Sensors & Actuators: B. Chemical 270 (2018) 327–332

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

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

Paper transducers to detect plasmon variations in colorimetric nanoparticle biosensors

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ARTICLE INFO

Keywords:
Smartphone
Gold
Nanosensor
Paper-based analytical device
Point of care
LSPR

ABSTRACT

Detecting variations in the localized surface plasmon resonance (LSPR) of gold nanoparticles is a widespread approach for developing colorimetric biosensors. This is usually performed with a large spectrophotometer, which is not suitable for in-field measurements, or with the naked eye, which only allows detecting large spectral variations leading to clear changes in color. Here we demonstrate that patterns printed on paper can transduce LSPR variations caused by the aggregation of plasmonic nanosensors using a mobile device as the reader. The sensitivity of the proposed paper transducers is tested with a new enzyme-less signal generation mechanism for biosensors based on triggering the aggregation of gold nanoparticles in the presence of neutravidin. A competitive immunoassay using this mechanism and the proposed transducers can detect the model analyte C-reactive protein with a limit of detection of $3{\cdot}10^{-8}$ g mL^{-1} within 1 h, which is comparable to an ELISA using a spectrophotometer to detect the signal. The fabrication of the transducers only requires a common toner printer, and the signal can be detected with the ubiquitous smartphone using a downloadable app, which makes the proposed detection platform ideal for developing mobile biosensors for global health applications.

1. Introduction

The exceedingly large extinction coefficients of noble metal nanoparticles make these materials ideal building blocks for the fabrication of colorimetric biosensors [1–5]. A common approach to design nanoparticle-based biosensors consists of triggering the aggregation of the colloids via biorecognition reactions [6,7]. This red-shifts the localized surface plasmon resonance (LSPR) of the nanoparticles, and broadens and dampens their extinction spectrum, which may lead to changes in the color of the nanoparticle suspension detectable by eye [8–10]. For example, red-colored solutions of spherical gold nanoparticles may become blue- or grey-colored when large aggregates are formed [8–10]. Detecting color changes with the naked eye is advantageous in that it does not require any equipment to detect the signal, which makes the biosensors more portable and affordable [11]. However, small spectral variations leading to subtle changes in color may not be detectable with the naked eye, or may be subject to personal differences in color differentiation and ambient light effects. Such variations can only be detected with confidence using a spectrophotometer, which is expensive and not suitable for in-field measurements. Although portable and affordable versions of spectrophotometers exist, they are not ubiquitously available, and their manipulation is not obvious for untrained users. In this context, it would be desirable to find an alternative approach to detect small variations in the extinction spectrum of nanoparticle biosensors that did not require expensive or complicated gadgets [12,13] or large pieces of equipment [14] that are only found in specialized laboratories. Such an approach could make a great impact in resource-constrained areas by enabling the detection of pathogens, contaminants and disease biomarkers affordably and reliably.

Here we introduce a new type of colorimetric transducer that is capable of detecting small changes in the extinction spectrum of plasmonic nanosensors. The transducers consist of a piece of paper printed in toner with a specially designed pattern that is recognized by an augmented reality app using the camera of a mobile device as the reader (Fig. 1). When the pattern is recognized by the app, a digitally augmented message is generated on the screen of the mobile device. Previously it was demonstrated that colorimetric signals with high optical density could block pattern recognition when the patterns where printed on a transparent sheet that was overlaid onto the assay [15]. Although this approach detected changes in optical density resulting from biospecific interactions, it was not determined whether it could detect changes in the state of aggregation of plasmonic nanoparticles. Furthermore, it required a separate transparent sheet in order to evaluate the colorimetric signal, which had to be aligned on top of the colored spots. Here we adapt this concept for detecting changes in the extinction spectrum of gold nanosensors resulting from the

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https://doi.org/10.1016/j.snb.2018.05.052
Received 13 February 2018; Received in revised form 10 May 2018; Accepted 11 May 2018
0925-4005/ © 2018 Published by Elsevier B.V.

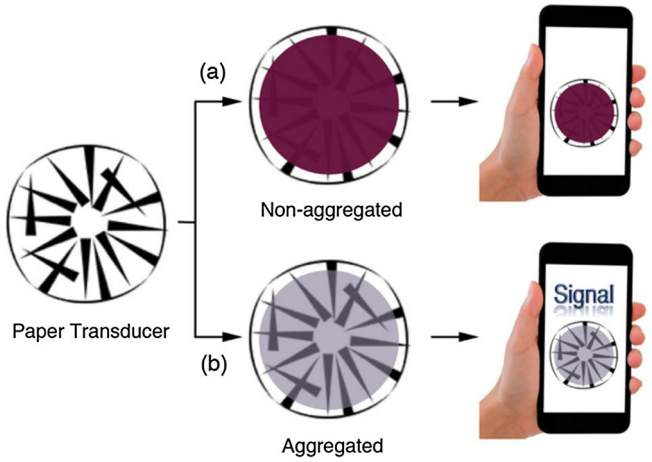

Fig. 1. Schematic representation of the signal transduction mechanism with the proposed paper sensors; A pattern with a unique design is printed with toner on filter paper; (a) Suspensions of non-aggregated gold nanoparticles block pattern recognition by the augmented reality app, and no signal is generated; (b) Aggregated nanoparticles do not impede pattern recognition and a signal in the form of a digitally augmented message is generated.

aggregation of the colloids with paper transducers. To detect nanoparticle aggregation, a small drop of the colloidal suspension is spotted on the paper transducers. When non-aggregated spherical gold nanoparticles are added, the intensely colored colloidal suspension lessens the local contrast, and the pattern is not recognized by the app (Fig. 1a). However, when the nanoparticles aggregate their extinction spectrum broadens and dampens, therefore absorbing less visible light and having less impact on the local contrast of the pattern. In this case, the augmented reality app can recognize the pattern and generates a message on the screen of the mobile device as shown in Fig. 1b. Compared to approaches based on taking photographs and analyzing colors, our method does not require the utilization of a light box for controlling ambient light conditions [16] because pattern recognition is less affected by the room illuminance [15]. Compared to apps that analyze colors, it also does not require internal standards or data processing software that may be difficult to utilize by untrained users [17,18]. The patterns can be downloaded and printed with an inexpensive toner printer, which makes the resulting paper transducers exceptionally low-cost, light in weight and disposable. The app that reads the transducer only requires placing a camera on top of the pattern to obtain a result in the form of an easy-to-understand digitally augmented message superimposed over the pattern. These features make the proposed detection platform accessible to everyone regardless of their location, educational background or financial status.

The suitability of the proposed paper transducers for detecting small variations in the extinction spectrum of gold nanoparticles will be tested here with a new signal generation mechanism in colorimetric biosensors. It is based on aggregating gold nanoparticles in the presence of the protein neutravidin [19], which is a deglycosylated form of the biotin-binding protein avidin. The aggregation of 40 nm gold nanoparticles triggered by this protein generates broad and dampened LSPR, and these spectral changes are transduced by the toner-printed patterns as shown in Fig. 1. Since the degree of aggregation of the nanosensors is directly related to the concentration of neutravidin, this phenomenon can be used as the signal generation mechanism in immunoassays when the concentration of neutravidin changes as a function of the concentration of biotinylated detection antibodies, which, in turn, depends on the concentration of the target molecule (Fig. 2). We will demonstrate that the proposed paper transducers enable the detection of spectral changes triggered by small variations in the concentration of neutravidin that are undetectable by eye. It will also be shown that a competitive immunoassay using the proposed signal generation mechanism and paper transducers can detect the model analyte C-reactive protein (CRP) with a limit of detection of $3{\cdot}10^{-8}$ g mL^{-1} within 1 h, which is comparable to the limit of detection obtained with a competitive ELISA that requires an enzyme-amplified colorimetric signal generation step and a spectrophotometer to read the signal. Biotin-binding proteins are extremely thermostable (their denaturation temperature is higher than 80 °C), as opposed to commonly used enzymes in biosensing such as horseradish peroxidase (HRP, inactivates rapidly at temperatures higher than 42 °C) [20]. This makes the proposed signal generation mechanism more suitable for in-field analyses, in which keeping the ambient temperature within the optimal range of the enzyme might be unduly challenging.

2. Materials and methods

2.1. Pattern design

The target images were designed with Blender using published guidelines for optimizing target detection and tracking stability from the Vuforia library. Specifically, the principles of feature distribution and high local contrast were important to the design of small targets of about 2 cm in diameter. According to the guide, the augmented reality software recognizes sharp edges and corners as feature points in a target image. In order to optimize the amount of features that could be recognized in a small space, triangles were chosen as the preferred shape for providing detail in the targets. A circular boarder was chosen as a way to frame the target without adding feature points around the periphery, thereby concentrating the detectable feature points towards the center of the target. Starting contrast was maximized with a simple black and white color scheme. The suitability of the target images for the augmented reality app was evaluated with a tool provided by Vuforia that assigns target images a star rating based on how well they adhere to the guidelines. When a target image is uploaded to the database, it receives a rating from one star (poor detection and tracking) to five stars (excellent detection and tracking). Using trial and error with the star rating system from the database, a target was designed and optimized to a 4 star rating as shown in Fig. S1 in the Supplementary Information. Information about the optimization of target size can be found in Fig. S2 in the Supplementary Information. The patterns were printed on Whatman 41 quantitative paper with tonner using a brother MFC-1910W printer.

2.2. Neutravidin-induced nanoparticle aggregation

Nanoparticle aggregation was triggered by mixing equal volumes of 0.5 nM gold nanoparticles and 12.5 mM citrate buffer pH 5 containing neutravidin at different final concentrations for 10 min.

2.3. Modification of magnetic beads with CRP

1 mL of carboxylate-modified magnetic beads (1 μm diameter, Dynabeads® MyOne™ Carboxylic Acid, ThermoFischer Scientific) was washed 3 times with deionized water and re-suspended in 500 μL of a solution containing 0.5 M 4-morpholineethanesulfonic acid (MES) pH 5.5, to which 1 mg of (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) (Pierce™ EDC, No-Weigh™ Format) and 2 mg of sulfo-NHS (*N*-hydroxysulfosuccinimide sodium salt, Sigma) in 500 μL of the same MES solution were added. After 10 min the beads were accumulated with a magnet and the solution was removed, and 1 mL of a solution containing ca. 0.1 mg mL^{-1} CRP in 0.1 M phosphate buffer pH 7.4 (PB buffer) was added. It should be noted that the CRP stock solution (3.3 mg mL^{-1}, human C-reactive protein, Millipore) was previously purified with a desalting column in order to remove preservatives that could interfere with the coupling reaction. After 2 h, beads were concentrated with a magnet and the protein solution was substituted for a blocking solution containing 0.1 M glycine and

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