted in a custom designed multilayered microfluidic channel system based on poly(dimethylsiloxane). As illustrated in Figure 3(a-b), this multi-inlet/outlet fluidic platform allows us to actively control the fluidic flow in three dimensions through the plasmonic nanohole openings. Convective flow over different surfaces of the plasmonic sensor is realized by running the solutions in between input→output lines on the same side, such as 1→2/3→4 (Fig. 3(a)). In this arrangement, mixing of liquid flowing above the gold surface and below the SiN_x membrane is minimal (diffusive) and the convective flow in separate channels is nearly independent. In actively controlled (targetted) delivery scheme, the convective flow is steered perpendicularly towards the plasmonic sensing surface by allowing the flow only through one inlet/outlet on either side of the plasmonic sensor (Fig. 3(b)). Flow could be directed from top-to-down and down-to-top directions by enabling flow between 1→4 and 3→2, respectively.

2.3 Dramatically Improved Sensor Response Time

As shown in Fig.4(a), high quality of the fabricated plasmonic nanohole arrays is reflected as spectrally narrow resonances (20nm) and large refractive index sensitivities of $\Delta\lambda/\Delta n = 630\text{nm}/RIU$, which is obtained in water ($n_{DI}=1.33$), IPA ($n_{IPA}=1.377$) and chloroform ($n_{Chl}=1.49$). Figure of merit of the sensitivity (FOM=40) are the best recorded values in literature based on plasmonic resonances. Time dependent spectral measurements are performed to compare the efficiency of the analyte delivery for the diffusive and targeted schemes (at a flow rate of $4\ \mu\text{l}/\text{min}$). To quantify the analyte transport efficiency of the both delivery schemes, a lower viscosity analyte solution (IPA) with higher refractive index is introduced from the bottom inlet. The plasmonic sensor responds only to the refractive index change due to the perpendicularly diffused or actively delivered IPA solution depending on the implemented flow scheme. This way, a good quantitative measure of the transport limit is created in the perfect collection case.

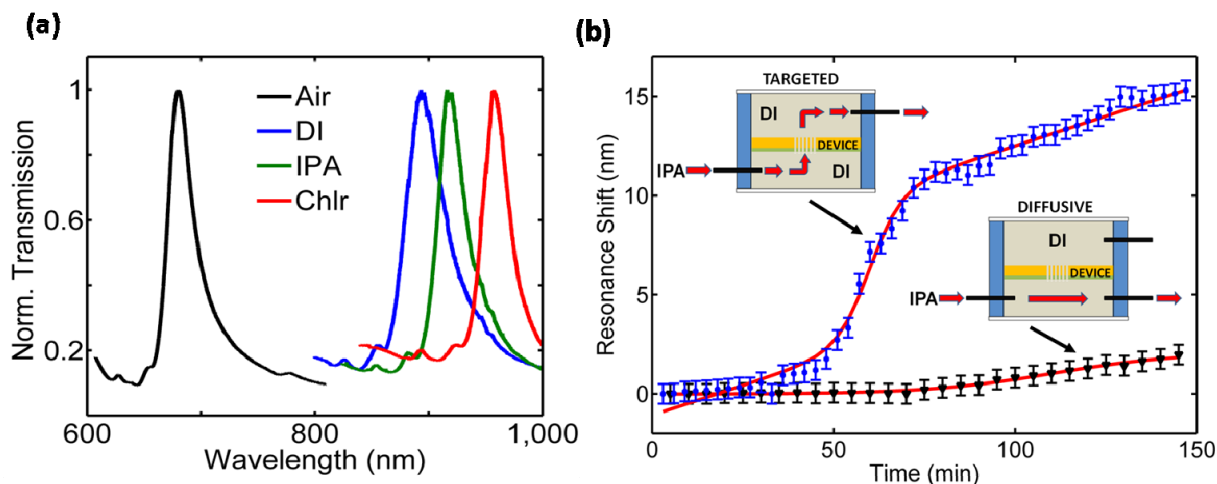


Fig. 4. (a) Bulk refractive index sensitivity of the plasmonic nanohole arrays are obtained in different solutions. Efficiencies of the passive (triangles) and targeted (squares) delivery of the analytes are compared in real time measurements (b). 14-fold improvement in mass transport rate constant is observed for the targeted delivery scheme.

As shown in Fig. 4b, the directed delivery results in a larger resonance shift compared to the passive one, indicating a much more efficient analyte delivery to the biosensor area. Experimentally observed resonance shifts are (least squares) fitted to a sigmoid function of form $A_b + (A_t - A_b) / (1 + e^{-k(t-t_0)})$. The mass transport rate constants appear in the exponents are obtained as $k_{diff} = 0.0158 \text{ min}^{-1}$ and $k_{targ} = 0.2193 \text{ min}^{-1}$ for the diffusive and targeted transport schemes, respectively. This corresponds to more than 14-fold improvement in rate constants which is crucial for enhancing the performance in immunoassay based applications. After more than 10 hrs of operation at compatible flow rates for biosensing applications ($4 \mu\text{L}/\text{min}$), we observed that the membranes and the plasmonic devices are intact. Similarly, no structural deformations are observed in the spectral measurements showing the reliability of the devices.

2.4 Antibody Detection

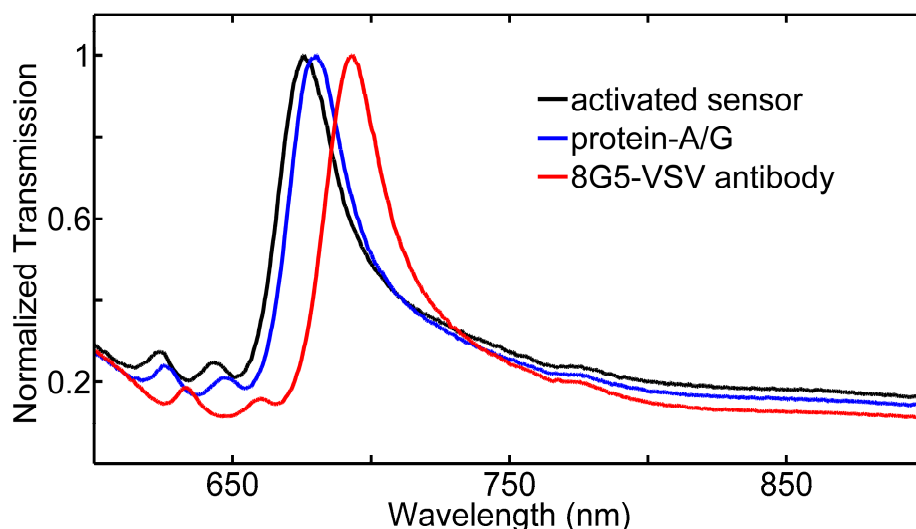


Fig. 5. Detection of biomolecules is demonstrated by capturing mouse IgG proteins.

Hybrid sensors are also tested in detection of proteins as shown in Fig. 5. Initially protein-A/G is spotted on a functionalized plasmonic surface at high concentration ($n_{AG} = 1 \text{ mg/ml}$). Capturing of the Mouse-IgG antibody at a concentration of $n_{mouse} = 0.5 \text{ mg/ml}$ is observed with a red shifting of $\Delta\lambda = 21 \text{ nm}$ after 20min.

3. CONCLUSION

In conclusion, we have proposed and demonstrated a hybrid biosensing system merging nanoplasmonics and nanofluidics in a single platform with targeted delivery of analytes to the sensor surface. To realize our proposal, we developed a lift-off free nanofabrication scheme allowing us to manufacture plasmonic nanohole biosensors with ease and high reliability/uniformity. High sensitivities ($\Delta\lambda/\Delta n = 630 \text{ nm} / RIU$) to the refractive index changes are obtained confirming the quality of the fabricated nanostructures. In order to control the convective transport in three dimensions, we introduced a multilayered microfluidics scheme enabling an extra degree of freedom in fluidic/sensor design. We demonstrated 14-fold improvement in the mass transport rate constants. Such improvements in the exponential term reflect the superior mass transport capability of the targeted delivery scheme demonstrated here. These hybrid biosensors can find wide range of applications in point-of-care applications as well as research studies on drug development and protein-protein interactions.

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