# 193nm Lithography Fabricated High Sensitivity Photonic Crystal Microcavity Biosensors for Plasma Protein Detection in Patients with Pancreatic Cancer

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**Abstract:** High sensitivity L13-type two-dimensional photonic crystal microcavities with nanoholes were fabricated by 193nm photolithography. 0.03 picomolar concentration pancreatic cancer biomarker in patient serum samples was experimentally detected to 10× lower dilution than ELISA.

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For early bio-marker detection, a sensor with highest sensitivity is desired. A sensor with the high sensitivity also enables a patient sample to be diluted so that several more experiments can be potentially performed with the same critical sample volume. In recent years, various integrated optical devices have been developed for label-free bio-sensing, such as ring resonators [1], wire waveguides [2], surface plasmon resonance (SPR) [3] and photonic crystal (PC) microcavities [4-6]. Of these, the two-dimensional PC microcavity in silicon has shown the highest sensitivity and detection limits amongst all competing technologies.

In resonator based sensors, our theoretical studies showed that analyte absorbance, equipment limited spectral noise and temperature noise, significantly contribute to the final achievable detection limit for all platforms [7]. However, from the device perspective, two parameters that significantly influence the final achievable detection limits are resonance quality factor (Q-factor) and analyte fill fraction. The high Q enhances the interaction time between the optical mode and the analyte while the larger mode volume results in larger fill fraction, both factors resulting in higher sensitivity [7]. In addition, PCs offer the unique characteristic of slow light significantly enhances light-matter interaction and lowers the detection limit in 2D photonic crystal microcavity coupled waveguide structures. We demonstrated experimentally in our side-coupled two-dimensional (2D) PC cavity-waveguide architecture, that the magnitude of the slow-down factor in the coupling waveguide contributes to enhanced light-matter interaction [7]. Over successive generations, we demonstrated experimentally 50 femto-molar (3.35pg/ml) sensitivity to the detection of the specific binding of avidin to biotin with a L55 type PC microcavity (55 missing holes) [8]. The role of analyte fill fractions was also investigated simultaneously and an elaborate design incorporating all factors of Q, fill fraction and slow light led to detected concentrations of 1femto-molar for the specific detection of avidin binding to biotin [7].

In this paper, we experimentally demonstrate the detection of three plasma proteins in patients with pancreatic cancer . Two types of L13 PC microcavities, with and without nanoholes, but similar Q-factors were investigated and biomarkers were detected in samples with varying dilution. All devices were fabricated from a commercial foundry using 193nm UV photolithography.
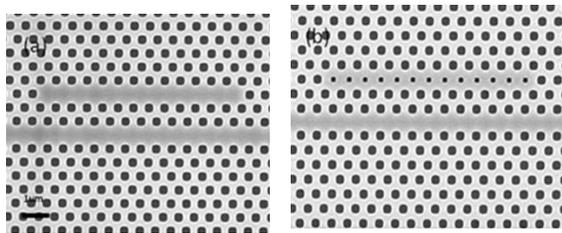


Fig. 1: SEM images (a) L13 PC microcavity and (b) L13 PC microcavity with nanoholes, fabricated by 193nm UV lithography in commercial foundry.
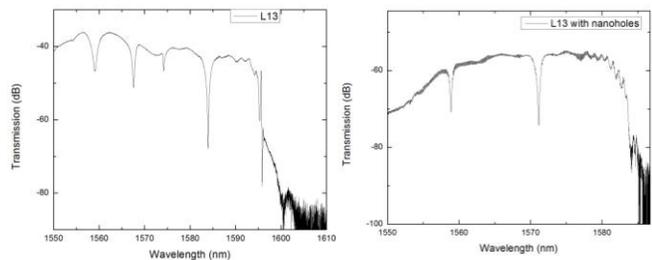


Fig. 2: Transmission spectrum showing sharp resonances in (a) L13 PC microcavity and (b) L13 PC microcavity with nanoholes corresponding to Fig. 1.

Fig. 1 shows scanning electron micrograph (SEM) images of L13 PC microcavity devices, with and without nanoholes, fabricated by photolithography followed by reactive ion etching. The microcavities are fabricated in 220nm silicon in a silicon-on-insulator (SOI) wafer within a photonic crystal defined by a triangular lattice of air

holes with hole diameter $d$=225nm. The nanoholes, defined as smaller diameter air holes within the L13 PC microcavity, have diameter $d_{NH}$=0.6$d$ and are located in the lattice positions to coincide with the antinodes of the mode in the center of the L13 PC microcavity. We previously showed that such nanoholes can increase the bulk sensitivity by almost a factor of 2 in nm/RIU (RIU=refractive index unit). [7] The corresponding transmission spectra are shown in Fig. 2. Sharp resonances with Q>15,000 are observed. The chip was treated with 2% APTES in toluene to coat a thin layer of silane. Then probe protein (fas ligand antibody) was applied on the device. The chip was then put in a humidity chamber and stored in 4 ℃ for 10 hours. Before target test, 1% BSA was used to block any binding sites that have not been covered by probe proteins.

Plasma samples from five patients with pancreatic cancer and four non-cancer healthy controls were obtained from a case-control study of pancreatic cancer conducted at UT MD Anderson Cancer Center. Three protein markers, i.e. hepatic growth factor, chemokine ligand 4 and fas ligand were previously tested using ELISA.

Before applying any target solution, resonance spectrum for each device was recorded. The resonance position was used as a baseline. The chip is then incubated in target solution for 45 min. Several concentrations of the target were measured. After each incubation, the chip was washed with PBS and new spectra were tested and resonance positions were recorded. Fig. 3(a) shows the resonance wavelength shifts versus time as measured by our optical spectrum analyzer (OSA) for the L13 PC microcavity without nanoholes. The relative shift from the baseline was calculated from experimental wavelength shift measurements for each dilution and plotted in Fig. 3(b). Three dilutions, 5×, 10× and 100× of the provided human plasma targets was done. The dashed line in Fig. 3(b) at 0.04 nm represents the noise level of our detection, mainly from the +/- 0.02nm wavelength inaccuracy of our optical spectrum analyzer. In our L13 PC microcavity devices, the temperature dependence of wavelength shift is 0.08nm per degree Celsius. During measurements, it was ensured that the chip temperature is stable to within +/- 0.1℃. Hence, only resonance wavelength shifts greater than 0.04nm were considered as actual shifts caused by the specific binding between the probe and target. As observed in Fig. 3(b), the L13 PC microcavity is able to detect pancreatic cancer biomarkers with 1× concentration. Two samples were tested, at 0.09pM and 0.06pM as determined by independent ELISA measurements. As expected, a smaller resonance wavelength shift is observed at 0.06pM than in 0.09pM.
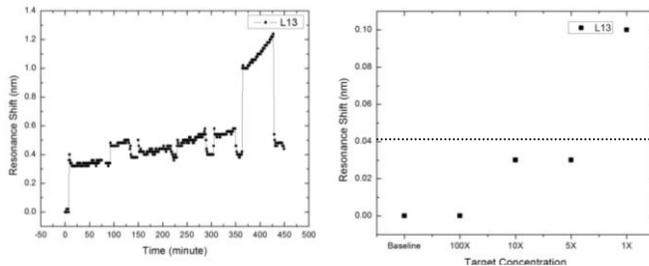


Fig. 3: (a) Resonance wavelength shift vs time for L13 PC microcavity in Fig. 1(a) for different dilutions. (b) Magnitude of resonance wavelength shifts versus target sample dilutions.
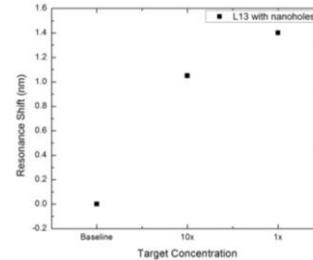


Fig. 4: Magnitude of resonance wavelength shifts versus target sample dilutions for L13 PC microcavity with nanoholes in Fig. 1(b).

Fig. 4 shows the experimental wavelength shift for each dilution with the L13 PC microcavity with nanholes. The 1× sample for this test had a concentration of 0.03pM. As observed in Fig. 4, a large resonance wavelength shift was observed for the 10× sample dilution. ELISA is unable to detect to such low concentrations. In fact, the large resonance wavelength shift observed for 10× dilution implies that it may be possible to detect pancreatic biomarkers in a human plasma sample with 100× dilution, if not larger dilution. Measurements are in progress and will be presented later.

Our measurements show the potential of our device to detect plasma proteins in patients with pancreatic cancer with higher sensitivity than ELISA, which translates into small sample volume requirement, both critical parameters for cancer biomarker development and eventual use in medical diagnostics.

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