Wide Dynamic Range Specific Detection of Therapeutic Drugs by Photonic Crystal Microcavity Arrays

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Abstract: Six orders of magnitude wide dynamic range (0.1ng/ml to over 100μg/ml), label-free detection of gentamicin small molecules with silicon photonic crystal microcavity biosensors multiplexed by multimode interference power splitters was experimentally demonstrated. Detection specificity was confirmed.

OCIS codes: (280.0280) Remote sensing and sensors; (050.5298) Photonic crystals; (130.0130) Integrated Optics

On-chip photonic biosensors have become a fast growing research topic driven by the need for high sensitivity, high throughput, short response time and label-free bio-detection methods. Various devices, using surface plasmon resonance [1, 2], microring resonators [3], silicon nanowires [4], nanoporous silicon waveguide [5], 1D or 2D photonic crystal microcavities [6, 7], have been demonstrated for medical research use. The 2D PC cavity sensor stands out among them for its slow light enhanced sensitivity within miniature footprint and its flexibility in creating various designs that cover a wide detection range of target concentrations. We have proposed PC microcavities with *n* missing air holes like L13, L21, L55, L13 with defect holes, which provide various detection ranges and minimum detection sensitivities separately from as low as 1fM to over 1μM (avidin as target analyte) [7-10]. Combining those devices would enable a detection range as wide as 6 orders of magnitude or higher. The high sensitivity not only lowers the detection limit for regular protein or antibody detections, but also facilitates the detection of small biomolecules, like antibiotics. This is of particular importance to therapeutic drug development and its clinical practice. In this paper, we experimentally demonstrated 6 orders of magnitude wide dynamic range detection in a sensor array consists of different types of PC sensors. A common antibiotic, gentamicin (molecular weight = 480 g/mol), was used as the target. It was captured by anti-gentamicin antibody immobilized on the sensor surface prior to the test and detected by the resonance shift in the output spectra. Two other antibiotics, vancomycin and tobramycin, were used to verify the specificity of the gentamicin detection.

The devices were fabricated with CMOS compatible 193nm UV lithography process on a silicon-on-insulator (SOI) wafer. The device comprises a 1×4 MMI (multimode interference) power splitter that splits the input light into four optical paths. On each path, an L-type PC microcavity sensor with different sensitivity is located, namely L3, L13, L55 and L13 with defect holes. Fig. 1(a) shows a microscopic image of the MMI and the four optical paths. Figs. 1(b)-(e) show the scanning electron microscopic (SEM) images of the individual PC sensors. The chip was treated chemically and the probe protein (anti-gentamicin antibody) was immobilized on the surface. Before target test, 1% bovine serum albumin (BSA) was used to block any binding sites that have not been covered by probe proteins. After a thorough wash in phosphate buffered saline (PBS), the device was ready for test.

Before applying any target solution, resonance spectrum for each device was recorded and the resonance position was used as baseline. The chip is then incubated in target solution for 40 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. 2 shows the resonance in the transmission spectrum of the L55 PC sensor for different concentrations. The red-shift of the resonance for increasing concentrations of target can be observed. The relative shift from the baseline for all four devices was calculated and plotted in Fig. 3. In the figure, the dashed line at 0.04 nm represents the noise level of our detection, mainly from wavelength inaccuracy of our optical spectrum analyzer.

From the data points in Fig. 3, the different detection ranges of the four types of PC sensors can be identified. Below 5×10^{-3} μg/mL, only the most sensitive device, L13 with defect holes, show resonance shift over noise level. At 5×10^{-3} μg/mL, the shift for L55 reaches 0.04nm showing the biomolecule binding has been detected. L13 and L3 starts to detect effectively after reaching 0.5μg/mL. Furthermore, there is a range of concentrations within which the resonance shift is linearly proportional to the log of the concentration. The ranges are approximately (1) lower than 5×10^{-3} μg/mL for L13 with defect holes; (2) between 5×10^{-3}μg/mL and 0.5μg/mL for L55, and (3) between 0.5 μg/mL and 500 μg/mL for L13, as depicted in Fig. 3 by different colors. We expect the detection range for L3 extend over 500 μg/mL, giving us a total range of at least 6 orders of magnitude. Beyond each of the ranges, the shift gradually reaches an upper limit when the target captured at the PC sensor saturates the effective sensing area.

The more sensitivity the device, the lower the upper-limit concentration, but the linear detection range also tends to be lower. With the help of the on-chip MMI structure, individual PC sensors now can be integrated in an array, enabling a wide dynamic range in a single detection. Further investigation is ongoing and more comprehensive data will be presented.

To verify the specificity of our test, another two types of therapeutic drugs, vancomycin and tobramycin, were introduced as non-specific binding targets. Anti-gentamicin antibody was still served as the probe on the sensor surface. After BSA blocking, vancomycin and tobramycin (both in 500 μg/mL in PBS), were applied and tested successively, followed by the test of gentamicin at the same concentration. The resonance shift is shown in Fig. 4. The slight red-shift for vancomycin and tobramycin are below the noise level of 0.04nm and hence indicates that no detectable binding between probe and target has occurred. After applying gentamicin, however, there is 0.075 nm resonance shift, indicating the specific binding of gentamicin to its conjugated antibody. Therefore, our detection method shows good specificity even by introducing high concentration non-specific biomolecules.

In summary, more than six orders of magnitude wide dynamic range detection, from below 0.1ng/ml to over 100μg/ml, of small molecules (gentamicin) was demonstrated using PC sensors of different sensitivities multiplexed by a MMI power splitter. Detection specificity with respect to other small molecule drugs was demonstrated. The multiplexed wide detection range chip holds significant promise in therapeutic drug monitoring.

The authors acknowledge Army (USAMRAA) Contract # W81XWH-14-C-0029 for supporting this research.

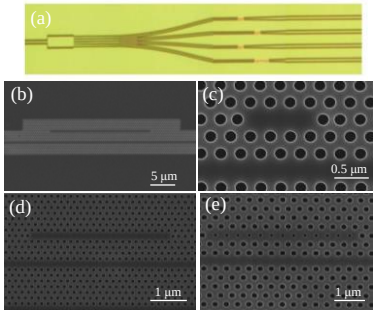

Fig. 1. (a) Microscopic image of the MMI coupler and four PC sensors on the four channels. (b)-(e) SEM images of PC microcavities coupled to PC waveguide: (b) L55 (c) L3 (d) L13 and (e) L13 with defect holes.

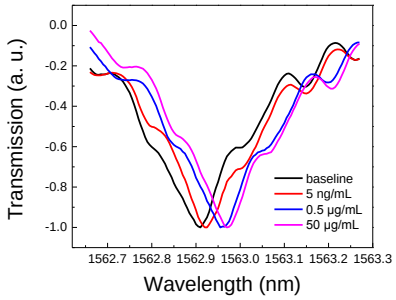

Fig. 2. Normalized spectra around one of the resonances in the L55 PC sensor after applying different concentrations of gentamicin solutions.

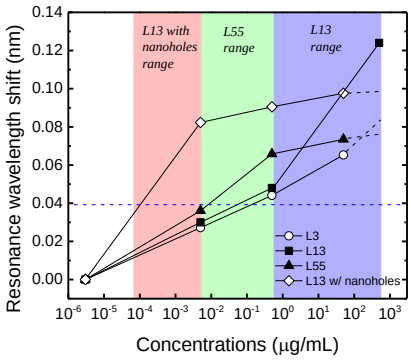

Fig. 3. Resonance shift of all four devices for different concentrations.

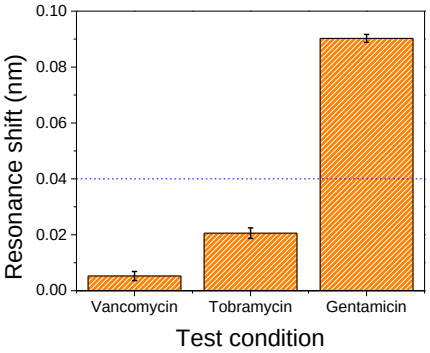

Fig. 4. Resonance shift for the three therapeutic drugs in the specificity test.

References

[1] A. A. Yanik, M. Huang, A. Artar, T.-Y. Chang and H. Altug, Appl Phys Lett **96** (2), 021101,(2010).
[2] B. Zhang, A. W. Morales, R. Peterson, L. Tang and J. Y. Ye, Biosensors and Bioelectronics **58**, 107-113 (2014).
[3] M. Iqbal, M. A. Gleeson, B. Spaugh, et al., Selected Topics in Quantum Electronics, IEEE Journal of **16** (3), 654-661 (2010).
[4] S. Janz, D. X. Xu, M. Vachon, et al., Opt Express **21** (4), 4623-4637 (2013).
[5] X. Wei, J. W. Mares, Y. Gao, D. Li and S. M. Weiss, Biomed. Opt. Express **3** (9), 1993-2003 (2012).
[6] F. Liang, N. Clarke, P. Patel, M. Loncar and Q. Quan, Opt Express **21** (26), 32306-32312 (2013).
[7] W.-C. Lai, S. Chakravarty, Y. Zou, Y. Guo and R. T. Chen, Appl Phys Lett **102** (4), 41111 (2013).
[8] Z. Yi, S. Chakravarty, D. N. Kwong, L. Wei-Cheng, et al., Selected Topics in Quantum Electronics, IEEE Journal of **20** (4), 171-180 (2014).
[9] S. Chakravarty, A. Hosseini, X. Xu, L. Zhu, Y. Zou and R. T. Chen, Appl Phys Lett **104** (19), 191109 (2014).
[10] C.-J. Yang, Y. Zou, S. Chakravarty, H. Yan, Z. Wang, and R. Chen, in *CLEO: 2014*, STh4H.5.