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Review

Localized surface plasmon resonance based biosensing

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Andrea Csáki, head of the workgroup "Nanobiophotonics" at the Leibniz Institute of Photonic Technology (IPHT) is working in the field of DNA-based molecular plasmonics and localized surface plasmon resonance (LSPR) based bioanalytics.

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Abstract

Introduction:

Bioanalytical sensing based on the principle of localized surface plasmon resonance experiences is currently an extremely rapid development. Novel sensors with new kinds of plasmonic transducers and innovative concepts for the signal development as well as read-out principles were identified. This review will give an overview of the development of this field.

Areas covered:

The focus is primarily on types of transducers by preparation or dimension, factors for optimal sensing concepts and the critical view of the usability of these devices as innovative sensors for bioanalytical applications.

Expert Commentary:

Plasmonic sensor devices offer a high potential for future biosensing given that limiting factors such as long-time stability of the transducers, the required high sensitivity and the cost-efficient production are addressed. For higher sensitivity, the design of the sensor in shape and material has to be combined with optimal enhancement strategies. Plasmonic nanoparticles from bottom-up synthesis with a post-synthetic processing show a high potential for cost-efficient sensor production. Regarding the measurement principle, LSPRi offers a large potential for multiplex sensors and can provide a high-throughput as well as highly paralleled sensing. The main trends are expected towards optimal LSPR concepts which represent cost-efficient and robust point-of-care solutions, and the use of multiplexed devices for clinical applications.

Keywords: localized surface plasmon resonance, plasmonic nanostructures, optical sensor, biosensor, sensitivity

1. Introduction

The use of plasmonic labels, sensors and read-out principles in current bioanalytics is steadily increasing (Fig. 1). The scientific field of plasmonics uses the unique optical behavior of metal and metal-hybrid nanostructures, based on the strong interaction of their free charge carriers with the incident light resulting in localized surface plasmon resonances (LSPR) at specific wavelengths. The charge oscillations in these nanoscale confinements induce a strong resonance band both in absorption and scattering and allow for a variety of different applications. Generally, plasmonic nanostructures offer a strong and characteristic optical response caused by inherent factors such as material, geometry, shape and dimension. The influence of the external factors (e.g. refractive index of the surrounding media) represents another extremely important parameter. So, the specific interaction of biomolecules (target or analyte) with recognition elements (receptor or capture) on the surface of plasmonic nanostructures can induce two different effects. First, a shift in extinction or scattering spectral peak to higher wavelength is observed (Fig. 2). Additionally, plasmonic nanostructures can increase non-elastic optical effects on molecules or quantum objects through local field-enhancement (Fig. 2).

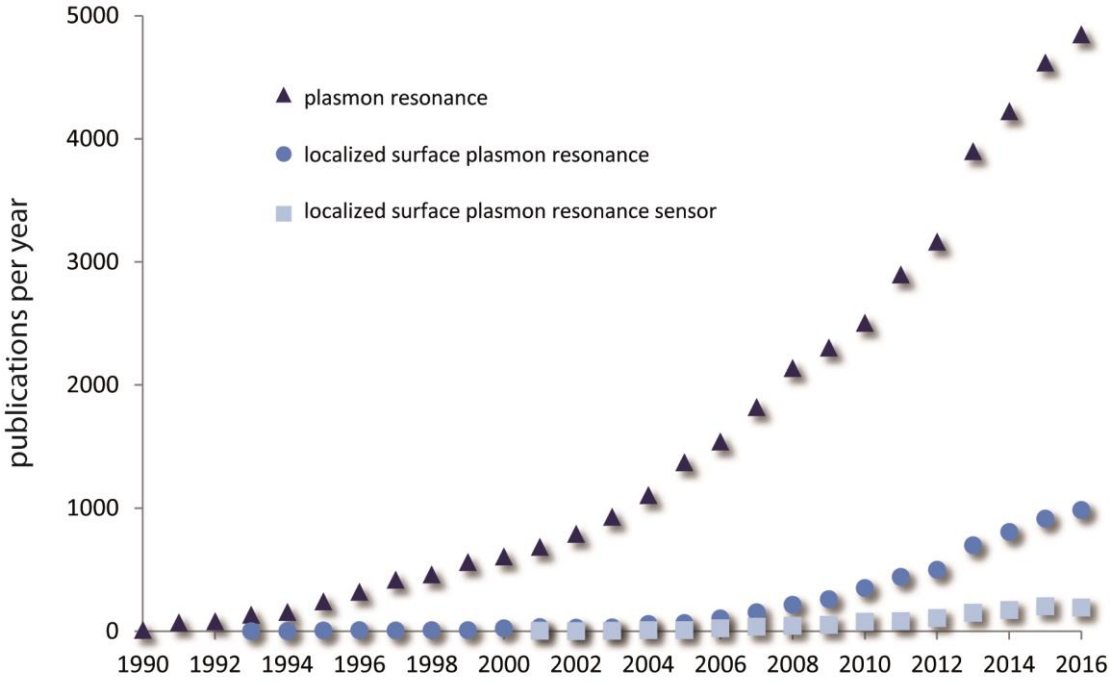


Figure 1. Increasing importance of plasmonic sensing measured by number of related scientific publications (Web of Science).

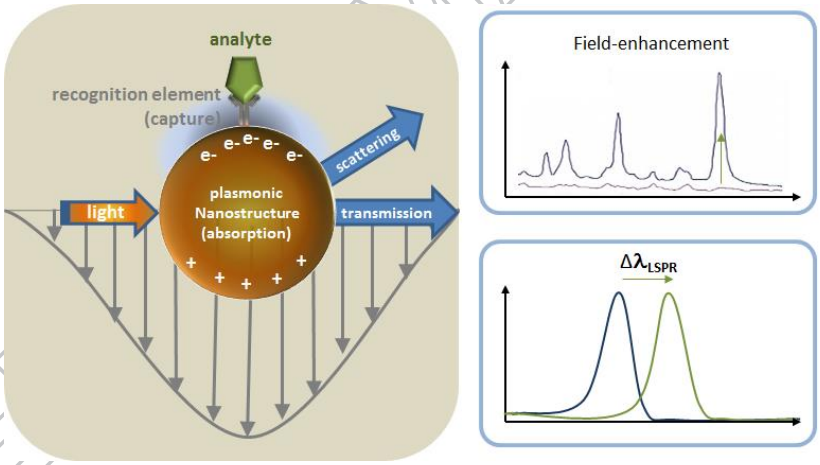
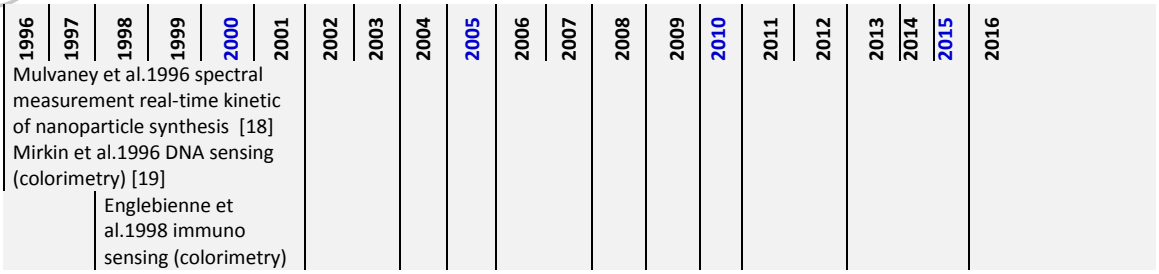


Figure 2. Scheme of the physical effects involved in localized surface plasmon resonance sensing.

Important cornerstones for the field of plasmonics have been laid by Mie in 1908 with the analytical solution to explain this behavior [1], and Kreibig in 1970s with introducing nanoparticles resonances [2]. Important works in the field of plasmonics [3,

4] and LSPR [5, 6, 7] were introduced in the middle and end 1990-ies. A current overview for plasmonics as a research field is given by Brongersma in 2015 [8].

In optical biosensing, surface plasmon resonance (SPR) based sensors are widely spread [9, 10, 11]. SPR is a closely related technology to LSPR based on propagating surface plasmons in thin plasmonic metal layers [12]. A possible improvement of this technology is a combination of both methods (LSP+SPR) [13, 14, 15, 16]. A quantitative comparison between both techniques SPR and LSPR has been conducted [17]. SPR sensing is an established method compared to LSPR; there are many commercial SPR products on the market. LSPR is a relatively new method in bioanalytical sensorics. At the end of the 90-ies some methods for the real-time optical characterizations of nanostructure have been established [18]*. First biosensing measurements with plasmonic principles were realized by Mirkin for DNA [19] and Englebienne for proteins [20]** (Fig. 3). One of the simplest biosensing model system, the specific binding of streptavidin on biotin, was demonstrated on silver nanoprisms by Van Duyne [21]** and at the single nanoparticle by the Feldmann group [22]**. The effect of the nanostructure (here nanoparticle) shape has been demonstrated [23]. Later different kinds of concepts of LSPR sensors were developed and their usability for applications was tested (Fig. 3). To get a clear image of the state-of-art in this extremely rapid development, this review attempts to give an insight of this large field including a classification of present devices. In the next section the LSPR sensing principle and transducer properties will be introduced.



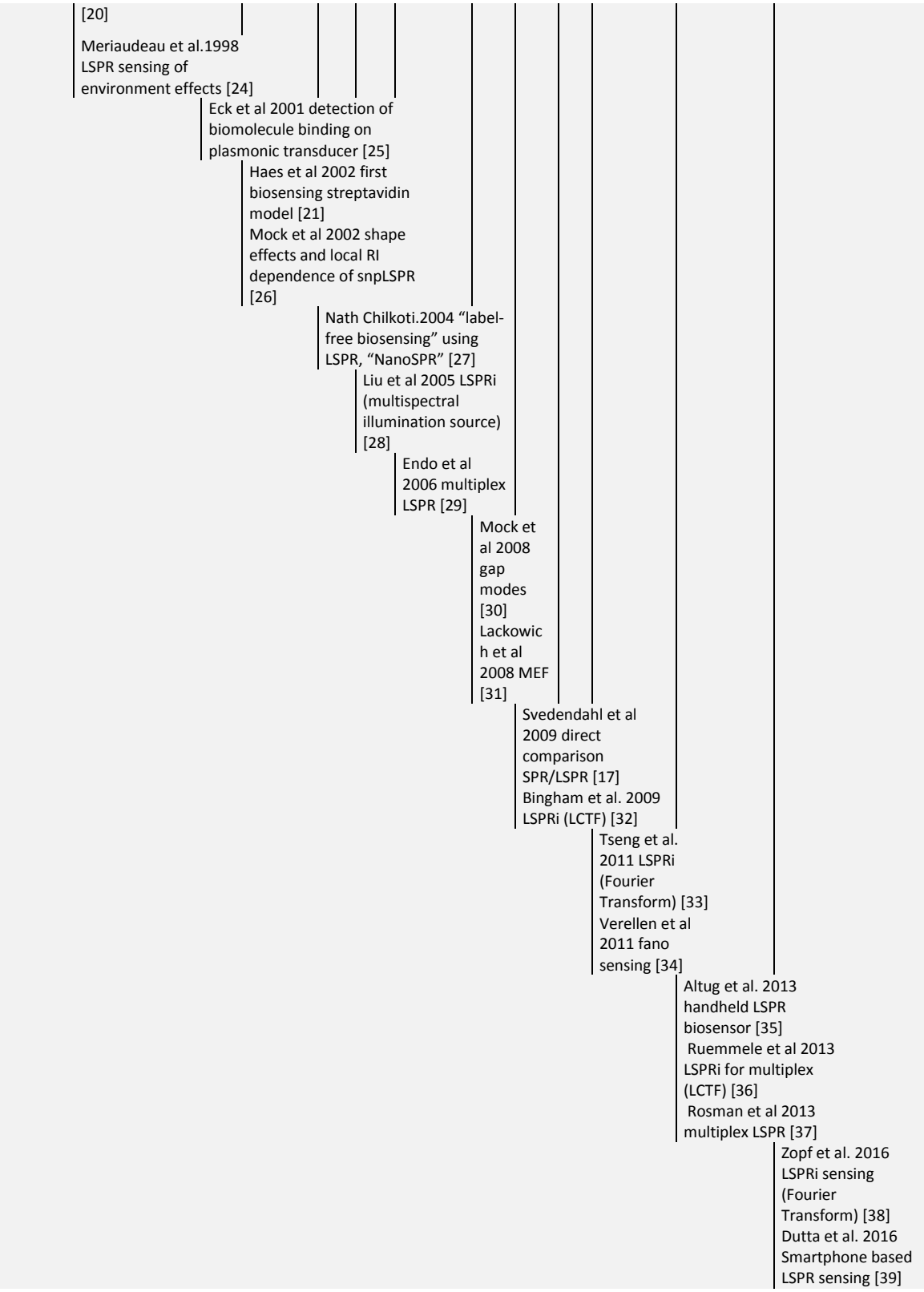


Figure 3. Important milestones in the field of LSPR biosensing.

2. Principles of the localized surface plasmon resonance sensing

The physical effect of LSPR sensing is based on delocalized charge carriers in noble

metal objects with a dimension smaller than the wavelength of light [1, 2]. The external electromagnetic field induces at a specific wavelength an oscillation of the conduction electrons with an excitation of localized surface plasmons with a sharp resonance band (LSPR). This resonance frequency strongly depends on several intrinsic factors; they are predefined by the preparation of the structures. The first intrinsic parameter is the material of the nanostructure. Fig. 4 presents a comparison of the scattering cross-sections of nanoparticles of different compositions [40, 41]**. Silver show the highest scattering efficiency, and therefore represents an excellent material for plasmonic sensing (Ag NP [42, 43, 44], Ag NR [45]). Gold exhibits a magnitude lower relative scattering efficiency; other materials such as copper are even lower [46]. Nevertheless, silver nanostructures have some problems regarding long-time stability under ambient conditions [47], therefore current concepts extends the plasmonic sensing to hybrids like cobalt shell on silver core [47] or other compositions [48]. Although exhibiting a high tendency to oxidation similarly to silver, aluminum is becoming more and more a material of interest in plasmonics [49, 50]. The origin for this importance is the spectral tunability in the UV/vis range by cost-efficient preparation approaches.

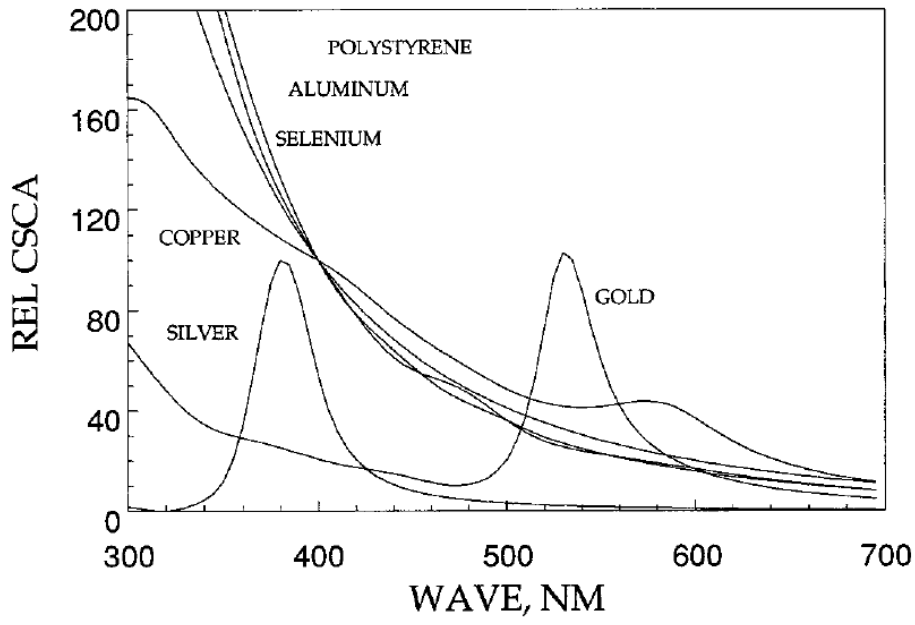


Figure 4. Comparison of the scattering of different nanoparticles (Reprinted from The Analytical Biochemistry, 1998, 262 (2), Yguerabide, J.; Yguerabide, E. E., Light-scattering submicroscopic particles as highly fluorescent analogs and their use as tracer labels in clinical and biological applications. II. Experimental Characterization, 157-176, Copyright (2017), with permission from Elsevier [41]). Normalized (Au and Ag for 100) scattering cross-section of particles in water versus wavelength.

An important factor for the sensing properties is the geometry of nanostructures, such as the shape of the nanoparticles [26, 51, 52]. Anisotropically-shaped nanostructures show generally a higher sensitivity and also a higher local electromagnetic (EM) field-enhancement than spheres [21, 53, 54]. Besides the sensitivity, also the position of the plasmon resonance strongly depends on the shape factor. The dimension of the nanostructures represents the third important intrinsic parameter for the LSPR [55]. For gold spheres, nanoshells and silver spheres, larger nanoparticles have higher bulk sensitivity (bulk, see in next section) [56, 57]. This applies also for elongated nanostructures, and particles with higher aspect ratio [53, 58].

The origin of the sensing potential of plasmonic nanostructures is their sensitivity for changes in the refractive index of surrounding media, because the frequency of the oscillation is strongly influenced by the optical properties of the medium as external factor. With higher density of the electrons the sensing response increases. For a quantitative description of plasmonic transducer both bulk- and surface-sensitivity can be used. The bulk-sensitivity describes thereby the response of the plasmonic sensor to changes in the refractive index of the embedding medium as a whole: the shift of the resonance maximum depends on the refractive index changes [59] (Table 1). The bulk-sensitivity of spherical nanoparticles shows a positive correlation with the particle diameter (Mie theory) [56, 58]. In general, LSPR bulk-sensitivity is much lower

compared to the SPR, because the penetration depth of the EM field of the nanostructures is limited in the case of particles: The EM penetration depth at LSPR is at least one order lower than in the case of SPR, it scales with sensor dimensions. Also, the effect of the substrate material below the nanotransducer affects the bulk and surface sensitivity [60].

Table 1. Comparison of the different type of quantitative descriptions for LSPR transducer.

type	term	description	comment
Bulk sensitivity	$S_B = \frac{\Delta\lambda_{\max}}{\Delta n_{medium}}$	sensitivity of the resonant wavelength to changes in refractive index of the surrounding medium [56]	first quantitative description of nanotransducer
Surface (refractive index) sensitivity	$S_S = \frac{\Delta\lambda_{\max}}{\Delta n_{layer}}$	sensitivity in dependency on the specific refractive index of the layer [56]	best description for molecular sensing
Figure of merit	$FOM = \frac{S_B}{FWHM}$	performance of the sensor: defined as sensitivity divided by the resonant band width [61]	quality description of the performance of the transducer
Generalized FOM	$FOM* = \left(S\frac{dI}{d\lambda}\frac{1}{I}\right)_{max}$	wavelength with the maximum intensity changes per refractive index [62]	generalized quality description for complex nanotransducers

$\Delta\lambda_{max}$ means the shift in the LSPR; Δn_{medium} the refractive index changes of the medium; Δn_{layer} means the refractive index of the thin layer around the nanotransducer; *FWHM* means full width at half maximum of the LSPR peak.

For an efficient sensing concept also other parameter are important, such as the used detection wavelength range (e.g. 700-1000 nm for gold nanorods) [63]. For this range, the ratio between the sensitivity and the FWHM is optimized, enabling a more efficient signal readout.

The sensing potential of nanostructures is limited by their robustness and long-time stability. Silver is a very good material for nanostructures with strong LSPR. Unfortunately, silver is not really long time-stable under ambient conditions in air and also in aqueous solution. Therefore, additional stabilization of these materials is needed [64, 65]. Also the ability for functionalization with capturing biomolecules is an important aspect for the usability of plasmonic sensor materials [66]. Here, gold

transducers are preferred. Sensor concepts with different preparation approaches for the transducer, of the signal development or the read-out principle will be presented in the next sections.

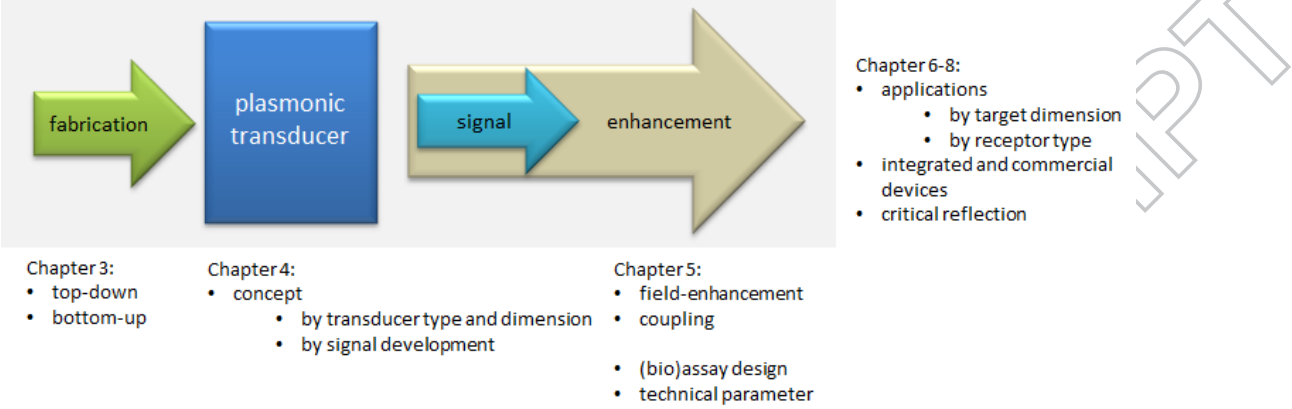


Figure 5. Overview of the topics of the review.

3. Overview of preparation technologies for localized surface plasmon resonance sensor devices

LSPR sensors can be classified in different ways. A simple classification is based on the type of the used transducer. The preparation concept can be differentiated into top-down and bottom-up nanostructures [67]. **Top-down** fabricated nanostructures are mostly realized using classical nano- and soft-lithographic methods [68] such as different photo lithographies (UV- and interference), electron-beam lithography (EBL) [69], different printing (micro contact [70] or µwet printing, dip-pen [71]), molding techniques (nanoimprint lithography – NIL) [72], laser-induced and other deposition techniques, nanosphere lithography (NSL) [73], colloidal lithography (CL) [74, 75] and hole–mask colloidal lithography HCL [76]. Typical examples are nanoholes, nanoslits, nanodisks, nanorings, or nano splitrings. Main advantages of the nanolithography are the controlled positioned arrangement of the nanostructures with defined dimensions and geometries. Other methods such as NSL and CL allow also a cost-efficient large-scale synthesis but

often only in repeating patterns, usually without control of the position of individual structures.

The synthesis of nanostructures using **bottom-up** techniques is a completely different approach. Here mostly chemical synthetized nanoparticles from colloidal chemistry are used as transducer for plasmonic sensing. The synthesis allows the exact tuning of the localized surface plasmon resonance by the determination of the material, shape and size of the particles. In contrast to most lithographic approaches (with exception of FIB-structuring of previously wet-synthesized large metal flakes), bottom up approaches yield much larger crystalline domains (often even single or twin crystals), resulting in better plasmonic properties due to less damping [77]. Best control of the particle shape and size may be achieved using the exact control of synthesis parameters by microfluidic preparation techniques [78, 79]. Table 2 gives an overview of possible particle shapes and their use as plasmonic transducer.

Table 2. Classification of plasmonic nanoparticles by material and shape and their use for plasmonic sensing.

Nanoparticle type	Sensor application examples
Au nanospheres [80, 81]	• Streptavidin model [82] • DNA [83] • Immunoassay: hFABP, hCGor hFer on AB [20]
Ag nanospheres [84]	• Refractomeric standards [23] • Hybridisation assay [85] • Colorimetric assay for miRNA [86]
Core-shell nanospheres [87]	• Sensitivity model glucose [88] • Au/Pd – sensitivity model glycerol [48]
Au nanoprisms [89]	• Streptavidin model [90] • Glucose [91] • Lactose intolerance (PCR fragment) [92] • Pancreatic cancer (miRNA) [93]
Ag nanoprisms [78, 94]	• Uric acid in Human serum [95]
Au nanorods [96]	• Immunoassay (IgG) [97] • Prostate specific antigen (PSA) [98]
Ag Nanorods [99]	• Sensitivity model glucose [45]

	• Proteins on aptamers [37]
Au Nanocubes [79, 100]	• SERS of 4-Aminothiophenol [101], sensitivity [102]
Ag Nanocubes [103]	• Protein sensing on membrane [104]
Nanostars [105]	• Refractometric standards [106] • Streptavidin model [107] • SERS of crystal violet [108]
Dumbbells/dog-bones [109, 110]	• SERS of 1-naphthalenethiol [111]
Nanocages [112]	• Refractometric standards [113]
Nanoshells [114]	• Refractometric standards [115]
Bipyramids [116]	• Refractometric sensing of QDs [117]
Multipods, Nanoflowers [118, 119]	• SERS of 4-Aminothiophenol [120]

Generally, larger nanoparticles with anisotropic shapes show also higher sensitivity with broader plasmon resonance peak. For nanorods, also the aspect ratio is important [121]. Nanorods with an aspect ratio between 3-4 show very strong plasmon resonances with high quality factors [62].

The combination of two types of different nanostructures can result in a novel quality of the transducer. Hybrid nanostructures can be prepared by combination of nanoparticles in form of core-satellite structures using chemical coupling [122], biomolecular interactions such as DNA-hybridization [66] or complex bio nanostructures, such as DNA-origami (allowing for e,g, chiral arrangements [123]). Also combinations of nanoparticles with top-down fabricated nanostructures result in innovative transducer structures. Last but not least the combination of different top-down techniques to prepare complex fano-structures or self-aligned 3D nanogap arrays [124] allow for highly sensitive sensor devices.

4. Classification by sensor concept (LSPR vs. LSPRi)

Device type and signal readout principle are another possibility to distinguish between different sensor concepts (Table 3). Generally, the measurement of the optical signal

(scattering or extinction, absorption) is possible at the single particle (snpLSPR) or at a spot of nanostructures (ensemble - ensLSPR), or as imaging spectroscopy of a whole field of view (LSPRi) [125]. On the other hand, transducer dimension and geometry play a central aspect. Nanoscale transducer can be arranged in 0/1 to 3 dimensions. The spectral detection at the single nanoparticle level (snpLSPR) provides an extremely localized as well as miniaturized detection volume and allows an exact characterization of the spectral behavior for quite small detection areas [126]. The resulting resonance band is sharp; an extremely narrow band is also possible by excitation with a single frequency [127]*. In contrast to this, the arrangement of transducers in 2D in spots or layers (ensLSPR) leads to a broader resonance over the population of nanostructures with a broad size distribution and increased detection volume [55]. Nonetheless, ensLSPR is realized mostly with cost-efficient readout devices and therefore favorable for applications like at the point-of-care. The colorimetry is one of the oldest LSPR methods. Here the quite drastic spectral changes of nanoparticle solutions switching from freely moving individual particles to induced (e.g. by molecules bridging neighboring particles) aggregates (or vice versa) are used for simple one-way bioassays.

Table 3. LSPR sensor concepts (by transducer type and dimension).

Transducer Dimension	LSPR	LSPRi
0/1D	snpLSPR • single NP (gold nanospheres [22], nanorods [128]) • single NS (nanoholes [129], silverprisms by NSL [21])	snpLSPRi • single NP (gold nanospheres [38]) • single NS

2D	ensLSPR
	• NP: nanoparticle single-spot
	• NP: gold nanosphere layer [130]
	• NS: gold nanoring layer [131]
		plasmonic-microarray
		• NP-arrays
		• NS-arrays
		  • nanohole-arrays [132]
		  • gold nanodiscs-arrays by HCL [75]
		  • gold nanocylinder arrays by HCL [36]

3D	colorimetry	• NP solution (silver nanospheres, gold nanospheres [85, 133, 134])

5. Plasmonic enhancement strategies

The performance of the optical signal for a given sensor is primarily defined by the sensitivity of the used nanotransducer determined by material, dimension and geometry as described before. A higher intensity of the plasmon resonance peak and a sharp bandwidth would allow for a better sensing performance. However the sensitivity increase given by these values is limited. The thickness of the sensing layer at the sensor surface is limited to tens of nanometers, because the LSPR decays exponentially with the distance [135, 136]. So enhancement strategies for better signals are necessary to optimize the detection limit. For this, two main strategies are possible (Table 4). On the one hand, the local electromagnetic field can be further increased by shape anisotropy of the NP and induction of local hot-spots on and between nanostructures. Such EM enhancement effect is used by different Raman spectroscopy techniques or by metal-enhanced or -quenched fluorescence (MEF or MQF). Plasmonic nanostructures can induce different effects: near plasmonic surfaces, a quenching influence can be observed, but also an increase in the quantum yield of the fluorophores, resulting in higher fluorescence signal, whereas their lifetime is decreased [137, 138, 139]. Additionally, the radiative decay rate can be increased. For MEF, typical factors are [140]: particle size, shape, distance between nanoparticle and dye (enhancement/quenching), spectral overlap with excitation and/or emission spectra of fluorophore. Also resonance coupling can play a role here. In conclusion: A complex parameter adjustment can lead to an optimal enhancement [141].

Table 4. Plasmonic enhancement strategies.

	Local field-enhancement
Effect:	• shape anisotropy • hot spots between nanostructures
Type:	surface-enhanced Raman scattering/spectroscopy (SERS) [142, 143, 144]
	surface-enhanced resonance Raman spectroscopy (SERRS) [145]
	surface-enhanced hyper Raman spectroscopy (SEHRS) [146]
	surface-enhanced infrared absorption spectroscopy (SEIRAS) [147, 148]
	tip-enhanced Raman spectroscopy (TERS) [149, 150, 151]
	shell-isolated nanoparticle-enhanced Raman spectroscopy (SHINERS) [152, 153]
	metal-enhanced fluorescence (MEF) [154, 155, 156]
	metal-quenched fluorescence (MQF) [139, 157, 158]
	Resonance coupling
Effect:	• coupling of two resonances
Type:	simple coupling • colorimetry [19, 159] • NP enhancement on solid transducers [160]
	fano-resonances [161, 162]
	spectral overlap • energy transfer to/from dyes or QDs [163] • Förster resonance energy transfer (FRET) • nanometal surface energy transfer (NSET)[164, 165] • molecular plasmonic switching [166]

Another possibility to push the LSPR signal is based on interactions between plasmonic nanotransducer with other plasmonic structures. Resonant coupling can induce a completely novel plasmonic behavior by plasmon hybridization [167]. The simplest example here is the coupling of two nanospheres in solution which are connected e.g. using DNA-hybridization [19]. The resulting resonance is a coupled dipole mode [168], which results in a colorimetric assay in simple and explicit visible resonant shift similar as described before for the case of particle aggregation. A particle distance of about 2.5 times of particle radii is optimal for coupling of two resonances [169]. For coupled nanostructures, also the position of the analyte relative to the sensor geometry is an important factor. Analytes located directly in the hot spot between the nanodiscs have a

four times higher plasmonic signal per bound molecule related to individual discs [170]. Fano-resonances show additionally a narrow spectral response and a more asymmetric line-shape [171]. This results on the basis of frequency interferences in two system modes, between resonant scattering process and background or between different scattering resonances of plasmonic nanostructures [172]. The consequence is a sensor device with an ultra-high figure of merit [162].

Enhancement of the LSPR sensing is also possible in the (bio)assay design. Different concepts have been proposed besides one-step affinity binding in order to realize a better sensing efficiency: the use of competitive assays, dendromeric enhancement concepts, enzymatic enhancement or target recycling [173]. By increasing the mass and by decreasing the binding radius of the analyte a higher sensor response is expected [174]. The sensor response can be increased when measuring occurs in dried state [121, 175]. The use of additionally plasmonic nanoparticles as label results in a significantly higher signal response. Chromophores as labels induce also a spectral shift enhancement, particularly in the case of resonance overlap of the plasmon peak with the absorption spectra of the chromophores [164, 176, 177]. Conformational switches, e.g. by reduction reactions, allow a better differentiation of resonant and non-resonant states (molecular plasmonic switching) [178]. By adjusting of the interaction, e.g. by nanoparticle heterodimers, the interparticle distance can be modulated using conformational changes of the bridging molecules actively [179].

One special type of the sensors are based on assays utilizing Förster resonance energy transfer (FRET [180]) between plasmonic components and fluorophores [181]. By the so called nanoparticle surface energy transfer (NSET) based assays, plasmonic particles act as acceptor and the fluorophores as a donor in the system [182, 183].

Additionally to these parameters, another limiting factor is the spectroscopic measurement set-up with their spectral range, illumination and detection system [121]. A detection range in the near-IR to IR increases usually the signal-to-noise ratio and induces an extremely high FOM [184]. The data evaluation can be also optimized: the use of the inflection point at the red side of the LSPR peak maximum shows a higher refractive index sensitivity than the resonance maximum itself [185]. From the aspect of the device construction, bright illumination sources are useful for an optimal spectral detection. In the next section, different signal-readout principles will be discussed.

5.1 Sensor devices with special signal enhancement

The common readout principle in LSPR biosensing is the measurement of the changes in extinction or scattering on the plasmonic transducer during the sensor reaction. By the cavity ring-down (CRD) technique, the optical signal inside of an optical cavity is amplified, so the measurement on plasmonic nanostructures can be realized with a higher sensitivity [186, 187]. CRD-setups allow to measure relative low loss changes and enable so the detection of 3 fM DNA [188]. Whispering gallery mode (WGM) sensor devices can be utilized in combination with plasmonic nanostructures, thereby inducing a frequency split in the WGM by backscattering from the plasmonic structure and leading to changes in their optical quality (Q) factor. This combination achieves a signal enhancement of one order of magnitude or even higher [189, 190, 191]. WGM-plasmonic hybrid sensing concepts have a predicted sensitivity allowing for the label-free detection of single molecules [192]. The use of WGM resonators as cavities results in drastically narrowed resonance peaks in this plasmonic-photonic hybrid systems [193]. Similarly, the combination of an interferometer with plasmonic transducers can induce a sharper sensor signal. The amplitude of the transmission is here influenced by

the interference between the mirror layer and the plasmonic nanostructures by their strong backscattering [194, 195].

6. Applications for localized surface plasmon resonance sensing

The increased importance and the diverse types of plasmonic sensor concepts allow to address a broad range of bioanalytical applications. Bioanalytical sensing aims at the detection of biomarkers for e.g. pathogens, cancer or other diseases, for food contaminants and environmental factors (Table 5). Additionally biochemical reactions, such as binding kinetics and enzyme activity assays can be investigated. The sensor concept determines primarily the kind of analytes. The method is sensitive to mass changes preferably nearby the surface, so sensors with low performance will not detect a few molecules of a small-sized analyte, or analytes in a larger distance to the transducer. The specificity of biosensing is based on the strong bioaffinity of the targeted analyte molecule to a selected recognition element (receptor or capture) on the transducer surface. The strong key-lock-like biomolecule-biomolecule interaction allows for a highly specific binding of the target to the sensor. Examples for such receptors, which are complementary to the target molecules, are presented in Table 5. The biofunctionalization of the nanotransducer with a recognition element for the selected analyte is possible using different binding and conjugation techniques [165, 196].

Sensing applications can be distinguished according to their analyte type and the type of the used receptor. In following part, different LSPR sensors will be presented related to target dimension. The direct sensing of whole **cells** has many applications, such as in pathogen detection for water or food testing. Here the response of cells on environmental factors can be investigated or the growth of a cell layer on gold surfaces

also in nanostructured form [197]. The geometry of the nanotransducer can be adjusted to the kind of cells to be detected [198]. The sensitivity can be pushed by the used geometry, e.g. complex 3D nanostructures of Au nanosquares on top of SU-8 nanopillars and Au nanoholes on the bottom allow for a highly sensitive detection of the cell culture growing of cancer cell types (lung cancer A549 cells, retinal pigment epithelial (RPE) cells, and breast cancer MCF-7 cells) [199]. A specific recognition is possible with antibodies as capture element on the nanosensor.

Microbial pathogens with their complex surface compositions can be identified by Raman-based spectroscopic techniques. The SERS or TERS fingerprint of **bacteria** cell surfaces allow for a specific discrimination [200, 201, 202]. However, the standard clinical diagnostics is still antibody-based (immunoassays). Following this approach, several LSPR sensors for the detection of different type of microorganisms were realized using antibodies as selective receptors [203]. Bacterial pathogens such as *Escherichia coli* [204], *Staphylococcus aureus* [205], *Salmonella ssp.* [206], can be detected using antibodies for extracellular adherence protein (EAP) or surface epitopes. An example of aptamer-based multiplex detection of different bacteria is described by Yoo et al. [203]. Here gold-coated particle array acts as LSPR transducer. In different spots of the microarray different aptamer captures were immobilized. *Lactobacillus acidophilus*, *Salmonella typhimurium* and *Pseudomonas aeruginosa* could so successfully detected on one chip. Another type of special recognition for bacteria is based on the use of bacteriophages or bacteriophage-displayed peptides as receptor [207, 208, 209]. Here, the natural recognition of the host for the bacteriophages can be used for specific detection.

Comparable to other microorganisms, the detection of **virus** pathogens follows the

similar recognition principle by specific interaction between surface antigens of the virus, and antibodies or aptamers on nanotransducers. The detection of the hepatitis B virus (HBV) was realized with gold nanorods with antibodies (monoclonal hepatitis B surface antibody HBsAb) for the hepatitis B surface antigen (HBsAg) as a replication biomarker [210]. Avian influenza virus was detected with gold covered silica nanoparticle arrays [211], M13 bacteriophage and influenza A virus with colorimetry [212, 213], HIV with anti-gp120 polyclonal antibody modified nanoparticles [214] (Figure 6a), dengue virus with anti-NS1 antibody-coated nanoparticles on optical fibers [215], and respiratory syncytial virus (RSV) with antibody-coated gold, silver and copper nanoparticles [216].

Exosomes become more and more important for cancer and disease diagnostics. These nanoscale exocellular vesicles play an important function in spreading of cancer in the body [217, 218, 219]. By their intracellular biogenesis, exosomes offer a mirror of the origin cell and carry their components, such as nucleic acids, lipids as well as fusion and surface proteins (f.e. integrin and tetraspanin) to other parts of the body. The direct detection of exosomes or the use of exosomal biomarkers in biosensing is therefore of high diagnostic-relevance for early cancer diagnostics. Novel sensing devices were developed for this application [220]. This kind of sensors has an innovative character and allows point-of-care measurements at low costs [221, 222, 223, 224].

Table 5. LSPR sensor receptor types for different human diseases.

Receptor	Ligand	Applications
antibody	virus	pathogen diagnostics
	bacteria	pathogen diagnostics
	fungi	pathogen diagnostics
	exosomes	cancer diagnostics
	antibody	autoimmune diseases
	cancer biomarkers	cancer diagnostics
	toxins	food-/env. analytics
aptamer	virus	pathogen diagnostics
	bacteria	pathogen diagnostics

	fungi cancer biomarkers protein biomarker toxin	pathogen diagnostics cancer diagnostics cancer diagnostics food-/env. analytics
oligonucleotides (DNA, PNA, LNA)	RNA/DNA PCR fragment miRNA	pathogen diagnostics genetic diseases cancer diagnostics
bacteriophage	bacteria	pathogen diagnostics
peptides	cancer biomarker	cancer diagnostic
bacteriophage-displayed peptides	bacteria	pathogen diagnostics
saccharides	protein	immunodiagnostics
proteins	saccharide	diabetes tests

Similar to DNA-chip techniques, also LSPR genosensing (the detection of **nucleic acid** species) is able to detect the origin of diseases such as microbial pathogens by sensing the presence of their respective DNA [225]. Recognition element can be synthetic DNA, PNA or LNA-oligonucleotides, and peptides. As analyte some model systems with synthetic short oligonucleotides were used to confirm the sensing principle (binding of the target DNA/RNA on capture oligonucleotides) [175, 226]. Using an enhancement strategy, a direct discrimination of 16s rRNA could be demonstrated [227]. However, common DNA-based (geno-) sensors are based on the detection of amplicons from polymerase chain reaction (PCR) [228]. In the case of bacteria, the conserved 16S ribosomal DNA (rDNA) or the 23S rDNA region are often used as a template for the PCR fragments [229], allowing for an amplification of whole sets (families) of organisms with just one PCR reaction. So the specifity of the developed assay is much higher and allows the discrimination between different species. Several examples such as *Chlamydia trachomatis* genosensing [230], the discrimination of 6 different bacteria with gold nanorods [229], the discrimination of different pathogens using copper capped nanoparticles [231], or the detection of 4 different microorganisms by SERS [232] were demonstrated. Also detection of other DNA-based biomarkers, such as lactose intolerance factors, is possible based on the amplification of the DNA

region of interest and the subsequent hybridization on capture oligonucleotides (gold triangles and snpLSPR [92]). Alternative amplification techniques or target recyclings such as hybridization chain reaction (HCR, Figure 6b) [233] or bio-bar-code amplification (BCA) [234] help to improve the sensing signal. Colorimetric detection of *E. coli* DNA were demonstrated in only one hour and with a high sensitivity using HCR [235] .

miRNA are small (~23 nt, 17-25 nt) non-coding intercellular nucleic acids with an important regulatory function in cell activities [236, 237]. These molecules are excellent biomarkers for cancer and other diseases. The detection of miRNA using BCA were realized on nanoparticles with LNA receptors [238]. Several sensors were developed to detect miRNA from real samples directly, without amplification techniques. The detection of pancreatic cancer-related exosomal miRNA on plasmonic nanotriangles was realized [93, 239].

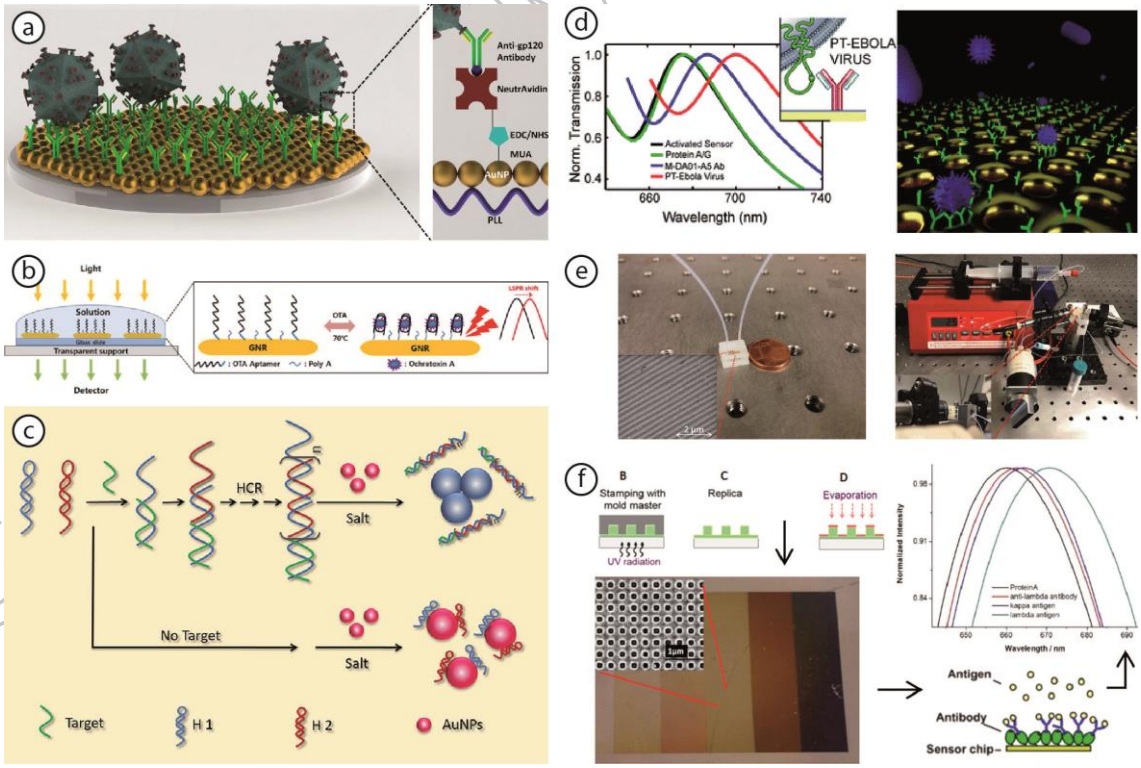


Figure 6. Examples of novel LSPR sensors: a) detection of intact HI virus using antibodies on gold nanoparticle layer from unprocessed blood samples (Reprinted (adapted) with permission from [214]. Copyright (2017) American Chemical Society). b) Detection of ochratoxin A using aptamers as recognition element on gold nanorods (Reprinted from the Biosensors and Bioelectronics, 2014, 59, Park, J.-H.; Byun, J.-Y.; Mun, H., et al., A regeneratable, label-free, localized surface plasmon resonance (LSPR) aptasensor for the detection of ochratoxin A, 321-327, Copyright (2017), with permission from Elsevier {Park, 2014 #18260}) c) Colorimetric detection of *E. coli* DNA using HCR amplification on gold nanoparticles (Reprinted with permission from [235]. Copyright (2017) American Chemical Society). d) Sensor based on extraordinary light transmission effect in plasmonic nanoholes. The viruses from medical samples were detected using group-specific antibodies (adapted with permission from [240]. Copyright (2017) American Chemical Society). e) Blu-ray-based plasmonic nanostructures for the antibody mediated tumor-associate antigen (TAA, related to colorectal cancer) measurement (Reprinted from the Biosensors and Bioelectronics, 2017, 96, López-Muñoz, G. A.; Estevez, M. C.; Peláez-Gutierrez, E. C., et al., A label-free nanostructured plasmonic biosensor based on Blu-ray discs with integrated microfluidics for sensitive biodetection, 260-267, Copyright (2017), with permission from Elsevier [241]). f) Detection of leukemia from blood on gold nanohole array on plastics with antibodies (Reprinted with permission from [242]. Copyright (2017) American Chemical Society).

The immunoassay-based LSPR sensors are widely established. Here the range of studied analytes has been extended from the complete pathogens down to smaller analytes, such as different **proteins** like bacterial membrane proteins [243], cytokine as biomarker for immune monitoring [244, 245], or biomarkers for Alzheimer´s diseases

[246]. Many applications are focused on cancer diagnostics and clinical sensing [11]. Examples are the selective detection of pathogen-related antibodies by infections (colorimetric test of *Treponema pallidum* in patient sample [247]), the measurement of blood group antigens in human serum [248], the detection of kidney cancer biomarker (membrane protein urine aquaporin-1, AQP-1) [249], prostate cancer marker (PSA) [205] and other cancer biomarker such as human alpha-feto-protein [250]. In LSPR-based protein immunoassays the receptor can be a selective antibody [20, 29], a peptide [251] or an aptamer [252, 253]. Aptamers are nucleic acids folded in a defined 3D structure, and selected (in their binding strength) against a certain target structure by the SELEX method [254, 255], which act as receptor for specific protein sensing. Several examples of protein sensing were realized [37, 256]. Thrombin can be detected using aptamers on gold nanorods [257]. Using aptamers actually seven different proteins could be colorimetrically discriminated [258]. For protein sensing, also saccharides (sugars) can act as receptor. So mannose was used to bind concanavalin A (ConA) on silver triangle sensors [259].

Small bioanalytes are low-molecular biomarkers or metabolites, (food-borne or environmental) toxins, antibiotics, heavy metals or other chemical environmental factors. For these also all of the previously discussed recognition principles are available. *Staphylococcus aureus* enterotoxins B (SEB) were detected using antibody as receptors on NSL nanotriangles. Antibiotics such as pefloxacine in seafood were detected with antibodies on gold nanorods [260]. Mycotoxins such as ochratoxin A (OTA) were detected with gold nanorods sensors and aptamer receptors (Figure 6b) [261]. ATP can be measured on gold nanorod sensor using aptamers [262]. Saccharides were detected by competitive colorimetric assay [263]. Heavy metals as fatal environmental factors and their detection represent another established field in

plasmonic sensing. The LSPR sensing of mercury [264, 265], Co, Ni and Cd [266], and heavy metal ions in general on gold nanorods is described in a review by Jayabal et al. [267]. Also hydrogen sulphide is an environmental factor with health effects. A plasmonic sensor consisting of immobilized nanoparticles with the protein cytochrome-c (CitC) as receptor [268] can be used for the detection of this compound.

7. Integrated and commercial LSPR sensors

One current trends in bioanalytical sensing is towards point-of-care (POC) sensors (overview integrated microfluidic [269], and optical sensors [270] including LSPR sensor). These sensors enable rapid, accurate, multiplex-compatible, and cost-efficient measurements. Some novel sensors exhibit simple sensing principles with a smartphone-based optical readout or portable sensor providing a simple interface also for untrained users [39, 271, 272, 273]. A novel trend is also the use of multiplex platforms e.g. plasmonic microarray based systems (MEF [156], NSL array [274], EBL nanorods for cancer diagnostics [250]). Microarrays enable for a parallel readout of several biomarkers in one measurement [245]. The use of colorimetric assay with nanorods in channels allows the multiplex readout of different disease biomarkers [37, 243, 275]. Paper as novel material for biosensing is more and more considered in the development. A paper based colorimetric assay for pathogens is described [276].

In the last decade, several LSPR principles were established as a commercial platform, product or sensor device (overview of current LSPR-related companies with products for sensing can be found here: [277]). Lateral flow-assays (LFA) represent certainly an initial use of plasmonic nanoparticles for commercial biosensing in the 1980ies [278]. Here antibody conjugated gold and silver nanoparticles acted as an optical label in the detection of e. g. pregnancy. Currently the assay *First Response* from Carter Wallace

(hGC in urine), *Duopath* from Merck for verotoxin and *ImmunoCap* from Phadia Inc. for 10 allergens are typical examples. An overview of current LFAs (not only plasmonic related) is given by [279]. The use of plasmonic nanostructures as SERS substrates is also widely developed, such as *SERStrates* from Silmeco, *P-SERS*™ from Diagnostic anSERS Inc. on paper or in microtiter plates, or *RAM-SERS-AU* (gold), *RAM-SERS-AG* (silver) or *RAM-SERS-SP* (nanosponge) by Ocean Optics. For the in-vivo detection of tumors, the handheld *SpectroPen* established based on SERS has been established [280]. For diagnostics, ensLSPR represents a simple principle for commercial use, here the use of sensitive transducers - as shape-anisotropic nanoparticles - allow for an enhanced sensing [281, 282, 283]. An overview of selected companies active in the field of plasmonic biosensing is given in Table 6.

Table 6. Selected companies with LSPR sensor concepts or products.

Company	Country	Founding	LSPR principle	Link
Abaxis	USA	1989	colorimetry, LFA	https://www.abaxis.com/
Alere	USA	1991	colorimetry, LFA	http://www.alere.com
BBI Solutions	UK	1959	colorimetry, LFA	http://www.bbisolutions.com
Biosensia	Ireland	2009		http://www.biosensia.com
BioMérieux	France/USA	1963	colorimetry, LFA	http://www.biomerieux.de/
Creative Diagnostics	USA	2005	colorimetry, LFA	http://www.creative-diagnostics.com/
DuPont	France/USA		colorimetry, LFA	http://www.dupont.com/
SmartFlare by Merck			colorimetry (fluorescence) [284]	http://www.merckmillipore.com
Cosingo	Spain	2008	LSPR	http://www.cosingo.com/en/
Insplorion	Sweden	2010	ensLSPR	https://www.insplorion.com/en/
Lambda Gen	USA	2010	ensLSPR [281]	http://lamdagen.com/
Nanoprobes	USA	1990	nanoparticles for colorimetry	http://www.nanoprobes.com/
nanoRETE	USA	2011	colorimetry, LFA	http://www.nanorete.com
OpenSPR Sensors by Nicoya Lifesciences	Canada	2014	ensLSPR	https://nicoyalife.com
Quiagen	Germany	1984	Resonant light scattering (RLS)	https://www.qiagen.com
Synkera	USA	2003	SERS, LSPR	http://www.synkerainc.com/

Technologies Inc.			samples	
Verigene system by Luminex	USA	1995	nanoparticles as optical label	https://www.luminexcorp.com/clinical/our-technology/verigene-nanogrid-technology/
SERStrate by Silmeco	Denmark	2013	SERS substrate	http://www.silmeco.com/
P-SERS™ by Diagnostic anSERS Inc.	USA	2012	SERS substrate [285]	https://www.diagnosticansers.com/
RAM-SERS-AU, RAM-SERS-AG, RAM-SERS-SP by Ocean Optics	USA	1989	SERS substrate	http://oce.oceanoptics.com/product/sers/

8. A critical reflection of localized surface plasmon resonance sensing

The rapid development of LSPR sensing for bioanalytical applications indicates the huge potential of this principle. Nevertheless, the number of the commercial products and devices is still rather limited. The nanostructures usually used in biosensing are gold nanospheres and gold nanohole substrates. On the other hand, silver particles would offer a better sensing performance. The reason for this discrepancy is the high stability of gold nanocolloids compared to other materials. Gold is chemically stable and represents so an excellent material for bioconjugation. Other plasmonic sensor material has to be somehow protected in order to ensure long time stability as an important point for commercial use. For LSPR sensing, technical realizations are important. The penetration distance for sensing depends on the nanostructure radius, material and shape. This value can be optimized by dielectric coatings over the metal surface [205]. Additionally, the sensitivity for shape-anisotropic particles should be considered regarding their geometry for an optimum sensing concept [286]: When analyte molecules bind at the right position (representing a high local enhancement of the electromagnetic field) of e. g. nanorods, the sensitivity is significantly enhanced compared to other locations at the sensor. The dimension and the distance of the analyte to the capture molecule play an important role for biosensing [136]. Generally, small

analytes can be efficiently detected using LSPR principles [287] and short range molecular interactions. The sensor response for such small changes is proportional higher compared to changes in the whole sensing volume in other concepts (SPR) [126].

Related to the bioanalytical focus, antibodies as receptors are cost intensive, their preparation involves ethical issues, and their use in sensing needs an exact assay design. Another limitation lies in the often missing long-time stability such as for storage or transport. Therefore, in future the investigation of stable and specific capture molecules (receptors) is becoming more and more important.

One of the main advantages of the LSPR-sensors represents their potential for miniaturization and integration. Point-of-care applications and personalized medicine in future are only possible with robust, user-friendly and low-cost sensor devices and the potential to adaptation this sensors for different analytes. LSPR technique allows this development. Optimal LSPR sensor concepts combine high sensitivity transducers with cost-efficient production, optimal bioassay in a multiplex design, and integrated microfluidics [288].

9. Expert Commentary

Plasmonic biosensing witnessed a rapid evolution over the last decades. Plasmonic transducers are robust and their preparation is possible in larger scale by innovative nanostructuring methods, such as soft-lithographic techniques, bottom-up colloidal synthesis or combinations. Transducers as core part are in the focus of future investigations, addressing the sensitivity enhancement by design, the use of resonant coupling as well as field-enhancement, and increased long-time stability. The wide range of spectral behavior and defined signal generation allows today and in future the innovative use of plasmonic transducers as point-of-care sensors. In case of optimal

sensor design with optimal transducer- and optical-read-out devices and adequate bioassay concept, sensors are implementable for all fields in life-science applications.

10. Five-year view

The variety of different plasmonic sensing concepts permits for each bioanalytical problem the adaptation of a specific LSPR sensor in a customized manner. SnpLSPR allows for the characterization of the sensor behavior of plasmonic transducer at the single-nanostructure level, promising ultrasensitive measurements. EnsLSPR-based devices exhibit a robust and quick sensor for point-of-care applications. Colorimetry allows for the simple use of plasmonic nanoparticles for a specific bioassay. The plasmonic microarray with LSPRi exhibits a high potential for multiplex read-out. Here a realization of completely multiplexed and miniaturized bioanalytical assays is possible in one measurement. Generally, plasmonic-based biosensing makes it possible to detect panels of pathogens based on their genetic materials, or antibiotic resistance-genes, or other biomarkers, and so to significantly improve diagnostics towards a personalized medicine and better health-care in future.

Key issues

- Biosensors based on the effect of the localized surface plasmon resonance (LSPR) allow a detection of the binding on analytes on recognition elements by optical signal The optical signal of the sensor depends on the kind of transducer (material, size, shape and fabrication type)
- Enhancement of the sensor signal is possible using field-enhancement and resonance coupling
- Small analytes and short intermolecular interactions can be efficiently detected using LSPR principles
- Main advantage of the LSPR sensing is given in their potential for miniaturization and integration
- Future LSPR sensing concepts aim at rapid and specific point-of-care devices

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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