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High-throughput detection of human salivary cortisol using a multiple optical probe based scanning system with micro-optics and nanograting coupled label-free microarray

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ABSTRACT

We demonstrate the use of a parallel detection system with a nanograting-based microarray to accomplish high-throughput analysis of bio-molecular interactions in a label-free manner. Well-type label-free microarrays were fabricated to eliminate the risk of cross-contamination and to minimize sample volumes. Parallel analysis without the use of spectrometer arrays or a moving platform was accomplished by using scanning multiple optical probes generated by a spatial light modulator and microlens array. Additionally, multiple optical probe spots focused by the microlens array reduced detection errors while enhancing the signal-to-noise ratio within a high-density microarray. Finally, we verified the feasibility of the parallel detection system by analyzing the peak wavelength value (PWV) shift of human salivary cortisol and anti-cortisol in a competitive binding experiment.

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1. Introduction

The use of microarray technology is accelerating in the areas of proteomics research, disease diagnosis and pharmaceutical research since it allows for the analysis of thousands of bio-molecular interactions simultaneously with high density and high speed [1–5]. Although microarrays can provide a high-throughput analytical platform for sample profiling and protein–protein interaction, most current studies have been confined to detection using fluorescence- or radioactive labeling-based techniques [6]. However, microarrays utilizing these labeling methods have drawbacks such as modified sample bioactivity, and inaccurate detection results can occur due to labeling efficiency, a time-consuming and labor-intensive process [7]. Label-free approaches provide an alternative solution for high-throughput analysis that can guarantee measuring accuracy while avoiding disturbances from fluorescent dye- or radioactive material-based labels [8–10].

One prominent label-free method utilizes an optical-based technique with a nanograting-based biosensor, which can measure biological activity with high sensitivity using the optical property changes of the sub-wavelength nanograting and waveguides [11]. As the binding event of antibody and antigen occurs, transmission or reflection peak spectra are shifted due to the thickness and refractive index changes adjacent to the nanograting. For this analysis a spectrometer is utilized because this system measures peak movement in spectra as the criteria for the prediction of bio-molecular interactions [12,13].

However, the application of this technology for the parallel detection of thousands of bio-molecular interactions has not been realized because it is not a suitable approach to equip spectrometer arrays with multiple matching optical probes, considering the total system size and cost. To solve this issue, the microwell arrays can be scanned with a single spectrometer by using a moving stage. However, that method has issues with system integration, miniaturization, scanning speed, and vibration compared with optical scanning. Another approach was done by Wong et al. They used a surface plasmon resonance imaging (SPRi) method consisting of an SPR chip array and a charged coupled device (CCD) [14]. However, this method has limitations when analyzing biomolecules with high sensitivity since a CCD, functioning as a detector by monitoring

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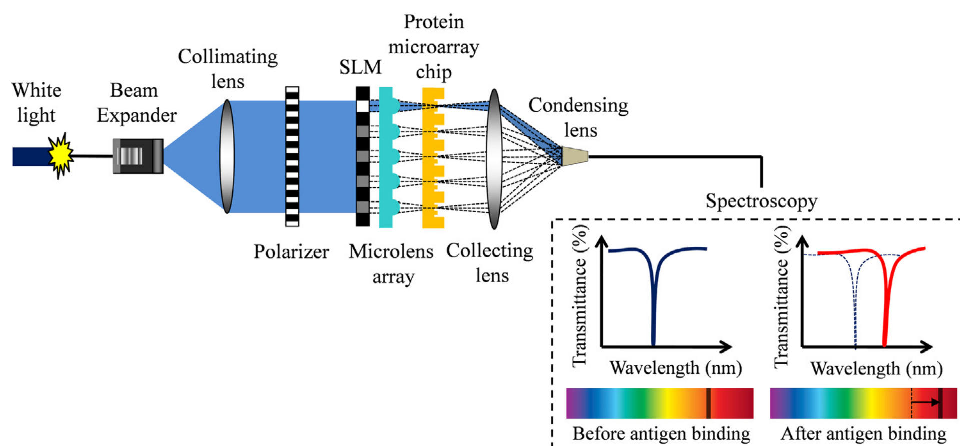

Fig. 1. Schematic design of the label-free parallel detection system comprising micro-optics, a spatial light modulator and a microwell array integrated with nanograting structures.

intensity modulation, has lower resolution than the spectrometer [15,16].

In this study, we propose a parallel detection system that utilizes multiple optical probes generated by a spatial light modulator (SLM) and micro-optics (as illustrated in Fig. 1). Using this system we were able to perform parallel detection by scanning multiple optical probes with high sensitivity with a single spectrometer. Moreover, signal enhancement was achieved within a high-density microarray without the amplification of signal detection with a fluorophore. Additionally, we fabricated a multi-scale microwell array integrated with nanograting structures by UV nanoimprinting to facilitate the identification of bio-molecular interactions in an aqueous solution while using physically separated cavities to eliminate the chance of cross-contamination [17]. Finally, we demonstrated the feasibility of this parallel detection system by analyzing the peak wavelength value (PWV) shift of cortisol and anti-cortisol binding. This method has the advantage of being a highly sensitive high-throughput label-free biosensor that can easily be configured in an array format to accept minimal sample volumes. These qualities make this platform well suited to disease diagnosis and pharmaceutical research.

2. Material and methods

2.1. Design of multiple optical probes and multi-scale label-free microarray integrated with nanograting structures

Prior to the construction of the microarray system, multiple optical probes generated by a SLM and micro-optics were designed for parallel detection. These multiple optical probes are formed by one-to-one matching between a SLM, for controlling multiple beams individually via optical switching, and a microlens array for focusing the multiple beams into the microwell array. The probe then delivers optical signal information to the spectrometer. parallel detection is achieved by storing data regarding independent biomolecular interactions acquired by each optical probe followed by sequential analysis with the spectrometer (Fig. 2(a)). However, as the size of the microwell in a high-density microarray becomes smaller, the optical signal is degraded, resulting in insufficient light intensity for analyzing spectra. To overcome this issue we designed and fabricated a microlens array to analyze antigen-antibody interactions in microwells that were hundreds of micrometers in size [18–20]. The design specification for fabricating this microlens array is shown in Fig. 2(b). The 16 × 16 microlens array is identical to the microwell array and utilizes a photopolymer (n = 1.51 at 680 nm, Ormocomp by Micro Resist Technology) on sodalime glass substrate. The microlens has a diameter of 700 μm, a sag height of 140 μm to provide a focal length of 1.0 mm and a numerical aperture (NA) of 0.35, and arrayed with a pitch size of 1.1 mm. Also, chrome (Cr) apertures that have a diameter of 700 μm were designed on the microlens substrate to reduce crosstalk between the microlenses.

The microwell based array was designed with close attention to the minimum spotting volume, the size of the SLM and the minimum light intensity for measurement (Fig. 2(c)). The resulting microwell structure of 16 × 16 arrays with a diameter of 500 μm and a height of 120 μm resulted in an area of 18.2 mm × 18.2 mm. Nanograting structures were patterned on the bottom of the microwell structures to facilitate analysis of multiple biomolecular interactions by optical detection. A simulation based on rigorous coupled wave analysis (RCWA) was conducted to predict peak wavelength value (PWV) of the biosensor. RCWA is a method of analyzing sub-wavelength diffraction gratings to determine the diffraction efficiency of spatial frequency by dividing grating structures into several thin layers and solving eigenvalues [21]. In this simulation, transverse electric (TE) polarized light had a normal incident plane into the nanogratings. For the simulation the nanograting (n = 1.49) had a pitch size of 450 nm, a duty ratio of 0.5, and a height of 160 nm, and the high refractive layer (silicon nitride, n = 2.05) had a thickness of 70 nm. Using these parameters the designed sensor had a PWV of 696.2 nm.

2.2. Fabrication of the nanograting coupled microwell array, microlens array and system construction for parallel detection

Then nanograting coupled microarray was fabricated by conventional patterning processes including photolithography and UV nanoimprinting, as shown in Fig. 3(a). As a first step, a silicon master with a pitch size of 450 nm, duty ratio of 0.5 and height of 160 nm was fabricated by photolithography with a KrF scanner and reactive ion etching (RIE). After that, a negative photoresist (ACT-CNR-4400-15T) was spin coated twice with a rotation speed of 400 rpm for 50 s on top of the nanograting, and the second photolithography was carried out to make microwell arrays with a diameter of 500 μm and height of 120 μm. Subsequently, polydimethylsiloxane (PDMS, Dow Corning Corporation) was cast over the multi-scale structures to form a negative replica of the nanograting coupled microwell array. Using the fabricated multi-scale PDMS mold the well-type microarray was replicated via UV nanoimprinting. UV nanoimprinting was performed using photopolymer (n = 1.49 at 680 nm, MINS-ERM by minuta technology co.,ltd.) on a glass substrate at room temperature with an UV curing dose of 2100 mJ/cm^2. Finally,

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