Sensors and Actuators B 254 (2018) 64–71

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Research Paper

Miniaturized surface plasmon resonance biosensor with vacuum-driven hydrodynamic focusing

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 4 July 2017
Accepted 7 July 2017
Available online 10 July 2017

Keywords:
SPR
Hydrodynamic focusing
Biosensor
Microfluidic

ABSTRACT

To apply surface plasmon resonance (SPR) biosensors into point-of-care testing (POCT), new techniques are required such as miniaturization, reduction of power consumption, and reduction of sample consumption. Although several miniaturized and portable SPR biosensors have been fabricated, they have not been developed for POCT because of the need for bulky liquid handlers, high power consumption, and large sample volumes. We developed a fully integrated portable SPR system with vacuum-driven vertical focusing microfluidics for POCT applications. The present SPR system was fully operated using a mobile PC battery by adopting an electric-power-free pump and an automated microfluidic system. Vertical focusing allowed the required sample volume to be significantly reduced (1/10 of that in conventional methods) without degrading sensitivity or measurement time. Additionally, the SPR system was found to be useful for detecting rare targets such as prostate specific antigen (PSA) in blood samples. We expect that the proposed system can be used in on-site monitoring systems in the fields of healthcare, food systems, and the environment.

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1. Introduction

Affinity biomolecular interaction-based label-free, real-time microfluidic biosensors have being studied as possible tools for diagnostics, analytic purposes, and point-of-care testing (POCT) [1–3]. Among all techniques used in real-time and label-free biosensors, surface plasmon resonance (SPR) biosensing has been used primarily in the field of biological [4] and environmental [5] sciences. SPR biosensors sensitively detect changes in the refractive index within the evanescent field due to reactions between the sensor chip's surface and the analytes [2]. Thus, detection using an SPR biosensor is considered one of the most precise, qualitative, and quantitative analysis methods.

Because of the high sensitivity and label-free detection characteristics of SPR sensors, its application has been broadly expanded to the analysis of life science technology fields [5], drug quality control [6], and even point-of-care (POC) applications. Typical POC applications using SPR include environmental monitoring [5], safety monitoring for foods and beverages [7], product quality control [6], and the rapid detection against the bio-terrorism [8]. To apply the SPR biosensor in POCT, improved performance such as miniaturization, reduction in power consumption, and reduction in sample consumption are required.

Several miniaturized and portable SPR biosensors have successfully been developed. Texas Instruments, Inc., has developed a portable SPR device called SPREETA™, a small and inexpensive sensor, 15 × 7 × 30 mm in size. This remarkable instrument integrates all the SPR optical components into a molded and compact device [9,10]. SPREETA™ was deployed for environmental monitoring and bacterial detection [9,10]. Additionally, recent miniature SPR devices include SPRmicro (K-MAC, Daejeon, Korea, 2012), SPIRIT (Seattle Sensing Systems Corporation, Seattle, WA, USA, 2007), Smart SPR SS-1001 (Mebius Advanced Technology, Tokyo, Japan, 2012) and Biosuplar 6 (Analytical μ-systems of Mivitec, Sinzig, Germany, 2012) [11].

The above miniaturized systems, however, are limited to using optical modules. Liquid handling systems (including peristaltic or syringe pumps for sample loading into SPR biosensors) are still bulky and result in large power consumption [12]. Recently, compact and power-free pump systems have attracted much attention for use in important POC devices. Several power sources have been used to drive the fluid in the power-free systems, including surface tension of the fluid [13], capillarity force of the channel [14], on-chip chemical reactions [15], and so on. Although most of these

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http://dx.doi.org/10.1016/j.snb.2017.07.041
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methods could be used to perform pumping, many are not able to maintain a steady flow rate and a long sampling time which are essential for application to SPR systems [12].

Despite miniaturizing the SPR biosensor using microfluidic modules, a large sample volume is still required because of the microchannel size limitations associated with clogging problems (H > 50 μm) [5]. In general, sample volumes of an SPR sensor range from the high-microliter to low-milliliter range [16]. In fact, most of the samples flow through a channel to a waste chamber without interacting with the sensor surface. It is worth noting that SPR biosensors can perform detection only when the analytes exist within the evanescent field of the sensor surface (within approximately 200 nm). Although nanotechnology makes it possible to fabricate sub-micron to low-micrometer-scale channel depths, this scale is accompanied by other unexpected problems such as channel clogging [16]. As an effective alternative method, Hofmann, Voirin [16] proposed a three-dimensional microfluidic confinement method for efficient sample delivery to fluorescence-based biosensor surfaces. This method reduced sample volume using a confinement flow; however, the system was complex and bulky because of the use of fluorescence detection and a syringe pump.

In this paper, we develop a portable system using a palm-sized SPR biosensor with a fully-integrated microfluidic system. A vacuum-driven electric-power-free pump can provide nearly constant vacuum pressure throughout the test period. To minimize the required sample volume, the proposed system adopted a hydrodynamic vertical focusing method in a microchannel near the SPR sensor surface, which resulted in a significant reduction in required sample volume. The proposed POC SPR system was verified by measuring prostate specific antigen (PSA) without diminishing the high precision and sensitivity associated with SPR.

2. Materials and methods

2.1. Materials

Streptavidin was purchased from Sigma-Aldrich (St. Louis, MO, USA). Prostate specific antigen and antibody (PSA and anti-PSA) were purchased from HyTest (Turku, Finland). We used 1X Phosphate-buffered saline (PBS) (Gibco PBS, Life Technologies, Gaithersburg, MD, USA), chloroform (99.5%, Sigma-Aldrich, St. Louis, MO, USA), and ethanol (99.9%, Burdick & Jackson, Muskegan, MI, USA). The biotin self-assembled monolayer (Biotin-SAM) (B564: Biotin-SAM Formation Reagent) was purchased from Dojindo Laboratories (Kumamoto, Japan). Polyether ether ketone (PEEK) was used for the material of the fluidic channel.

Valves (micro-metering valves) were purchased from Upchurch Scientific (USA). Tefzel (ETFE) tubings were purchased from Upchurch Scientific (USA) and Ismatec (USA). The syringe was purchased from Hamilton (USA). The light emitting diode was purchased from Opnext Inc., (Japan) and two-dimensional complementary metal oxide semiconductor (2D-CMOS) image sensor was purchased from IDS, Co., (Germany). We used a pressure sensor from Honeywell (USA). We used two electronic balances from Sartorius (Germany) and Hansung (Korea).

2.2. Configuration of the portable SPR system

The portable SPR system comprised the following main parts: i) a vacuum-driven electric-power-free pumping system (ViPS) including flow rate control valves, ii) a flow cell with vertical focusing, and iii) an optical module, as shown in Fig. 1**(a)**. The pressure-differential-based ViPS consists of a syringe (30 mL), a dead volume chamber (540 mL), and two flow rate control valves; it delivers the liquid sample to the SPR sensor with pulse-free, and continuous flow (i.e., at a constant flow rate) with zero electrical power consumption. Two flow tubes are connected in a flow cell for vertical flow focusing. The flow cell consists of two channels (both 1 mm × 6 mm × 0.12 mm) for calibration and testing, respectively. Each channel is sealed with an O-ring and includes a sample inlet, a sheath inlet, and an outlet. Fig. 1**(b)** shows a view of the manufactured portable SPR system.

A schematic illustration of the sensor of the SPR biosensor assembled using a flow cell is depicted in Fig. 1**(a)**. The sensor consists of a gold chip and an optical module. On the gold chip's surface, a thin gold layer (50 nm of Au on 2 nm of Cr) was sputtered. The opposite surface of the gold chip was tightly attached to a prism coated with an index-matching fluid so as to ensure continuous propagation of light. We used a 770-nm light-emitting diode as a light beam in our system. A *p*-polarized wedge-type incidence beam with an angle range of 7.296° (1 pixel = 0.0057°) was passed through a band-pass interference filter (770 ± 10 nm) and entered the SPR sensor chip via a half-cylindrical prism. Then, the intensity of the reflected light beam was monitored using a two-dimensional complementary metal oxide semiconductor (2D-CMOS) image sensor that had a 1/1.8-inch sensing area (1280 × 1024 pixels). The image sensor was located immediately in front of the prism; it allowed the SPR system to be fabricated without any other lenses. The images were processed using MATLAB software that we programmed in a previous work [17]. We characterized sensitivity and resolution of our lab-made SPR device. Various concentrations (0–6%) of glycerol solutions were prepared to evaluate the detection of limit (LOD) of the SPR sensor responding to the change in the refractive index of the bulk solution and the sensitivity of our sensor system. Prior to measuring the glycerol solutions, a baseline SPR signal was obtained with injecting DIw at a flow rate of 40 μL/min. The glycerol solutions were then applied to each channel at 40 μL/min for 10 min. We calibrated the sensor response in terms of refractive index unit (RIU) from the experimentally obtained refractive index data of the glycerol solution. Fig. S1(a). shows real-time sensorgram obtained by injecting glycerol–water solution of 0–8% range. We observed that the calibration curve had linearity with glycerol-water solutions of up to 6% in Fig. S1(b). The labmade SPR device and signal analysis algorithm achieved resolution of detection of 3×10^{-6} RIU. The presented SPR system was controlled by a laptop and required no external power supply. A detailed description is presented in the following sections.

2.3. Operation of the ViPS

The ViPS consists of a 30-mL syringe and a 540-mL empty chamber; it is connected to the flow cell outlet. The volumetric flow rate (Q) of the device depends on the applied pressure differential between the vacuum (internal, P_{in}) and initial (atmospheric, P_{atm}) pressure ($\Delta P = P_{atm} - P_{in}$) via Poiseuille's equation,

$$Q = \pi D^4 \Delta P / 128 \mu L \quad (1)$$

where Q is the volumetric flow rate, D and L are the diameter and length of tubing, ΔP is the pressure differential, and μ is the viscosity of the fluid medium. In our system, to initiate fluid flow, the piston is pulled backward and locked in place, as shown in Fig. 2**(a)**. Pulling back the piston expands the air volume in the syringe, generating a pressure differential following the formula $P_{in0}V_{in0} = P_{in1}V_{in1}$, where V_{in0} (540 mL) and P_{in0} (101.3 kPa, atmospheric pressure) are the initial internal volume and pressure, respectively, of air, and V_{in1} (570 mL) and P_{in1} (95.3 kPa) are the internal volume and pressure, respectively, after pulling the syringe. Here, pressure is measured using a pressure-sensor (001PDAA5, Honeywell, NJ, USA).

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