Trends in Surface Plasmon Resonance Biosensing: Materials, Methods, and Machine Learning

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Abstract

Surface plasmon resonance (SPR) proves to be one of the most effective methods of label-free detection and has been integral for the study of biomolecular interactions and in the development of biosensors. This Trend delves into the latest SPR research and progress built upon the Kretschmann configuration, a pivotal platform, and highlights three key developments that have enhanced the capabilities of the technique. We will first cover a range of explorations of novel plasmonic materials that have shaped SPR performance. Innovative signal transduction and collection, which leverages traditional materials and emerging alternatives, will then be discussed. Finally, the evolving landscape of data analysis, including the integration of machine learning algorithms to navigate complex SPR datasets, will be reviewed. We will also discuss the implementation of these improvements that have enabled new biosensing functions. These advancements not only pave the way for enhanced biosensing in general but also open new avenues for the technique to play a more significant role in research concerning human health.

Keywords: Surface Plasmon Resonance, Plasmonic Materials, Machine Learning, Biosensing, Kretschmann Configuration

Introduction

Surface plasmon resonance (SPR) has seen extensive growth and adoption since the milestone paper by Liedberg et al in 1983(1) based upon Krestchmann's account of surface plasmon polaritons in 1968(2). SPR biosensors have found broad use in a wide range of human health related research including drug discovery(3-5), pharmacokinetics(6-8), clinical diagnosis(9, 10), environmental monitoring(11), and biophysical investigations(12, 13). SPR's ability to monitor biological interactions sensitively in real-time without the need of reporters or labels has motivated its widespread adoption. Technological advances over past decades have impacted the field through new materials and sensing arrangements that have drastically changed the function of SPR. Materials that have been recently implemented generally come from three areas: alternative plasmonic metals(14), 2D substrates(15), and biomimetic interfaces(12). Further exploration of these advanced materials relies upon improvements in SPR sensing methodologies. Regarding expansions of SPR methodologies, SPR imaging (SPRi) utilizes the same Kretschmann configuration but significantly improved throughput by turning each pixel into a measurement element, allowing arrays of interactions to be visualized simultaneously(16). Additional methodologies have utilized changes in the excitation source to perform multiwavelength(17) and phase-sensitive(18) measurements, providing more information and higher sensitivity for the SPR sensor systems. Furthermore, by taking advantage of the large and complex datasets provided by SPR, SPRi, and these new methodologies, machine learning becomes a key tool in furthering sensor development. This Article aims to discuss the recent trends in SPR biosensing, which is encompassed by material advancements, novel data collection, and

mathematical tools, to provide a survey of how these improvements have been implemented to expand the capabilities of SPR biosensors.

SPR Methods

SPR is a label-free analytical technique built upon the fundamental photon-electron interactions on a plasmonic material as demonstrated by Ritchie(19). These interactions can be modeled by Fresnel equations(20) based on the properties of the materials and incident light. The coupling of the photons to a thin metal film through an optical coupler (i.e., a prism in the Kretschmann configuration) leads to a dipping in the reflection spectrum, and the angular shift of the incident minimum depends on the refractive index change above the plasmonic metal (Figure 1)(2). This relationship provides a highly sensitive detection of refractive index differences caused by the molecular binding events occurring at the sensor surface(21). Measurement can be realized through collection of reflected intensity for an array at a fixed angle, or through tracing the minimum of the reflection spectra. SPR sensors have been regularly utilized in pharmaceutical research to screen affinities between biomolecules(22). Innovations in the field have generated a variety of sensors for a range of tasks including protein analysis(9, 23), environmental monitoring(24), diagnostics(25), and even food analysis(26). The intrinsic sensitivity of SPR methods has allowed analysis of large biomolecules such as antibodies with exceptional performance; however, for small molar mass molecules, amplification of the detection signals(27) and/or improvement of signal transduction may be necessary. To this end, a plethora of innovative work has appeared and is discussed in this Trend to

show the substantial efforts undertaken in recent years to address technical issues associated with low signal and complex media.

New Materials

Gold films have been standard for SPR biosensing using Kretschmann configuration for decades and have proven to be highly effective for interrogating biological interactions. However, gold is not the only plasmonic substrate for this application; there are many other plasmonically active elements, alloys, and materials that have the potential to expand the capabilities of SPR sensors. These materials provide signal enhancement, antifouling properties, and new surface chemistries for functionalization, each enabling sensors to be tuned in a transformative way. There are two major approaches in materials development: a compositional method that explores material property itself, and a structural method that manipulates 2D and 3D constructs to derive new functions. Many research efforts bridge both methods, taking advantage of new structures derived from novel substrates.

Alternative Metals

One exciting advancement is shown in the development of alternative metals as plasmonic substrates against the traditional gold and silver. Aluminum has emerged as a particularly promising substrate due to its high plasmonic response under a wide range of excitation wavelengths, with Tanabe et al. demonstrating its effectiveness in the UV region(28) and Lambert et al. establishing aluminum thin film-based SPR sensing at 650 nm(14). The aluminum thin-film SPR has demonstrated improved sensitivity as compared to traditional gold films due to the steeper slope of the aluminum reflectivity dip, as shown

in Figure 2. Inherent anti-fouling properties of the native oxide layer on aluminum were reported, which can be highly advantageous for biosensing applications. Other metals such as copper(29) and palladium/platinum(30) have also been explored, but compared to gold they demonstrate limited benefits. Thiol chemistry has been the traditional functionalization method for gold (31), while other metals could be functionalized similarly(32). For aluminum substrates a shift to silane(33) or phosphonic acid(34) based SAM formation would be necessary, both of which have been employed extensively, including an example on SPR sensor chips with a thin layer of silica oxide(35). Nonetheless, the disclosed plasmonic preparties from these metal films prove to be valuable as they provide insights into key factors towards performance enhancement when searching for new alloy or layered SPR surfaces.

2D Materials

In addition to novel metals, surface manipulation/functionalization of thin films is an integral step in the development of new SPR sensors. 2D materials have seen frequent usage as SPR substrates due to their high uniformity, a necessary trait for Kretschmann configuration of SPR. Modification with 2D materials has been employed to increase sensitivity due to larger surface area, better analyte binding, and greater antifouling capability(36). A multitude of 2D materials have been explored including graphene(37, 38), molybdenum disulfide(39, 40), tungsten disulfide(15) and black phosphorus(41). Cai et al. demonstrated the combination of graphene and MoS_2, taking advantage of the increased surface area by graphene and the improved sensitivity from MoS_2 that stems from increased absorption of the excitation source(42), which showed 1.85 times higher signal than traditional gold substrates. In addition, these materials provide a unique set

of chemistries that expand the applicability of SPR sensing, through their unique π–π stacking interactions(43) or silane-based SAMs, for graphene oxide(44), molybdenum disulfide(45), tungsten disulfide(46), and black phosphorus(47). Clearly, the surface functionalization strategy is not limited to the 2D material space, and improvements have been made beyond plasmonic materials.

Biological Materials

Biomimetic surfaces for SPR have seen an increasing development due to the controlled environment favoring the study of interactions in biologically relevant events. Thus, enabling SPR biosensors to closely mimic the interactions used for detection allows for more accurate assessment of biomarkers. In particular, usage of lipid bilayers has been increasingly cited in literature due to its passivating effects reducing nonspecific interactions from complex media(42) and as a convenient host environment to probe interactions native to cellular membranes(48). Furthermore, the addition of functionally modified lipids allows for display of capture moieties enabling specified binding of the analyte targets(49, 50). Recently, these lipid platforms have been employed to investigate complex systems such as curvature sensing proteins(12, 51). Chadli et al. demonstrated the incorporation of transmembrane proteins, obtained from cell free expression, into lipid vesicles that were then spread on the SPR surface(52). Biomimetic surfaces are not limited to lipids; peptide polymers have also been employed as an effective avenue for functionalization of the sensor surfaces. Ozgur et al showed the use of peptide polymer in the design of molecularly imprinted polymers (MIPs) for the detection of whole *E. coli*(53). The biologically inspired surfaces on SPR biosensors play an equally critical role as the plasmonic thin films by providing desired presentation of the binding sites needed

for effective sensing. They also furnish new platforms to investigate challenging protein targets such as transmembrane proteins through new hosting environments.

Expanding Methodologies

Another area that has seen marked progress towards SPR improvement is the implementation of new sensing methodologies that can provide more information than traditional methods. While the concepts of multiwavelength(54) and phase-sensitive(55) SPR sensors have floated for some time, only recently have advancements in technology made them available for applications with SPR biosensing.

Multiwavelength SPR

While the concept of multiwavelength SPR sensing has been understood for many years(56) the complexity of instrument to monitor multiple SPR wavelengths at once was high. Therefore, very few multiwavelength SPR systems were reported. Multiwavelength measurements have seen considerable growth in recent years, largely owing to the availability of BioNavis' instrument. By detecting at two wavelengths, key information associated with thickness and dielectric properties of the organic layer/film can be collected, as described by Peterlinz et al(54). This expanded information enabled the analysis of many systems previously inaccessible, such as extracellular vesicles of different sizes, as demonstrated by Rupert et al. (17). More recently, it has been applied to monitor cellular uptake of extracellular vesicles that focus solely on intracellular events(57). Multi-wavelength measurements have also been employed to study mechanisms of the interaction between liposomes and influenza virus peptides(58). The thickness calculation from this work suggests distinct morphological differences upon

peptide introduction, showing a peptide insertion into the liposome surface at pH 4.5 while at pH 8 the peptides induced a decrease in signal associated with morphological changes. Clearly, dual wavelength SPR measurements can provide new insights into the properties of the membranes, facilitating elucidation of the interaction mechanisms.

Phase Sensitive SPR

While multi-wavelength SPR provides more information about the properties of the surface, phase-based SPR analysis has been exploited to enable highly sensitive measurement by monitoring the sharp phase shift that occurs at the SPR angle. However, phase shift measurement has met many technical problems as the complex optical configurations required to collect phase changes would limit the reproducibility of the sensor and thus its acceptance(18). In recent years, multiple advancements in phase based SPR sensing have been made, expanding the capabilities of the system by alleviating the main problems in sensor variability. Wu et al. showed an approach to mitigate the inconsistencies from film thickness and angular variations through an algorithm to build a phase-mapping function in data collection(59). Using this algorithm, they were able to identify the optical parameters that enabled optimal data collection for a multi-layer model and maintained the sensitivity and reproducibility of the measurements. The platform was successfully applied to monitor lung-tropic exosomes, eliminating the difference caused by film thickness variation that would normally impact sensor reproducibility in a negative way. Sang et al. have reported a multiplexed phase interrogating SPR by employing a wavelength-sequential selection technique to enable analysis across channels with reduced sampling time by optimizing the wavelength for each individual channel(60). The binding interactions between human transferrin and its

antibody were utilized to demonstrate the feasibility of the platform for monitoring interactions across six different channels (Figure 3). Further fine-tuning of the technique will no doubt facilitate the expansion and adoption of phase based SPR measurements due to the improved sensitivity.

Enabling SPR Sensors Through Machine Learning

Aside from new materials and novel sensing methodologies, there is an emerging *in silico* component that aids significantly in SPR measurements and processing of complex data from the sensors. Introduction of machine learning models have considerably improved the development, collection, and analysis of SPR sensors. These models facilitate the utility of new materials and deconvolution of signal complexities, enabling the sensing of increasingly complex samples and the development of novel surface chemistry. Machine learning has clearly shown the potential to motivate substantial advancements in SPR experimental design and analysis.

Enhancing Experimental Design

Recent research has provided a few good examples of using machine learning algorithms to improve sensor performance. For example, the design of new materials can be enhanced through ML models as demonstrated by Sebek et al., who utilized a genetic algorithm to generate highly sensitive SPR films composed of 2D materials based on a materials database(61). The algorithm identified a unique dual-mode SPR structure and was utilized to design an ideal substrate for SPR sensing at 633 and 785 nm excitation wavelengths. With machine learning assistance, the sensor surfaces provided ideal

starting points for experimental validation, which can then be fed back into algorithms to fine tune material recommendations.

Machine learning has also been used to estimate and quantify biological interactions measured on SPR biosensors. Palai et al. investigated the adsorption of serum proteins on various polymer films(62). By choosing descriptors of polymer structural and chemical properties, the machine learning algorithms predicted the structure-property relationship, providing key information and properties for blocking serum adsorption. They found that the hydrophobic nature of the polymer was most critical to antifouling behavior, followed by film thickness, number of C-H bonds, net charge, and polymer density. The potential for machine learning algorithms to predict interaction patterns and properties has a large impact on experimental design and can be instrumental to future SPR studies aiming at revealing insights into identifying the most impactful parameters, including key structural and chemical dimensions, for effective sensing.

Data Interpretation

Aside from aiding in experimental design, machine learning can also assist in extraction of important information from experimental data. For example, SPR is regularly used to assess the binding kinetics of biomolecular interactions. To streamline data acquisition, Chang et al. have used deep learning models to build a system for rapid determination of binding affinity(63), which proved to be highly useful in bioassay work that requires fast turnaround times. Different from works using machine learning models for *in silico* systems, Malinick et al. have applied machine learning to analyze

experimental data, allowing identification of cross-reactive species and separation of the response signals(35). The study involved an array of gangliosides to sense multiple sclerosis-specific antibodies, where the signals were heavily convoluted due to substantial cross reactivity arising from high structural similarity between the glycolipids. Machine learning algorithms yielded accurate identification of correct ganglioside-antibody pairs using the whole sensorgram data (Figure 4). Similarly, Jobst et al. have recently employed deep learning models to classify small molecule purines bound to graphene oxide sensors(64), which enabled small molecules with similar structure to be separated based on the minute differences in their binding affinities.

The significant advancements in machine learning assisted biosensing in recent years have changed the way how complicated and demanding detection is conducted, allowing identification of material combinations, prediction of surface fouling and isolation of individual interactions in an array system with ease. However, ML may mask the reasoning behind the results and becomes dangerous if the algorithms are blindly trusted(65). The training of ML models on biological datasets is prone to over fitting, yielding the illusion of effective classification that quickly collapses upon expansion to other samples(66). Therefore, ML application into SPR systems needs to be carefully implemented and appropriately controlled for future sensor analysis.

Biosensor Applications

New materials and machine learning algorithms have spurred a new round of applications towards disease diagnostics by SPR, as reflected by a growing number of SPR studies on biomarkers in biological media. By applying the innovative techniques

described in previous sections, high performing multiplexed diagnostics could be realized. SPR can be an extraordinary clinical tool; the small size, simple operation, and quick generation of data make the technique well suited for rapid diagnostics in a clinical setting. Complex media and desired modes of direct analysis of patient samples, however, adds significant complications in sample preparation and data analysis. More efforts for compelling clinical application of SPR detection have been seen, with studies being conducted on blood, sera, and cell lysate to demonstrate its capability for diagnostic purposes. The COVID-19 pandemic has also stimulated much new work with the urgent need to detect the virus and important markers associated with the infection.

COVID-19 Biosensors

In response to the COVID-19 pandemic, extensive efforts were made in the biosensor field to search for methodologies for detection and characterization of SARS-CoV-2 binding. Earlier sensing work had focused on SARS CoV-1 antibodies(67), which required new development to be applied to the COVID-19 pandemic. SPR proved to be effective due to the straightforward operation, adaptable surface properties, and potential for deployment in the field. Aside from pathogen/marker detection, SPR has found applications in other endeavors that aimed to control the pandemic. Abouhajar et al. investigated the sequence-specific binding variances of ACE-2 α 1-helix-mimicking peptides(68), which matched well with molecular docking predictions and proved well suited for studying mutable viral proteins. SPR sensors could function as an alternative method for diagnostics aside from conventional RT-PCR and ELISA for detecting either SARS-CoV-2 antigens or antibodies. Yano et al. reported a CoV-2 antigen biosensor that utilized nucleocapsid-capturing antibodies followed by antibody-conjugated gold

nanoparticles for signal amplification(69). The sensitivity reported by this work was similar to most RT-PCR assays, while SPR-based sensors offer simpler operation and quicker turnaround times of the test. Basso et al. developed COVID-19 antibody sensors with spike and nucleocapsid proteins anchored to the chip surface(70), capable of identifying IgG antibodies in patient sera and producing results in ten minutes. SPR sensors are not limited to the SARS-Cov-2 virus as work by Sharma et al. has shown its effectiveness for sensing of the Ebola virus(71). The quick adaptability and rapid turnover of diagnostic data demonstrated for SARS CoV-2 could serve equally well in analysis and diagnosis in other epidemiological settings.

Biosensing in Complex Media and Clinical Samples

There have been many studies targeting biomarkers in complex media for a broad range of diseases and health concerns(72-74), paving a solid path for SPR's adoption in clinical diagnosis. Recent work on cancer biomarkers, as shown in Figure 5, demonstrated the potential to rapidly detect HER2 cancer cells using an SPRi platform(75). The sensor can monitor the binding of cells and distinctly differentiate between HER2 positive and negative cells based on nanobody specific interactions. Similarly, Eletxigerra et al. utilized SPR to identify ErbB2 breast cancer biomarkers in both patient sera and lysates from breast cancer cell lines(76). Wong et al. have reported an SPRi sensor for microRNA cancer biomarkers in patient samples, further showcasing SPR's capability for clinical diagnosis(77). Others have employed SPR to monitor the changes of serum proteins between a control group and patients with non-metastatic or metastatic breast cancer(78), where data from the post-treatment metastatic patients provided insight into factors leading to biomarker protein's up- or down-regulation. The

study identified significant upregulation of proteins for patients with ER+ and HER2+ cancers and considerable downregulation in the metastatic group after 3 months of therapy, providing important information about treatment impact and outcome.

SPR sensors have also been developed for various other diseases including Alzheimer's(23, 79) and cardiovascular disease(80). Oldak et al. employed an SPRi immunosensor to quantify phosphor-Tau 181 in human plasma samples (81). Lee et al demonstrated the detection of TNF-α and NT-proBNP cardiac disease markers in patient serum using aptamers (82). While these studies highlight SPR's potential for clinical biosensing, it has yet to be formally implemented as a standalone tool in a clinical diagnostic setting. Nonetheless, the promising results from these studies suggest that we may soon be entering a stage where SPR devices will find more applications in clinical research or hospitals.

Small Molecule Biosensors

The broad sensing capability of SPR has been further reflected in recent efforts in the detection of small molecule biomarkers and metabolites. Li et al. developed an electrochemical-SPR system using electrically-polymerized dopamine to capture several amphetamines in both urine and serum samples(83), and reached nanomolar detection limits. The work demonstrates SPR's promise not only as a clinical diagnostic method, but also as a competent forensic tool. Yao et al. reported a portable SPR biosensor for the detection of methamphetamine and cocaine in saliva samples(84). SPR sensors have also been employed to detect antibiotic contamination of river water and milk in efforts to monitor the overuse that has led to antibiotic resistance(85). Food allergen detection is another area that shows SPR's involvement in small molecule sensing. Small allergens

such as histamine can be detected in food-based media of dairy and fish products, as demonstrated by Rahtuvanoğlu et al(86). In this case, amplification of the tiny histamine binding shifts was achieved using molecularly imprinted nanoparticles. In addition, SPR has been used to detect other small molecules, such as Aflatoxin B_1(87), okadaic acid(42), and glucose(88). These examples point to a level of considerable shift in SPR's development and applications. Converging with the end goal of serving clinical testing, the development of SPR sensors has aimed to improve performance when dealing with complex media, which will eventually lead to its transformation into a major technical platform for disease diagnosis and other human health related assessments.

Outlook

Today there is an increasing number of SPR biosensors focused on solving clinical problems, but they all face some limitations. The sensitivity limits of SPR with small molecular mass, which directly affects many of the emerging biomarkers, necessitate new strategies for improvement. Moving towards clinical applications entails effective sensing in complex matrices, which require new materials or methods to deal with surface fouling and nonspecific signals. Expansion into diagnostic use demands fast data processing and streamlined analysis. The recent advances in SPR sensors, which are driven by the introduction of new materials, methods, and the implementation of machine learning algorithms, begin to provide solutions to these problems. Many of the limitations in SPR systems are seeing marked improvements. However, much of the work is still in its early stage and will require continuous investigation and improvement. In recent years machine learning algorithms have shown a great potential in lifting SPR biosensing into a new

stage. For example, the possibility to identify yet untested material combinations that have the potential to enhance sensitivity is groundbreaking. Experimentally testing new materials pinpointed by algorithms to iteratively revise the datasets and parameters used for predictions could generate highly desirable conditions for sensing work. ML can also enhance new sensing configurations such as those recently introduced in multiwavelength and phase-based detection. As these improvements are integrated into commercial instruments, an expedited expansion of SPR adoption and utility in biomarker sensing can be forecast. Therefore, the collective improvements in surface chemistries, novel methodologies, and computational models discussed here will make SPR sensors more versatile and powerful, facilitating its transformation into a practical, simple, and fast diagnostic tool in clinical detection.

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Contributions

DDS: Conceptualization; Literature search; Writing—original draft; Writing—review and editing. WV: Literature search; Writing—original draft; Writing—review and editing. SV: Literature search; Writing—original draft; Writing—review and editing. ASL: Literature search; Writing—original draft. VH: Literature search; Writing—original draft; Writing—review and editing. QC: Conceptualization; Funding acquisition; Supervision; Writing—review and editing

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Ethics declarations

Conflict of interest

The authors declare no competing interests.

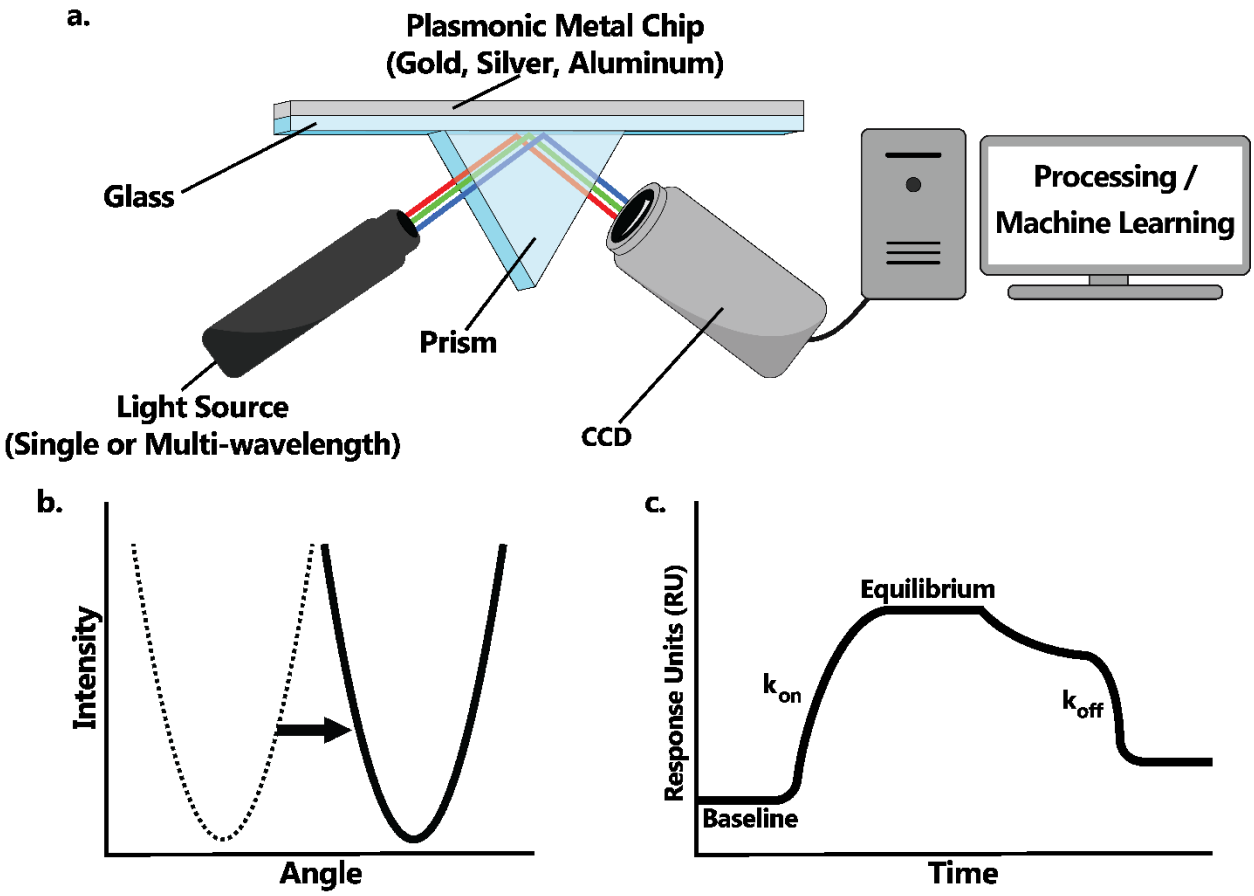

Figure 1. (a) Scheme of Kretschmann configuration SPR sensors. (b) Shift in reflectivity curve from analyte binding to the sensor surface. (c) Sensorgram of SPR real-time analysis of binding interactions showing association and dissociation of analyte.

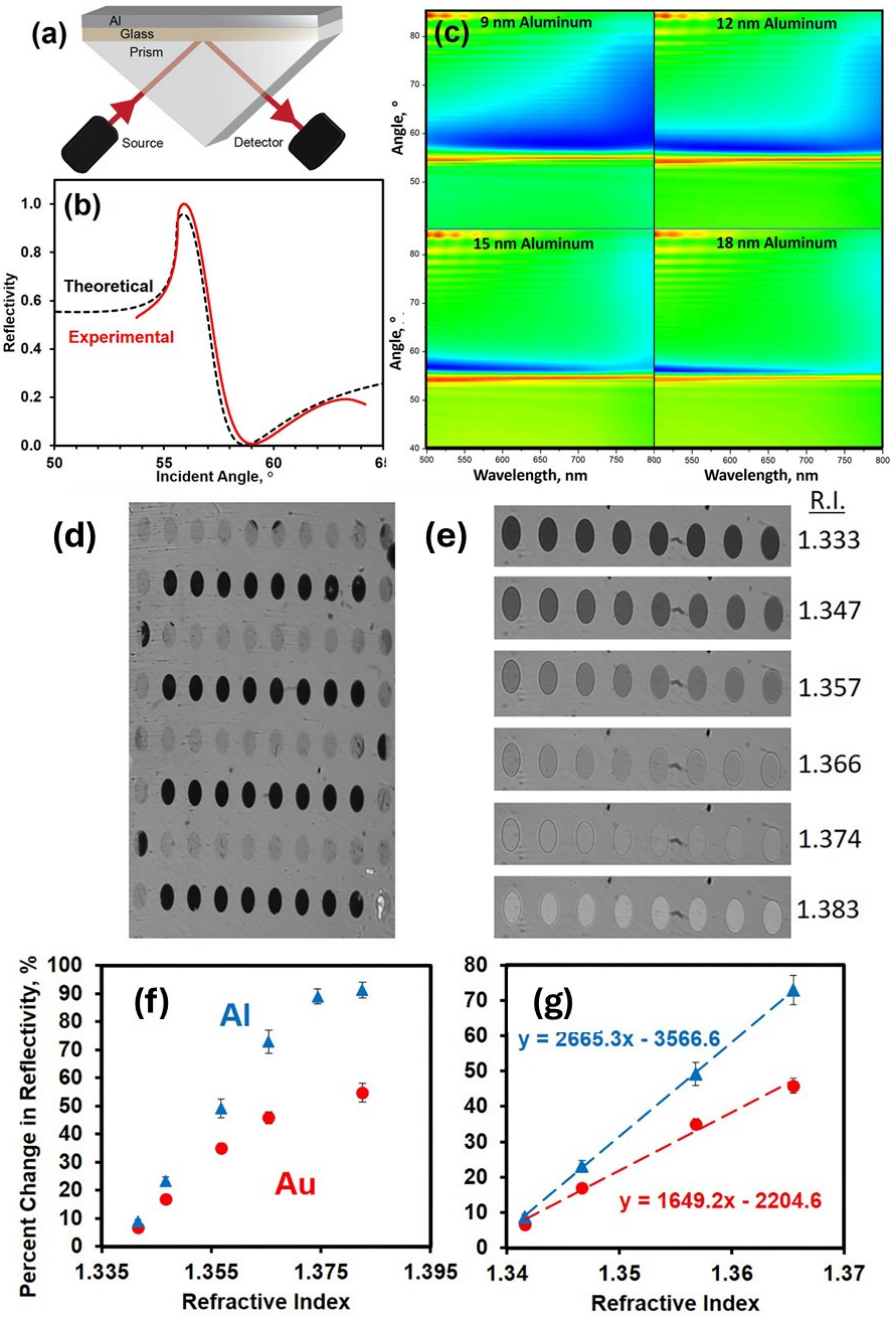

Figure 2. (a) Krestchmann configuration SPR with aluminum thin films. (b) Comparison between the theoretical calculated optical response and experimentally collected response to plasmon excitation. (c) Theoretical optimization of aluminum thin film thickness based upon wavelength. (d and e) Aluminum thin film microarray with SPR imaging. (f and g) Comparison in the refractive index sensitivity between aluminum and gold. Reprinted with permission from(14).

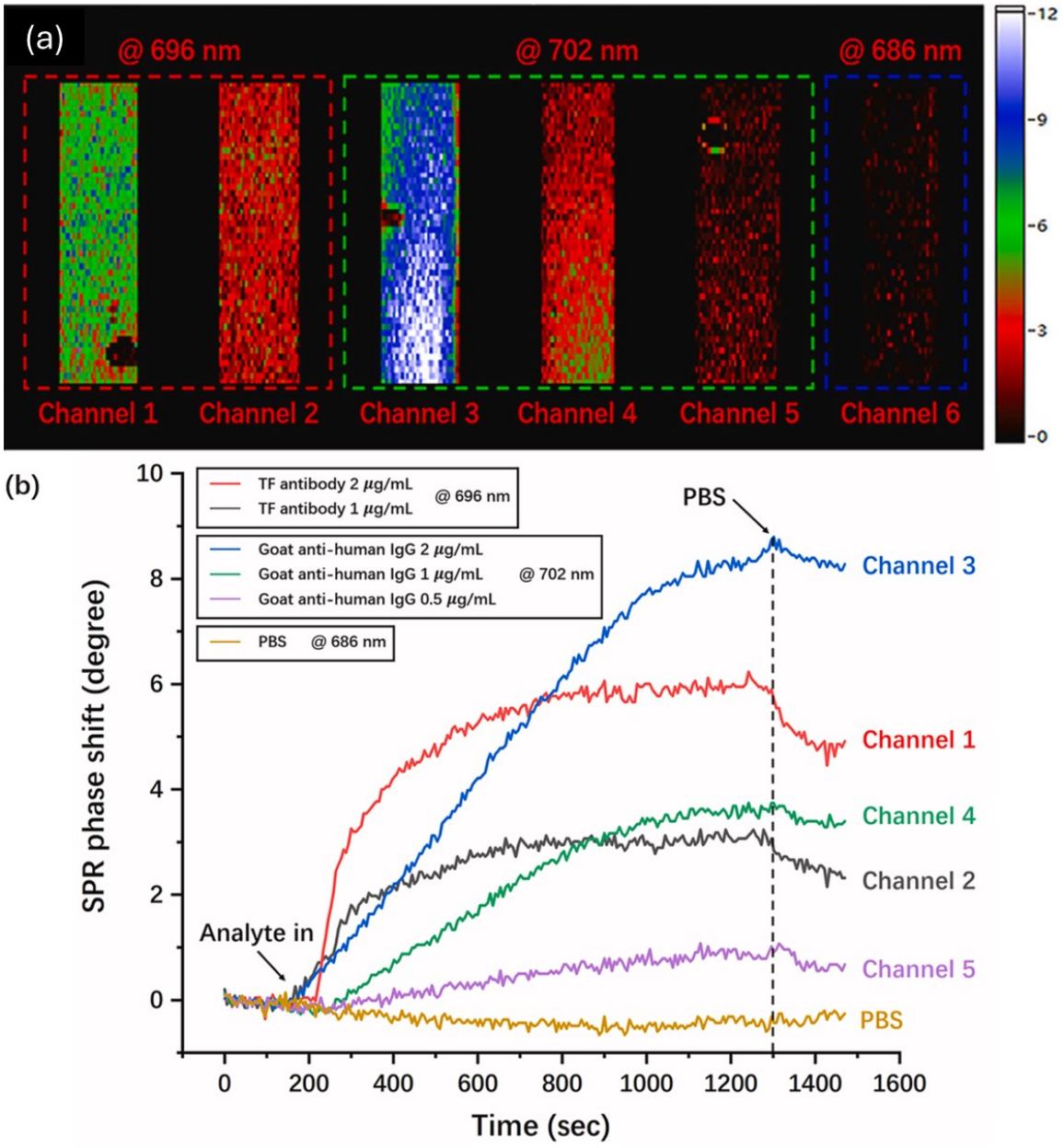

Figure 3. Multi-channel phase interrogation SPRi system with wavelength selection. (a) The optimal wavelength determinization for the six channels. (b) SPR phase shifts observed for different samples TF antibody and goat anti-human IgG. Reprinted with permission from(60).

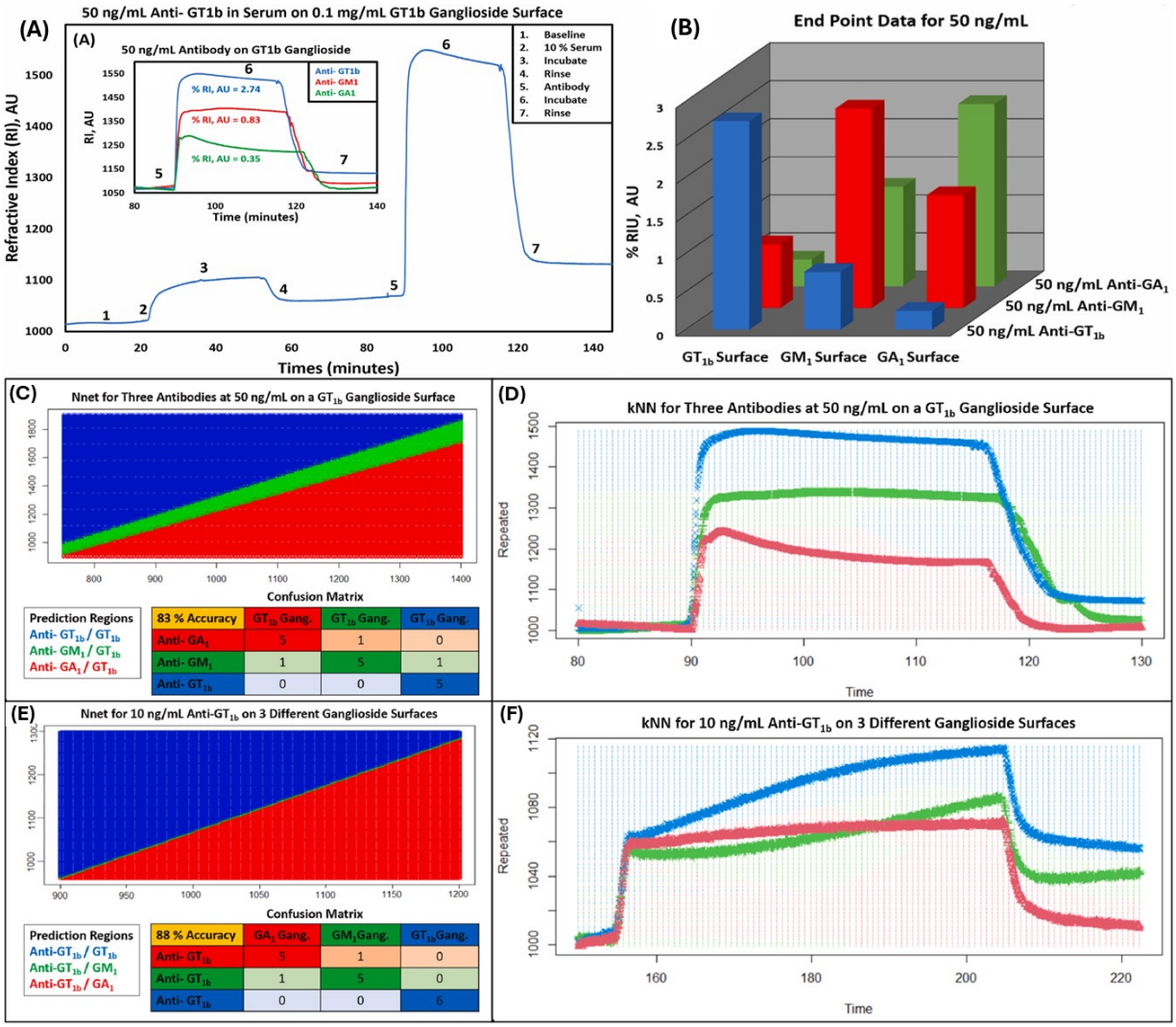

Figure 4. Multiplexed SPR imaging sensor for detection of multiple sclerosis antibodies with a ganglioside array. (A) Representative SPRi sensorgrams of surface setup and binding of three different antibodies to a GT1b ganglioside surface. (B) The column plot of the binding signal for corresponding antibodies on three different ganglioside surfaces (GA1, GM1, and GT1b). (C&E) Neural network analysis used to identify ganglioside-antibody interactions based on SPR data. (D&F) K nearest neighbor models trained on whole sensorgrams for classification based on antibody or ganglioside. Reprinted with permission from(35).

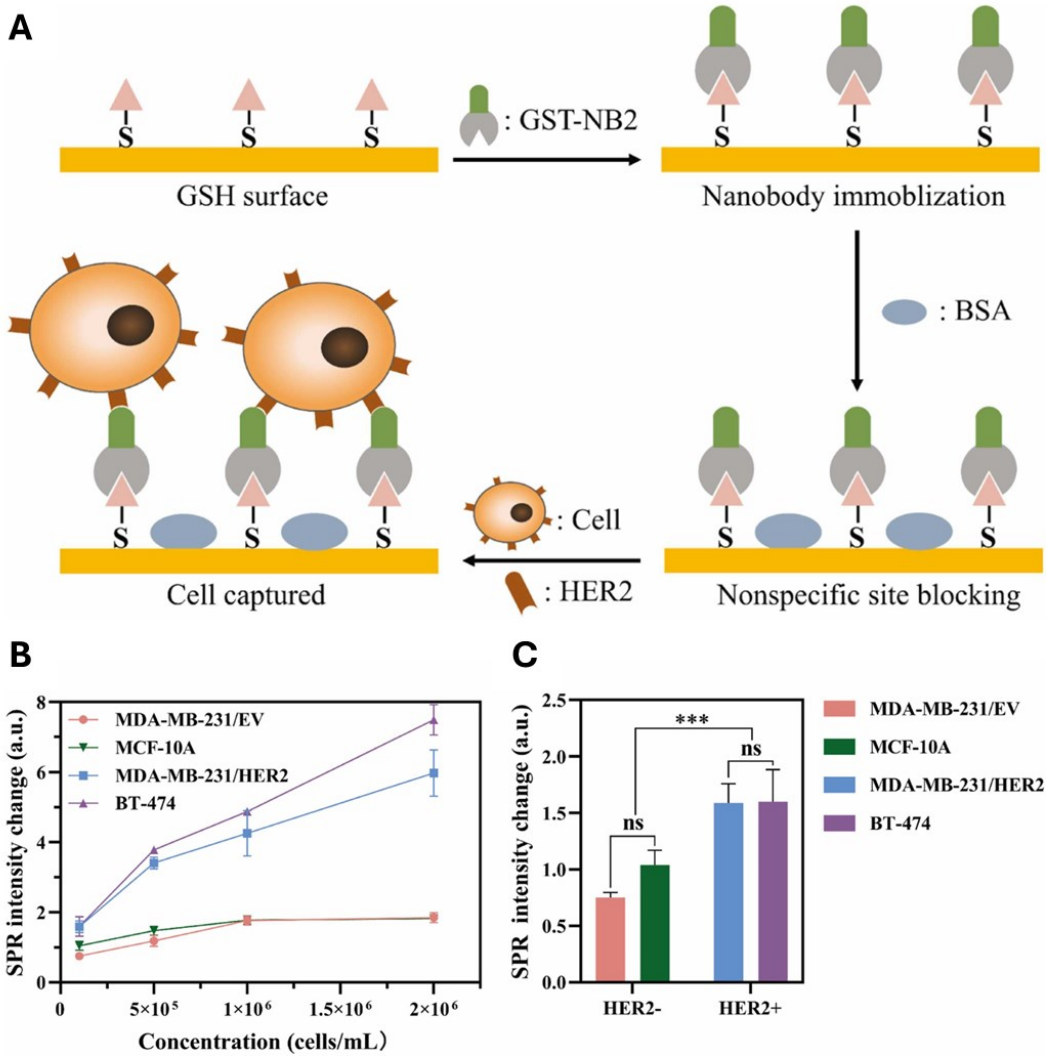

Figure 5. (A) Scheme of SPR sensors for binding of cancer cells based on immobilized nanobodies. (B&C) SPR results for HER2- and HER2+ cells that show specific capture and detection of HER2+ cells. Reprinted with permission from(75).

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