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Nanoparticles and DNA on Chips – Realization of a Nanobiotechnology Toolbox for Single Particle Bioanalytics

A newly emerging field in bioanalytics based on biomolecular binding detected label-free at metal nanoparticles is introduced. Thereby particles which show the effect of localized surface plasmon resonance (LSPR) are used as plasmonic transducers. They change their spectroscopic properties (a band in the UV-VIS range) upon binding of molecules. This effect is even observable at the single nanoparticle level using micro spectroscopy and presents the base for a new field of single particle bioanalytics with the promise of highly parallel and miniaturized sensor arrays. The paper introduces this approach and shows first result from our work regarding the detection of DNA binding at single nanoparticle sensors.

1. Introduction

Optical biosensing techniques

A rapid growth in the development of highly selective and sensitivity biosensors for drug discovery, medical diagnosis and monitoring of diseases, detection of pollutants and biological agents has occurred in the past two decades (Turner 2000). Optical biosensors are widely applied due to the advantages of a highly sensitive and real-time detection of biomolecular interaction. Various sensing transduction mechanism like fluorescence (Russell et al. 1999), chemiluminescence (Chan and Nie 1998; Chan et al. 2002), light absorption and scattering (Malinsky et al. 2001; McFarland and Van Duyne 2003), reflectance (Hicks et al. 2005), Raman scattering (Nie and Emory 1997; Jiang et al. 2003; Zhang et al. 2005) and surface plasmon resonance – SPR (Mrksich et al. 1995; Berger et al. 1998; Yonzon et al. 2004) are the basis of optical sensing techniques.

SPR vs. LSPR

The excitation of surface plasmon polaritons is a standard tool for measuring adsorption of molecules onto metal (typically gold and silver) structures as planar thin layers (SPR) or as nanoscale structures (LSPR). The label-free detection of binding-induced refractive index changes have been widely used to monitor analyte-surface binding interactions at or near a thin metal surface (Liedberg et al. 1983; Homola et al. 1999) including the adsorption of small molecules (Jung et al. 1998; Jung and Campbell 2000; Jung and Campbell 2000), antibody-antigen binding (Berger, Beumer et al. 1998), protein adsorption on self-assembled monolayers (Frey et al. 1995; Mrksich, Grunwell et al. 1995; Rao et al. 1999), ligand-receptor binding (Hendrix et al. 1997; Perez-Luna et al. 1999; Jung et al. 2000), DNA and RNA hybridization (Jordan et al. 1997; Nelson et al. 2000; Pe-

terson et al. 2000; Heaton et al. 2001), and DNA-protein interactions (Brockman et al. 1999). While surface plasmon resonance is highly sensitive to refractive index changes down to $2x10^6$ nm RIU^{-1} (Jung, Campbell et al. 1998), localized surface plasmon resonance at metal nanostructures shows a short (and tunable) characteristic electromagnetic field decay length (5-15 nm or 1-3 % of the light's wavelength) providing the LSPR nanosensor with its enhanced sensitivity (Haes et al. 2003; Haes et al. 2004; Kvasnicka and Homola 2008). The small sensing area (down to a single particle) with its enormous parallelization and integration potential, the temperature independency and also the dramatic difference in costs (Haes, Zou et al. 2004) make the LSPR sensor a promising tool for bioanalytics.

LSPR basics

Early understanding of the physics of nanoparticle plasmons dates back to Faraday (Faraday 1857) and Mie (Mie 1908), and the extraordinary optical properties have been the subject of extensive studies (Kreibig and Vollmer 1995; Bohren and Huffman 2007). Noble metal nanoparticles exhibit a strong UV-visible extinction band which is not present in the spectrum of bulk material (Mulvaney 1996; Link and El-Sayed 1999; Haynes and Van Duyne 2001). This phenomenon is known as localized surface plasmon resonance (LSPR) and the extinction band occurs when the incident photon frequency is resonant with the collective excitation of the conduction electrons. It is well established that intrinsic parameters like size, geometrical shape, material and composition, but even more extrinsic parameters such as charge distributions and dielectric properties of the nanoparticle's immediate environment strongly influence the maximum peak wavelength of the LSPR spectrum (Kreibig and Vollmer 1995; Mulvaney 1996; Haynes and Van Duyne 2001; Kelly et al. 2002; Sönnichsen et al. 2002).

Ensemble – particle layer – single particle

The nanoparticle-based optical sensing technique allows for a quantitative detection of biological and chemical targets (Malinsky, Kelly et al. 2001; Yonzon, Jeoung et al. 2004). The high sensitivity of noble metal nanoparticles to adsorbate-induced changes in the dielectric constant in the environment is the basis of this sensing principle. The LSPR extinction maximum of an ensemble of nanoparticles is thereby measured by UV-visible extinction spectroscopy (Jensen et al. 2000; Malinsky et al. 2001). Various kinds of nanoparticles like spheres, rods or prisms (gold, silver) have been used to investigate biomolecular recognition of distinct biological systems such as biotin-streptavidin binding, antibody-antigen interaction or PNA/DNA hybridization (Nath and Chilkoti 2004; Endo et al. 2005; Beeram and Zamborini 2009). Arrays of triangular silver nanoparticles for example were employed to sense streptavidin with a subpicomolar limit of detection (Haes and Van Duyne 2002). Tuning of the plasmon frequency of nanoparticles across the visible to near-infrared by utilizing different geometries and sizes has been demonstrated (Haynes and Van Duyne 2001). While these measurements are based on ensemble-averaged spectral properties, the extension of LSPR-sensing to single nanoparticles will provide several important improvements like reducing the absolute detection limit down to a few molecules on the particle surface (Riboh et al. 2003), small sample volumes (attoliter range), the noninvasive nature making them an ideal platform for in vivo quantification (Xu and Kall 2002), implementation in multiplex detection schemes by controlling size, shape and chemical modification of individual nanoparticles, and the development of sensing technique with a high signal-to-noise ratio to measure the LSPR scattering spectrum of single nanoparticles.

Single particle spectroscopy

While the visual observation of individual nanoparticles by ultramicroscopy was reported by Zsigmondy already hundred years ago, recently many groups combined this dark field illumination technique with micro spectroscopy to characterize the optical properties of single particles by measuring the LSPR scattering spectrum (Mock et al. 2002; Mock et al. 2003; Nehl et al. 2004). Investigations of tuning the LSPR frequency by changing the material composition and shape of chosen nanoparticles demonstrated the potential of this single particle spectroscopy (Wang et al. 2005; Becker et al. 2008; Henkel et al. 2009; Khalavka et al. 2009). In 2003, Feldmann and coworkers reported the biomolecular recognition of biotin-streptavidin interaction on single gold nanosphere by detecting the spectral shift using micro spectroscopy (Raschke et al. 2003). Many other biological issues have been approached by applying the binding of biotin to streptavidin (Sönnichsen et al. 2005; Baciu et al. 2008; Nusz et al. 2008). Interparticle coupling effects with DNA spacer molecules between the nanoparticles for a defined distance have been monitored by several groups (Sönnichsen, Reinhard et al. 2005; Lee et al. 2008; Sannomiya et al. 2008). Also different biological systems like antibody-antigen interaction (Cao and Sim 2009), aptamer-avidin binding (Hernandez et al. 2009), oxidation of ascorbic acid (Novo et al. 2008) and antibody unbinding-studies (Mayer and et al.) have been examined in detail. Of great interest in molecular biology are detection and analysis of specific DNA sequences via nucleic acid hybridization (Marrazza et al. 1999; Minunni et al. 2001). A fast and reliable determination of nucleic acid sequence plays an important role in clinical diagnosis, food safety monitoring and forensic and environmental analyses (Tichoniuk et al. 2008).

Sensing of DNA hybridization

A first step in determining the hybridization event of nucleic acids on individual nanoparticles by micro spectroscopy was done by C. Sönnichsen in 2005. A single-stranded oligonucleotide was attached on the surface between two gold nanospheres. Binding of a second single-stranded DNA molecule with complementary sequence to the immobilized oligonucleotide was monitored as a slightly red shifted LSPR spectrum (Sönnichsen et al. 2005).

Own work

In this work we demonstrate the use of single gold nanoparticles as sensing platform for a label-free detection of hybridization events of single-stranded capture oligonucleotides with complementary target sequence.

2. Experimental

Chip preparation

Biosensing experiments were performed on borosilicate glass substrates with a microstructured chrome grating (as finder structure for relocation of individual particles) created by standard lift-off photolithographic process. Before usage a protecting resist layer was removed and the chips were pre-cleaned with organic solutions (acetone and ethanol) and water in ultrasonic bath for 10 minutes. After drying the glass substrates they were cleaned by plasma etching (2 x 6 min, 50 W, 5 Pa).

Immobilization of nanoparticles

After the cleaning procedure the chips were silanized wet-chemically with 3-aminopropyltrieth-oxysilane (APTES) for 10 minutes followed by cleaning with water in ultrasonic bath for 5 minutes. For immobilization, a nanoparticle solution was given onto the substrates and was incubated for one hour on a thermo mixer at room temperature. Surface characterization was done by dark field microscopy and AFM measurements.

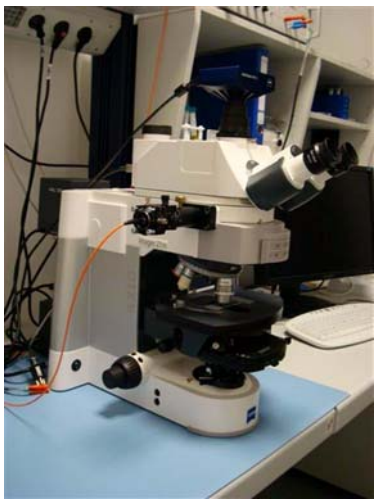
DNA immobilization and hybridization

After immobilizing the gold nanoparticle on a glass substrate via silane chemistry, single-stranded capture oligonucleotides bearing a thiol-functionalization at their 5'-end were attached to the particle surface by thiol-gold interaction for 2 h in 1 M KH_2PO_4 buffer. Afterwards the single-stranded target DNA with a complementary sequence was hybridized in 2 x SSC buffer for 2 h to the capture oligonucleotide. Towards each step the scattering spectra of the particle was recorded and compared with each other.

Combined dark field microscopy and micro spectroscopy

Visualization of the immobilized nanoparticles was done by dark field microscopy in transmission and reflection mode. The spectra of individual gold nanoparticles were collected by an AxioImager Z1m (Carl Zeiss Microimaging, Göttingen, Germany) optical microscope in dark field geometry. A tungsten halogen lamp with a continuous spectrum and a color temperature of 3200K serves as light source. The dark field configuration blocks the directly transmitted light, whereby only the scattered light was detected by passing through a pinhole to a spectrometer. The pinhole was coplanar to the tube lens, i.e. the pinhole was in the magnified, real image, and has a diameter of 100 µm. The light from pinhole is passed through a multi mode fiber to a Acton Research SpectraPro 2300i micro spectrometer (Princeton Instruments, Trenton, NJ, USA) with a grating with 150 lines and a peltier cooled CCD camera.

(a)



(b)

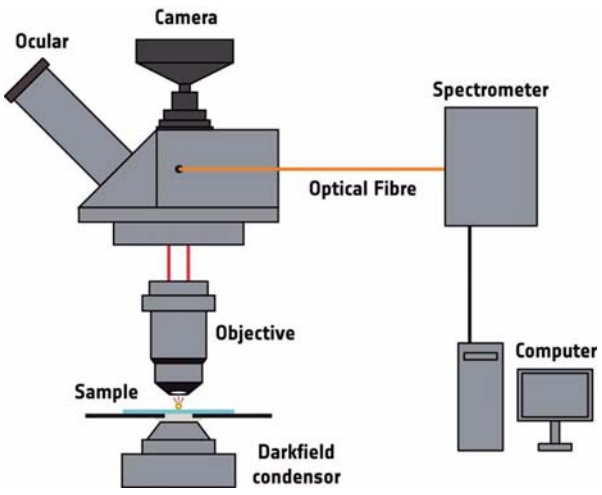


Fig. 1: (a) AxioImager optical microscope for visualization of individual gold nanoparticles in dark field geometry. A micro spectrometer for detecting the spectral information of chosen nanoparticles is coupled to the microscope by a mutli mode fiber (orange). (b) Scheme of the experimental setup for investigating the optical properties of single nanoparticles.

3. Results

The maximum peak position and intensity of the LSPR plasmon band strongly depends on refractive index changes in the local environment of noble metal nanoparticles. A first recognition layer was attached to the surface of glass immobilized nanoparticles and cause a red shift in the LSPR resonance due to refractive index changes from that of air (n_{air}) to that of the biological layer (n_{DNA}). Binding of analyte molecules leads to a further red shift of the LSPR maximum. Spectra of each step could be visualized by micro spectroscopy for detecting the LSPR maximum shift. A scheme for the LSPR sensing principle is shown in Figure 2.

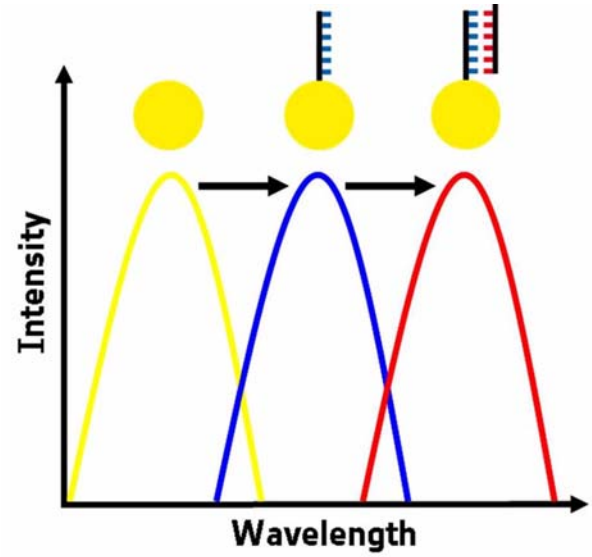


Fig. 2: Schematic presentation of the LSPR resonance of a single nanoparticle (yellow). A red shift due to the binding of capture DNA on an individual gold nanoparticle (blue) followed by a further red shift due to the hybridization of complementary target DNA to the capture DNA (red) is shown.

In our experiments, 80 nm gold nanoparticles served as plasmonic transducer for detecting the binding events. The first step was to measure the spectral information individual gold nanoparticles immobilized at glass surface (Fig. 3, lower curve). A dominant peak at about 550 nm is observed, as expected for gold nanoparticles of this size range. A zoom (inset) gives a more precise picture. In a following step, the capture oligonucleotide, containing a thiol group at the 5'-end, was attached to the particle surface by a thiol-gold interaction. As result, the particle surface is now covered with a rather continuous layer of terminally attached single-stranded DNA molecules. Because this arrangement changes the dielectric properties at the particle surface one would expect an effect in the measured spectrum. The spectrum (center curve in Fig. 3) shows (compared to the spectrum discussed before) a red shifted LSPR maximum due to a local refractive index change near the particle surface from air (nanoparticle with air as surrounding medium; $n_{air} = 1{,}00$) to that of DNA ($n_{DNA} = 1{,}75$). Afterwards the complementary target oligonucleotide was hybridized to the particle immobilized capture DNA and a further spectrum was measured. Again, a red shift could be detected. The larger red shift (from 549 nm to 579 nm) could be observed for the immobilization step of the capture DNA because of the obvious refractive index change (see Figure 3). A smaller red shift was observed for the hybridization of the analyte DNA molecules (from 579 nm to 595 nm). This difference could be attributed to a not 100 % efficiency of DNA hybridization (so that some capture DNA are still single-stranded) and/or to the larger distance from the surface of the target DNA compared to the surface-attached capture molecules.

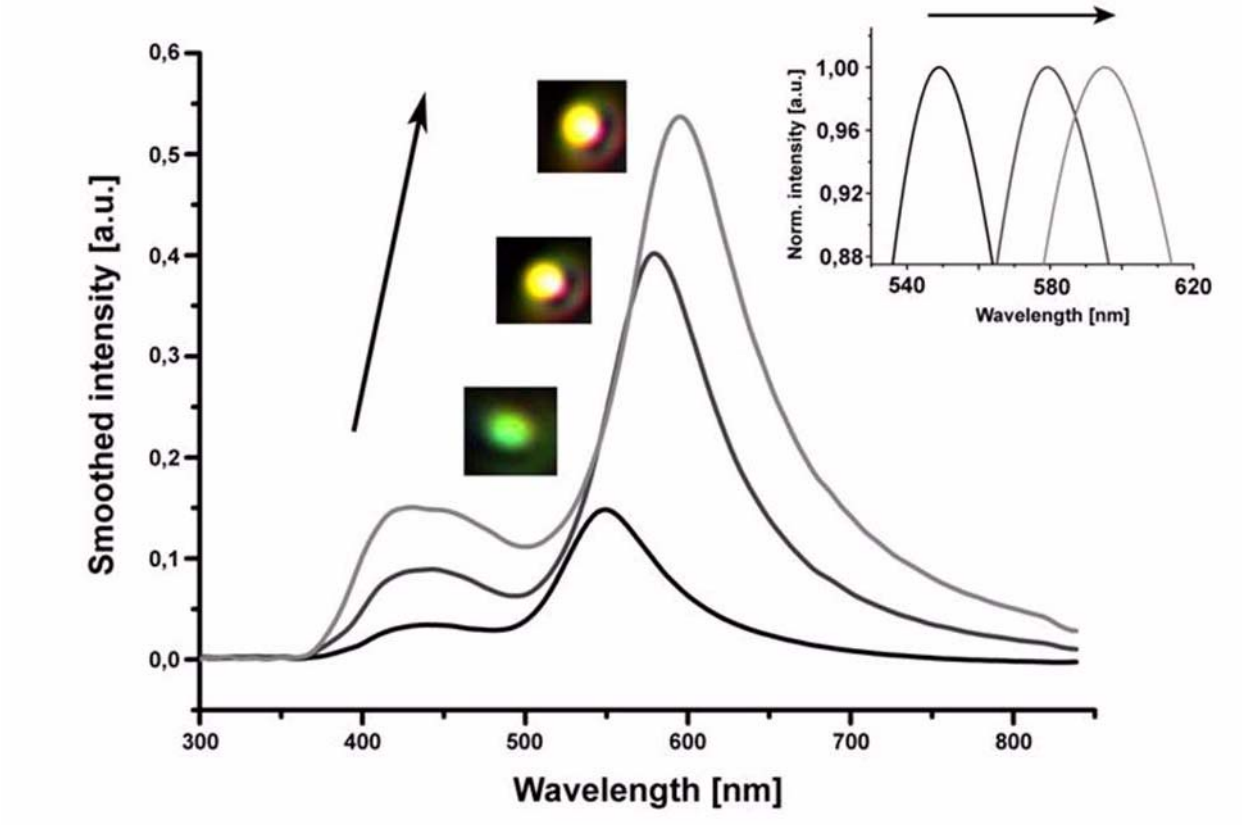


Fig. 3: Sensing of DNA hybridization on an individual 80 nm gold nanoparticle. The shift of the LSPR maximum can also be seen by the naked eye in the dark field images (color change from green to yellow).

4. Conclusion and Outlook

The results show that biomolecular binding events can be detected even on the very small surface area of individual nanoparticles. It is possible to monitor the success of certain surface modification steps by this label-free bioanalytical approach. In contract to other label-free techniques such as SPR sensing (e.g. the Biocore principle), the demonstrated technique has a comparable sensitivity but requires less sophisticated readout equipment. Moreover, extended miniaturization as well as parallelization is feasible. One can expect that detection schemes based on the demonstrated principle are important contributions for method developments in bioanalytics.

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Ein neu aufkommender Bereich in der Bioanalytik, der auf einer labelfreien Detektion von biomolekularen Bindeereignissen basiert, wird vorgestellt. Als plasmonische Signalgeber werden dabei Partikel verwendet, die den Effekt der lokalisierten Oberflächenplasmonresonanz (localized surface plasmon resonance – LSPR) zeigen und ihre spektroskopischen Eigenschaften (eine Bande im UV-vis-Bereich) durch Anbindung von Molekülen ändern. Dieser Effekt kann sogar auf Einzelpartikelebene mittels Mikro-spektroskopie beobachtet werden und bildet damit die Grundlage für einen neuen Bereich der Einzelpartikel-Bioanalytik, die hoch parallele und miniaturisierte Sensorarrays verspricht. Der Beitrag stellt diesen Ansatz vor und zeigt erste Ergebnisse unserer Arbeit bezüglich der Detektion von DNA-Anbindung auf Einzelpartikelsensoren.

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