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Coupling Variation Induced Ultrasensitive Label-Free Biosensing by Using Single Mode Coupled Microcavity Laser

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Optical label-free biosensors detect unmodified biological analytes by measuring the effective refractive index (RI) change after the analytes are adsorbed on a sensor surface.[1] Varied strategies have been developed for sensitive biosensing, among which optical microcavities are considered to be one of the most promising structures. In spherical or cylindrical microcavities, light is trapped inside the cavities and forms high Q ($Q > 10^7$) whispering gallery modes. A tiny change of the surface structure will introduce a resonance wavelength shift, thus providing ultrahigh sensitive detection of biomolecules.[2] Furthermore, combined with thermal-optic effects, single molecule detection was reported.[3] However, detection using ultrahigh Q passive microcavities requires stringent measurement conditions. For example, overcoupling will drastically spoil the Q value of the system, and ultranarrow line width tunable single frequency lasers are needed to detect slight resonance frequency change.[4] In contrast, optical active sensing using a microcavity laser provides a much simpler (therefore more stable) and higher signal level detection method. Nevertheless, the detection limit instead relies on spectrometer resolution.[5]

Here we report on a novel active optical sensing method by using a single mode coupled microcavity laser as a sensor. Instead of monitoring resonance wavelength shift, we detect the laser light intensity change when the coupling condition changes. We experimentally achieved a sensitivity of 80 pg/mL for bimolecular detection, which is equivalent to a passive microcavity sensor with a $Q > 10^7$.[6] However, our sensing scheme only needs nanometer spectral resolution, which can be easily realized by using a pocket-size spectrometer.

The structure and the working scheme of the single frequency laser was described earlier.[7] Our microcavity laser is a coupled microring cavity which forms with two rings of slightly different size. The coupled-resonator structure suppresses the multi-WGM resonance and generates single frequency laser emission with good directionality. The cavity surface and the coupling area are fully exposed to the environment for sensing applications.

The microcavity was immersed in liquid and optically pumped in a horizontal plane. The emitted laser light was side collected and spectrally resolved by a CCD equipped spectrometer. In liquid RI detection, the RI is controlled at 1×10^{-4} RI unit (RIU) resolution through changing the water−glycerol proportion. In protein concentration detection, analyte is directly added to a saline solution.

The RI change induced single frequency laser wavelength shift was detected. Figure 1A plotted the relation between resonance frequency shift versus RI of the surrounding liquid. A linear fitting gave a 16.7 nm/RIU sensitivity and a 6×10^{-4} RIU detection limit, if a laser line width detection limit of 0.01 nm was assumed. This sensitivity is of the same order as other passive and active circular microcavities.[6,8] However, since the coupled cavity emits single frequency light in a certain direction, the detection becomes much more convenient with a very good signal level.

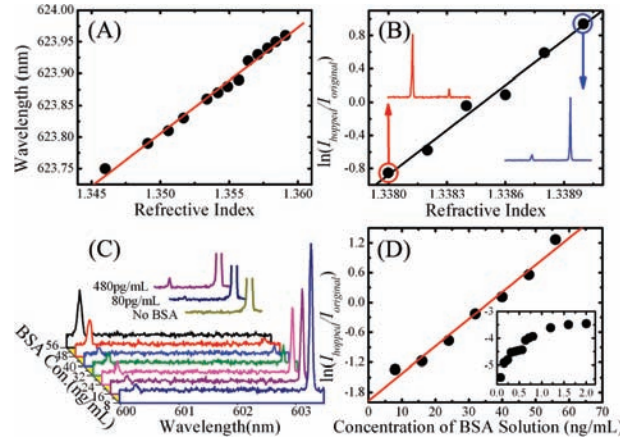

Figure 1. RI detection when (A) lasing frequency shift or (B) mode hopping is monitored. In (B), the lasing spectra at the two RI values are given. (C) Plot of the step-by-step changed spectra at different BSA concentrations. (D) Plot of the intensity ratio of the two lasing modes versus concentrations of BSA solution. Insets in (C) and (D) are from another sample that allows detection of ultralow BSA concentration.

With the continuous change of RI, the emission light wavelength does not show continuous shift. Instead, in an RI range of 1.3380−1.3390, mode hopping is observed. Figure 1B shows that $\ln(I_{hopped}/I_{original})$ changes linearly with RI. Here $I_{original}$ and I_{hopped} are the light intensity of the original laser line and the hopped laser line respectively. The laser mode hopping occurs because the asymmetric ring structure responds slightly different from the change of surrounding RI; therefore the single-ring resonance does not shift synchronously. There is also another possibility that the slight change of RI changes the coupling efficiency of the two rings. We will see in the following part that the change in coupling efficiency plays an important role in achieving ultrahigh sensitivity in biosample detection.

Mode hopping provides a novel scheme for optical sensing. Note that hopping occurs between two laser lines that are spectrally far apart (several nm), which makes detection of the spectrum very easy. Moreover, instead of measuring wavelength shift, light intensity is monitored. Taking $\ln(I_{hopped}/I_{original})$ as the transducer signal and considering the lowest detectable lasing intensity change is 10 counts, we estimated the lowest detection limit to be $5\times$

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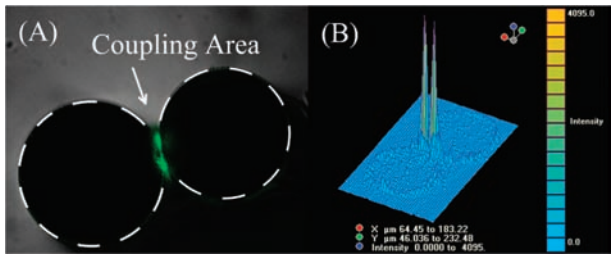

Figure 2. (A) Florescence image of microcavity cross section after immersing in solution of FITC labeled BSA. (B) The fluorescence intensity map of (A). They clearly show that BSA is selectively adsorbed in the coupling area.

10^{-6} RIU (see Supporting Information), 120 times more sensitive compared with that of the wavelength shift detection scheme (6×10^{-4} RIU).

The sensing ability of the coupled microcavity laser to biosamples was tested. Bovine serum albumin (BSA), goat immunoglobulin, and egg white lysozyme were used. Here we concentrated on analysis of BSA detection. The sensor also works for the other two proteins (see Supporting Information), although their sensitivities are different due to the different molecular weight and adsorbing ability to the cavity. Figure 1C plotted, for BSA detection, the step-by-step lasing spectral change when BSA was added into 50 mL of normal saline. Figure 1D plotted the $\ln(I_{hopped}/I_{original})$ changes with BSA concentrations. The sensor responds linearly to the BSA concentration in a range of 8−56 ng/mL. Unlike RI detection, now the lower detection limit relies on the measurable lowest hopped laser mode intensity. Experimentally the lowest detectable concentration we achieved is 80 pg/mL (see insets of Figure 1C and Figure 1D) by using thermally consolidated coupled microcavities (see Supporting Information). This value is comparable to the detection limit achieved with a $Q > 10^7$ passive optical microcavity.[6] We believe that if the spectrometer is equipped with a lower noise level photodetector, even pg/mL detection is possible. However, when the concentration decreased to 80 pg/mL, the mode hopping became irregular at 3 ng/mL, and as can be seen in the inset of Figure 1D, the sensor responds nonlinearly to BSA concentration. Note the nonlinear response was also observed in the ultrahigh Q passive microcavity sensor where the resonance wavelength shift was monitored.[3] For concentrations higher than 50 ng/mL, the lasing wavelength shift will be larger than 0.02 nm (see Supporting Information), which is detectable by a normal spectrometer. Therefore, in principle, with mode hopping and mode shift combined, the single frequency coupled cavity laser provides a detection range from pg/mL (limit of mode hopping) to μg/mL (limit of mode shift).

Further experiments were carried out to explore the laser mode hopping mechanism. We suspect that the adsorption of protein in the coupling part of the cavity may lead to the hopping of the modes. For a clear view of the adsorption process, fluorescein isothiocyanate (FITC) labeled BSA, which has the similar property of BSA, was used to label the adsorption area on the cavity. The coupled microcavity was immersed in an FITC-BSA solution for a short period of time (~10 min) and was pulled out. The fiber pair was then cut to expose the cavity cross section. The cavity cross section was then placed under a confocal microscopy to take the fluorescence image. Figure 2 shows that intense fluorescence comes from the coupling area, which means that protein is preferably adsorbed there, most probably because of the abrupt change of the curvature.

For further confirmation that laser mode hopping comes from protein adsorption in the coupling area, two types of coupled cavity

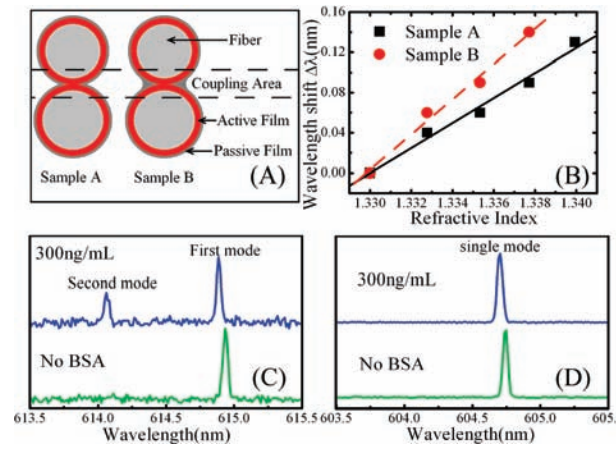

Figure 3. (A) Plot the structure of samples A and B. (B) Plots of the frequency shifts of single frequency versus RI in samples A and B respectively. Spectra in solution with no BSA and with BSA concentration of 300 ng/mL in sample A (C) and in sample B (D).

(samples A and B) were prepared. The coating of sample B is thick so that we can assume that the coupling area is safely blocked. Meanwhile, the coating on sample A is very thin so that the coupling area is still partly "open". RI sensing measurements (see Figure 3B) show that both cavities have a similar RI sensitivity. However, results on coupling sensing were significantly different. When 300 ng/mL BSA was loaded, sample A still possessed the laser mode hopping property (Figure 3C), but sample B was totally inert to the BSA loading (Figure 3D). The results clearly distinguish the novel coupling sensing from conventional RI sensing. Local protein adsorption contributes to only a slight change in cavity mode wavelength but can obviously alter the coupling coefficient which determines the single mode laser emission property. That is the reason why coupling sensing can reach a much higher sensitivity.

In conclusion, we demonstrated experimentally a new optical sensing scheme by using a coupled microcavity laser. The ultrasensitive sensing comes from the slight change in the coupling condition for the coupled microcavity, which in turn influences the single mode laser emission property.

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Supporting Information Available: Microcavity material description, experimental setup, hopping results of other proteins, estimation of detection limit and dynamic range, characterization of the additional coatings on single frequency coupled microcavities. This material is available free of charge via the Internet at http://pubs.acs.org

References

(1) Fan, X.; White, I. M.; Shopova, S. I.; Zhu, H.; Suter, J. D.; Sun, Y. *Anal. Chim. Acta* **2008**, *620*, 8–26.
(2) Vollmer, F.; Arnold, S. *Nat. Methods* **2008**, *5*, 591–596.
(3) Armani, A. M.; Kulkarni, R. P.; Fraser, S. E.; Flagan, R. C.; Vahala, K. J. *Science* **2007**, *314*, 783–787.
(4) Cai, M.; Painter, O.; Vahala, K. J. *Phys. Rev. Lett.* **2000**, *85*, 74–77.
(5) Francois, A.; Himmelhaus, M. *Appl. Phys. Lett.* **2009**, *94*, 031101.
(6) Zhu, H.; White, I. M.; Suter, J. D.; Dale, P. S.; Fan, X. *Opt. Express* **2007**, *15*, 9139–9146.
(7) Shang, L.; Liu, L.; Xu, L. *Opt. Lett.* **2008**, *33*, 1150–1152.
(8) Lu, M.; Choi, S. S.; Irfan, U.; Cunningham, B. T. *Appl. Phys. Lett.* **2008**, *93*, 111113.

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