Advanced Nanoporous Anodic Alumina-Based Optical Sensors for Biomedical Applications

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Close-packed hexagonal array nanopores are widely used both in research and industry. A self-ordered nanoporous structure makes anodic aluminum oxide (AAO) one of the most popular nanomaterials. This paper describes the main formation mechanisms for AAO, the AAO fabrication process, and optical sensor applications. The paper is focused on four types of AAO-based optical biosensor technology: surface-Enhanced Raman Scattering (SERS), surface Plasmon Resonance (SPR), reflectometric Interference Spectroscopy (RIfS), and photoluminescence Spectroscopy (PL). AAO-based optical biosensors feature very good selectivity, specificity, and reusability.

Keywords: nanoporous, anodic aluminum oxide (AAO), self-ordering anodization, Optical biosensor, Detection

INTRODUCTION

Al, the third most abundant element and the most abundant metal, makes up about 8% of the Earth’s crust. Taking advantage of its reactivity with naturally occurring oxygen in the atmosphere, Sir Humphrey Davy, physicist Hans Christian Ersted, and Karl Bayer were able to refine and improve the manufacturing of alumina from bauxite ore (Poinern et al., 2011). Today, Alumina (Al₂O₃) is widely used in many applications and has become the most widely produced non-ferrous metal (United States Geological Survey, 2011).

In the mid 1920s, anodization using Al in chromic acid was developed (HM Wire International Inc. 2010). The oxide structure consists of two distinct layers. The first forms a non-porous barrier layer, while in the second a thicker, porous oxide structure, an anodic aluminum oxide layer, is formed. The porous nature of anodic alumina films was discovered by S. Setch and A. Miyatain in 1932 (Setoh and Miyata, 1932) and further characterized by F. Keller’s group in 1953 (Keller et al., 1953) and J. P. O’Sullivan’s group in 1970 (O’Sullivan and Wood, 1970). In 1974, the Boeing Company used chromic acid, sulfuric acid, or phosphoric acid in producing anodic aluminum oxide membranes (Smith, 1974). Because of AAO’s uniform nanostructure, it began to attract interest during the late 1980s in the area of nanotechnology. In the mid-1990s, AAO was applied for bottom-up templated nanofabrication (Masuda and Fukuda, 1995; Masuda et al., 2001). Oxide layers generated during anodization can also be produced on materials such as niobium (Nb) (Lu et al., 2005; Sieber et al., 2005; Stróz et al., 2019; Altomare et al., 2020), silicon (Si) (Xia et al., 2000; Rodriguez et al., 2005; Formentín et al., 2015; Elia et al., 2016), tantalum (Ta) (Sieber et al., 2006; Barton et al., 2009; Wei et al., 2009; Yu et al., 2013; Wang et al., 2015; Fialho et al., 2020), titanium (Ti) (Kim et al., 2014; Zheng et al., 2014; Nguyen et al., 2017; Anitha et al., 2018), etc.

Since 2000, AAO has become more popular, both in research and in industrial fields such as biosensing, bio-detection, drug delivery, etc (Pan et al., 2003; Vlassiouk et al., 2004; Takmakov et al., 2006; Flamme et al., 2007; Yang et al., 2007; Alvarez et al., 2009a; Wang et al., 2001). AAO-based optical biosensors are widely used in broad range of fields. The four optical methods most commonly
used in AAO are: surface-Enhanced Raman Scattering (SERS), surface Plasmon Resonance (SPR), reflectometric Interference Spectroscopy (RIfS), and photoluminescence Spectroscopy (PL). In this review, we will first introduce the structure and fabrication process of AAO, then illustrate several main formation models for the origin of pore nuclei and the exact mechanism of pore nucleation, and finally discuss AAO-based optical biosensor applications.

FACTORICATION, STRUCTURE AND FORMATION MECHANISMS OF AAO

Fabrication of AAO

During the mid-1990s, Masuda, H’s group, fabricated AAO using 0.3 M chromic acid at 0°C and with 40 V applied voltage for 160 h anodization time, resulting in the type of highly ordered AAO shown in Figure 1A (Masuda and Fukuda, 1995). In further research, Masuda and Fukuda developed the two-step anodization process (Masuda and Fukuda, 1995). In the first step, thick aluminum plates are placed in acidic solution for 2–24 h to form a nonuniform nanoporous structure, enabling propagation and self-organized growth of cylindrical nanopores from top to bottom during the course of the second anodization step. Samples are rinsed in DI water and dipped in an etching mixture of H₃PO₄ and chromic acid (H₂CrO₄), removing the oxide layer formed during the first anodization and leaving weak points at the Al plated surface for the second anodization carried out using similar apparatus. Table 1 (Poinern et al., 2011) shows the major acid components used to produce AAO.

This fabrication process can be performed using commonly available laboratory equipment (Figure 1B; Poinern et al., 2011). A dual-wall container is first prepared with acid and cooling water used in the anodization process, with a cooling system connected to an RF machine for cooling water to a temperature of 2°C–8°C, after which an acid solution functioning as an electrolyte is poured into the container. Most researchers tend to use oxalic, phosphoric, and sulfuric acid, etc. (Santos et al., 2013a). Two working electrodes, aluminum as the anode and platinum as the cathode, are needed during the anodization process. A rectifier is used to apply a DC voltage across the two electrodes, and the Al is gradually anodized to form a nanoporous structure. As shown in Figures 1A,C stirring bar and magnetic stirrer at the tank bottom are used to ensure uniformity of the acid concentration and assure a smooth and stable anodization process.
There are other methods to obtain ordered alumina porous membranes. One uses a SiC single-crystal wafer as a mold with a hexagonally ordered array of convexes to generate an array of concavities on the surface of Al (Masuda et al., 1997), followed by immersion in an oxalic acid solution under constant-voltage conditions with Al anodization. The result confirms that the predetermined pattern formed by mechanical deformation can act as asset of initiation points and guide the growth of channels in the oxide film. While this method can fabricate a long-range-ordered channel array with a high aspect ratio, it involves significantly high preparation costs and a complex process.

Self-ordered AAO can be described as close-packed arrays of hexagonally arranged cells. Several parameters define the AAO structure (Anglin et al., 2008). First, pore density describes how many pores exist per $\text{cm}^2$, with porosity defined as the percentage occupancy of pores over an AAO surface, normally ranging from 5–50%. Pore diameter ($d_p$) usually lies between 10 and 400 nm. Interpore distance ($d_{int}$) is the distance between the middle points of two neighboring nanopore walls (50–600 nm), and pore length ($L_p$) is the thickness of the AAO layer ($\tau_{obl}$), typically ranging between 10 and 150 nm. Figure 1B shows a typical AAO structure (top and cross-section).

All AAO parameters can be precisely adjusted by controlling the anodization process (Losic and Losic, 2009; Santos et al., 2011). A variety of acids can be used in the anodization process to produce different nanopore diameters, and some experiments have used a combination of acids for this purpose. Table 1 shows the major acid components used to produce AAO. There are four types of porous anodization processes: mild anodization (MA), hard anodization (HA), pulse anodization (PA), and cyclic anodization (CA), and most experiments have used the MA process at moderate voltages and temperatures. Various studies have described use of aqueous solutions of sulfuric acid ($\text{H}_2\text{SO}_4$), oxalic acid ($\text{H}_2\text{C}_2\text{O}_4$) and phosphoric acid ($\text{H}_3\text{PO}_4$) as electrolytes for an anodization process at voltages of 25, 40, and 195 V, respectively (Alkire et al., 2008; Lee et al., 2008; Losic et al., 2009; Santos et al., 2011; Lee and Park, 2014).

Table 2 shows some of the voltage settings and times used in the fabrication of a nano-porous oxide layer (Poinern et al., 2011). In this section, while we present a AAO fabrication process

### Table 1 | Major acid components of typical electrolyte types used to produce porous oxide layer on an aluminum substrate (Poinern et al., 2011).

| Main acid used in electrolyte | Molecular formula | Concentration (M) | Pore size Range (nm) |
|------------------------------|-------------------|------------------|---------------------|
| Acetic                       | $\text{CH}_3\text{CO}_2\text{H}$ | 1                | Not specified       |
| Citric                       | $\text{HO}_2\text{CO}_2\text{H} \cdot (\text{OH} \cdot \text{CO}_2\text{H} \cdot \text{CH}_2\text{CO}_2\text{H})$ | 0.1 to 2         | 90 to 250           |
| Chromic                      | $\text{H}_2\text{CrO}_4$ | 0.2 to 0.44      | 17 to 100           |
| Glycolic                     | $\text{HO}_2\text{CrO}_4$ | 0.15 to 0.3      | Not specified       |
| Malic                        | $\text{HO}_2\text{CH}_2\text{OH} \cdot \text{CO}_2\text{H}$ | 0.1 to 0.3       | Not specified       |
| Malonic                      | $\text{H}_2\text{CO}_2\text{H}_2$ | 0.2 to 0.5       | 20 to 80            |
| Oxalic                       | $\text{H}_2\text{PO}_4$ | 0.04 to 1.1      | 30 to 235           |
| Phosphoric                   | $\text{H}_2\text{SO}_4$ | 0.18 to 2.5      | 12 to 100           |
| Tartaric                     | $\text{HO}_2\text{CH} \cdot (\text{OH} \cdot \text{CO}_2\text{H})$ | 0.1 to 3         | Not specified       |

### Table 2 | Voltage and times of three commonly used electrolytes for the production of porous oxide layer on an aluminum substrate.

| Acid      | Concentration (M) | Voltage (volts) | Pore size (nm) | Time (hours) |
|-----------|-------------------|----------------|---------------|--------------|
| Oxalic    | 0.25              | 60             | 75            | 8.8 variable |
|           | 0.3               | 40             | Not specified | 8, variable  |
|           | 0.3               | 40             | 80            | 10.5 min     |
|           | 0.3               | 40             | 50            | 3.8          |
|           | 0.3               | 60             | 80            | 40 min,2 variable |
|           | 0.3               | 40             | 40–50         | 8.10         |
|           | 0.3               | 40.50          | 20.35         | 8.10         |
|           | 0.3               | 30             | 40            | 8.10         |
|           | 0.4               | 40             | 50            | 12,4,8,12 and 16 |
|           | 0.5               | 50             | 80            | 12,4,8,12 and 16 |
|           | 0.3               | 40             | 22            |              |
| Phosphoric | Not specified     | 195            | 200           | Variable     |
|           | 0.4               | 5 to 40        | 20 to 75      | 1 step/variable |
|           | 0.4               | 80             | 80            | 1 step       |
|           | 0.42              | 87 to 117      | 64 to 79      | 1 step/variable |
| Sulfuric  | 0.5               | 18             | 70            | 4, variable  |
|           | 0.42              | 15 to 25       | 13 to 27      | 2 step/variable |
|           | Not specified     | 12,25,40       | 25,60,100     | Not specified |
|           | 0.3               | 25             | 20            | 12,4,8,12 and 16 |
prepared by electrochemical anodization of aluminum, there are many other fabrication methods, as described in another review paper by Rath and Theato (Rath and Theato, 2020).

**AAO Formation Mechanisms**

**Thermodynamics and Kinetics**

It is well-known that the presence of oxygen is advantageous when aluminum is used to produce alumina, even at room temperature. For an Al-water system, 6 reactions are known to occur:

\[
\begin{align*}
2\text{Al} + 3\text{H}_{2}\text{O} & = \text{Al}_2\text{O}_3 + 6\text{H}^+ + 6\text{e}^- , \\
\text{Al}^{3+} + 2\text{H}_2\text{O} & = \text{AlO}_2^- + 4\text{H}^+ , \\
2\text{Al}^{3+} + 3\text{H}_2\text{O} & = \text{Al}_2\text{O}_3 + 6\text{H}^+ , \\
\text{Al}_2\text{O}_3 + \text{H}_2\text{O} & = 2\text{AlO}_2^- + 2\text{H}^+ , \\
\text{Al} & = \text{Al}^{3+}3\text{e}^- , \\
\text{Al} + 2\text{H}_2\text{O} & = \text{AlO}_2^- + 4\text{H}^+ + 3\text{e}^-. 
\end{align*}
\]

These equations determine the nature of the electrochemical reactions occurring in nature (reactions (Eqs. 1, 5, 6)). If the reaction is chemical in nature, it is determined by the Gibb’s free energy (reactions Eqs. 2–4). Different reaction equations can also occur if different acidic and basic solutions are used during the fabrication process. Reaction (Eq. 1) can be described as \(\text{Al}_2\text{O}_3\) grown thermodynamically in weak acidic and basic solutions, with a barrier layer known to grow under these conditions (Young, 1961; Diggle et al., 1969; Scully, 1983; Despić and Parkhutik., 1989). Reaction (Eq. 6) represents the anodization process that occurs in a strong acid such as perchloric acid through a process called electropolishing, involving Al dissolving into the solution (Despić and Parkhutik., 1989). If the anodization process uses mildly acidic solutions such as oxalic and sulfuric acids, porous alumina grows as a result of anodization (Young, 1961; Diggle et al., 1969; Scully, 1983; Despić and Parkhutik., 1989), where it is widely believed that a combination of the oxidation reaction (Eq. 1) and the Al dissolution reaction (Eq. 6) occurs (Diggle et al., 1969).

An anodic oxide grows simultaneously at both interfaces through ionic (\(\text{Al}^{3+}\) and \(\text{O}^{2-}\)) transport, and the most important electrolyte-related factor is its capability for maintaining a significant flow of \(\text{Al}^{3+}\) ions from the metal substrate into the electrolyte. There are two ways to achieve this goal: electrical-field-driven direct expulsion of ions, and dissolution of the forming oxide layer. \(\text{Al}^{3+}\) ions initially migrate from the metal substrate through the metal/oxide interface to the oxide layer, while \(\text{O}^{2-}\) ions from the water pass through the oxide/electrolyte interface into the oxide layer. At this stage, approximately 70% of the \(\text{Al}^{3+}\) and the \(\text{O}^{2-}\) ions form a barrier layer, while the remaining \(\text{Al}^{3+}\) ions dissolve into the electrolyte. The barrier layer then is transformed into a semi-spherical oxide layer of constant thickness that forms the pore bottom. Figure 2A is a schematic diagram of pore formation mechanism in an acidic electrolyte (Poinern et al., 2011).

The chemical reaction equation for Al anodization is:

\[
2\text{Al} + 3\text{H}_2\text{O} \rightarrow \text{Al}_2\text{O}_3 + 3\text{H}_2 \quad \begin{cases} 
6\text{H}^+ + 6\text{e}^- \rightarrow 3\text{H}_2 \\
2\text{Al} + 3\text{O}^{2-} \rightarrow \text{Al}_2\text{O}_3 + 6\text{H}^+ \\
2\text{Al}^{3+} + 3\text{H}_2\text{O} \rightarrow \text{Al}_2\text{O}_3 + 6\text{H}^+ 
\end{cases}
\]

(7)

The electric field at the base of the hemispherically shaped pores can force both \(\text{Al}^{3+}\) migration through the barrier layer and \(\text{O}^{2-}\) and \(\text{OH}^-\) migration from the metal/oxide interface into the pore base oxide layer, as shown in Figure 2A, explaining how the electric field can influence the size of the pore diameter. If the electric field is too small, there are not enough \(\text{Al}^{3+}\) ions to pass through the barrier layer, so there is less nanopore-forming reaction. The film growth rate is determined by each kinetic step and various authors have proposed anodic oxide growth models (Diggle et al., 1969; Lohrenigel, 1993; Zhang et al., 1998). The kinetics of Al anodization can also be described either with a high-field conduction model or the Güntherschultz-Betz (G-B) equation:

\[
\begin{align*}
\frac{\partial j_i}{\partial t} &= - \beta \frac{E}{j_i} \\
\beta &= \text{temperature-dependent parameters}
\end{align*}
\]

Here, \(j_i\) is the ionic current density due to the ion species \(i\), \(j_0\) and \(\beta\) are temperature-dependent parameters, and \(E\) is the electric field across the oxide. In general, the nanoporous oxide layer...
consists of a thin nonporous oxide layer continually regenerated at the base of the pore, with the pore wall increasing in height with time as it is being created.

During the fabrication process, both pore size and distance between pores are functions of the acid concentration, the anodic voltage, and the temperature. The nanopore diameter is the key parameter determining AAO’s performance, especially AAO used as an optical biosensor (Tinsley-Bown et al., 2000; Kazuhiro et al., 2010; Kumeria and Losic, 2012; Kant et al., 2014). In their initial work, Macias et al., fabricated AAO with three different pore diameters to detect serially dosing protein A, human IgG, and anti-human IgG using RIFS, with results that revealed no significant difference in optical signal shift observed when using nanopore diameters of 32 ± 4 nm, while the optical signal shift increased when the concentration of protein was increased using larger pore diameters (50 and 73 nm) (Macias et al., 2015). Another experiment has also demonstrated that the nanopore diameter should greater than 50 nm for efficient binding of both the detector and capture antibody (Tinsley-Bown et al., 2000). When pore diameters are too small, they can hinder protein diffusion inside the structure, and the limit of detection (LOD) for detecting theophylline using larger pore diameter (50 nm) is much lower than when using 10 nm AAO (Feng et al., 2018). These results indicate that the limit of detection of the nanopore sensors can be optimized by varying the nanopore size.

Pore-formation Mechanisms

The origin of pore nuclei and the exact mechanism of pore nucleation are still debated, with several formation models proposed (Hoar and Mott., 1959; Thompson et al., 1978). The first detailed AAO mechanism was investigated by Keller, et al. During the anodization process, high current initially flows through the Al plates and oxide forms rapidly; after a short time, current decreases to a relatively low steady state during which a “barrier” or “blocking” type of oxide coating is formed. At the same time, solvent action by electrolyte begins to occur, the thickness of the barrier layer is reduced, and the electrolyte temperature rises. The solvent action also forms a single point of oxide because current flow, heating, and solvent action will be localized and the pore enlarge in proportion to the amount of metal consumed, resulting in a hexagonal pore shape. Keller described two types of oxide that can be produced, a barrier layer and a nano-porous oxide layer. Akahori suggests a new assumption for describing the AAO film-growth mechanism; after the barrier layer and point are formed, the temperature at the bottom of the point is higher and the electrolyte would tend to evaporate, causing the aluminum to be dissolve. The O\(^{2-}\) at the bottom would then go through the oxide layer and react with liquid state aluminum, suggesting that the barrier layer is composed of both Al\(_2\)O\(_3\) and Al.

Hoar and Mott in 1959 first proposed the field-assisted dissolution model (Hoar and Mott, 1959). In that model, once the cell voltage drops, both proton passage into the barrier layer against the field and the dissolution rate of Al\(_2\)O\(_3\) are greatly enhanced. As shown in Figure 2B, the electric field increases at the pore bottom and the oxide dissolution rate also increases. Specifically, the Al\(_2\)O\(_3\) at the oxide/electric interface is spontaneously decomposed to Al\(^{3+}\) and \(\bar{O}^{2-}\) in contact with acids, and the \(\bar{O}^{2-}\) ions react with \(H^+\) to become OH\(^-\) ions in the acid that are transported to the metal/oxide interface by the high electric field to form new oxide at the metal/oxide interface. At this time, since Al\(^{3+}\) goes into the solution, pore depth begins to form, and during porous film formation, the barrier layer becomes slightly thinner. Once the first pore has been formed, a second pore would form at the edge of the first at the point where the heating effect is largest. O’Sullivan and Wood in 1970 present a more detailed description of the electrochemical dissolution reaction (Diggle et al., 1969; O’Sullivan and Wood, 1970; Cherki and Sieika, 1973) explaining why pores grow at all and why their size distribution is quite narrow.

These models show that the formation mechanism of alumina is not very clear except that it includes a dynamic process involving ions, and formation of a self-organized nanopore array has not been thoroughly explained. The main models used to explain this formation mechanism are a volume-expansion model (Jessensky et al., 1998) and a dielectric breakdown model (Su et al., 2012).

In 1998, Jesenskey’s group (Jessensky et al., 1998) proposed a new model, a volume-expansion model, to explain conditions leading to self-organized formation of ordered hexagonal structures in anodic alumina. Once the porous oxide has grown, since the atomic density of aluminum in alumina is lower than in metallic aluminum, mechanical stress will be generated at the metal/oxide interface through alumina formation, and this mechanical stress may cause a force between neighboring pores. Since the oxide is simultaneously formed at the metal/oxide interface, the material can only expand in the vertical direction, so existing pore walls are pushed upward. After the oxide has formed, alumina volume is larger than that of metallic aluminum, so volume expansion during oxide growth causes repulsive forces between neighboring pores during the oxidation process. To minimize the energy of the whole system, nanopores will form into self-organized hexagonal pore arrays. The model also demonstrates that the oxidation rate of aluminum, the volume expansion, the thickness of the alumina strongly depends on the anodizing voltage and which electrolyte is used.

Su’s group (Su et al., 2012) in 2012 described another model, the dielectric breakdown model. That study compared the formation mechanism of anodic aluminum oxide to that of anodic titanium oxide and also explained the formation of nanopores and nanotube anodic metal oxides shown in Figure 3. It has been suggested that the degree of localized dielectric breakdown, mainly determined by the dielectric strength and energy band gap of the anodic oxide, the electrolyte used, the anodizing field, and the temperature during anodization, has a significant effect on pore formation. During the anodization process, because of continuous dielectric breakdown, oxygen voids can grow and accumulate at the oxide/metal interface. If there is a sufficiently high degree of localized dielectric breakdown due to a large anodizing field, high temperature, or low dielectric strength of the resulting oxides, the dominant dielectric breakdown may occur at the oxide/metal
interface, possibly producing large enough voids at inter-pore area to cause pore separation.

**OPTICAL BIOSENSORS BASED ON AAO**

Because of their porous architecture, use of nanoscaled materials as become more and more popular in various fields of research. For example, AAO can be used to produce optical sensing active or passive platforms with capability for guiding, reflecting, absorbing, transmitting, emitting, confining, or enhancing incident optical waves emitted by a source. During the previous decade, the use of nanomaterials as optical sensing platforms has made it possible to develop optical sensing systems with outstanding capabilities and performance in terms of sensitivity, selectivity, versatility and applicability. Some examples of optical techniques successfully combined with nanomaterials are surface-enhanced Raman spectroscopy (SERS), surface plasmon resonance spectroscopy (SPR), localized surface-plasmon resonance spectroscopy (LSPR), reflectometric interference spectroscopy (RIFS), and photoluminescence (PL), summary shows in table 3.

**Surface-Enhanced Raman Scattering**

Surface-enhanced Raman scattering spectroscopy is an ultra-sensitive optical technique based on enhancement of the Raman scattering that takes place when biomolecules are absorbed on metal film surfaces featuring nanostructured roughness (Le Ru et al., 2007; Lee et al., 2011; Kumar, 2012; Gandhiraman et al., 2014). A SERS-AAO based substrate can be fabricated by sputtering or evaporating a layer of plasmonic materials such as gold or silver nanoparticles (NPs) on either top or bottom surfaces (Huang and Tsai, 2019), achieving remarkable SERS enhancement from “hot spots” (Manikas et al., 2014; Duan et al., 2011; Freeman et al., 1995; kneipp et al., 1997). Other approaches, including metallic membranes, decoration of nanopores with nanoparticles, and growth of nanowires, have also been used to produce AAO-based SERS substrates, (Grimes, 2007; Anglin et al., 2008).

Two theories, viz., electromagnetic enhancement (EM) and chemical enhancement (CM), have been used to explain the exact enhanced mechanism of SERS effect. In general, these two theories work in concert on the substrate, with EM enhancement playing the dominant role in terms of contribution to SERS enhancement. The most convincing explanation in terms of EM enhancement involves a localized surface plasmon resonance effect. When an external electromagnetic wave interacts with free electrons on a metal surface, the collective electrons will oscillate at the junction of the metal surface and the electromagnetic wave. When the oscillation frequencies for the free electron on the metal surface and the electromagnetic wave become equal, surface plasma will be generated. Since the intensity of the Raman signal is proportional to the fourth power of the electromagnetic field intensity, it makes a major contribution to the EF up to $10^4$ – $10^7$ (Li et al., 2010). In CM enhancement, charge transfer complexes are formed between chemical probe molecules and substrates, and CE is enhanced when the excitation frequency comes into resonance with charge transfer transitions (Zhao et al., 2018).

Over the years, SERS-AAO biosensors have become widely used in biomedical research and disease diagnose applications involving biological tissue, DNA, serum, and cancer cells (Su et al., 2019; Yang et al., 2019; Zhou et al., 2019). SERS-AAO biosensors exhibit high selectivity, high sensitivity, real-time sampling, and capability for non-destructive testing.

Zhang et al. used the Lee-Meisel method to fabricate a sandwich structured with silver nanoparticles (SNPs) and silver nanoarrays (Zhang et al., 2011), using this structure to probe molecular series concentrations of resonant (Rhodamine 6G) and non-resonant (melamine) structures. The intensity of the
diagnostic peak of R6G and melamine decreased with decreasing molecular concentration. The limit of detection (LOD) for R6G was $10^{-19}$ M and for melamine was $10^{-9}$ M. The AAO-based SERS sensor for the sandwich structure exhibited excellent reproducibility and good stability and could be used for quantitative analysis. Liu et al. fabricated highly ordered Ag-NPs@Ge nanocap arrays based on an AAO template and a quantitative analysis. Liu et al. fabricated highly ordered Ag-nanoparticles (Ag-NPs) embedded between Ag nanoarrays and Ag NPs (Liu J. et al., 2014). The reproducibility and good stability and could be used for many SERS applications (Yan et al., 2018).

TABLE 3 | The analytical performance of the optical biosensors by using AAO.

| Method                | Sensing substrate                      | Analyte                  | LOD        | Linear range | References                      |
|-----------------------|----------------------------------------|--------------------------|------------|--------------|---------------------------------|
| SERS                  | Au decorated Ag nanobranches           | R6G                      | $10^{-11}$ M | N/A          | Song et al. (2017b)             |
|                       | Au coated polystyrene nanoparticles    | 4-Methyl benzene thiol   | $10^{-9}$ M | $10^{-2}$-10^{-3}$ M | Zhang et al. (2017b)         |
|                       | Ag decorated AAO                      | 4-Mercaptopyridine       | $10^{-9}$ M | $10^{-6}$-10^{-9}$ M | Ji et al. (2009)              |
|                       | Sandwiched substrate (analyte molecules| Melamine                 | $10^{-9}$ M | $10^{-2}$-10^{-4}$ M | Zhang et al. (2011)          |
|                       | embedded between Ag nanoarrays and Ag NPs | Melamine                 | $10^{-9}$ M | $10^{-9}$-10^{-6}$ M | Zhang et al. (2016)        |
|                       | Ag dendrite integrated AAO membrane    | R6G                      | $10^{-11}$ M | $10^{-11}$-10^{-6}$ M | Zhang et al. (2016)          |
| Metallic glassy nanowire arrays | Rhodamine B                           | $10^{-8}$ M             | $10^{-6}$-10^{-9}$ M | N/A          | Liu et al. (2014a)              |
| Ag–AAO NPs arrays      | Adenine                                | $10^{-8}$ M             | N/A        | N/A          | Chen et al. (2017)             |
|                       | Ag-NPs-decorated germanium nanocap arrays | R6G                      | $10^{-11}$ M | $10^{-11}$-10^{-6}$ M | Liu et al. (2014b)          |
|                       | Transparent substrate with Ag-NPs     | Ractopamine residue on pork meat | $10^{-8}$ M | $10^{-4}$-10^{-8}$ M | Yan et al. (2018)            |
|                       | AAO-based multiplex vertical flow assay with Raman dye encoded core–shell -SERS nanotags | CRP                     | 53.4 fg/ml | 3.57-647.01 ng ml^{-1} | Chen et al. (2020)          |
| SPR                   | A gold-deposited AAO substrate        | CRP antigen              | 1 fg/ml   | 1 fg/ml-100 µg/ml | Yeom et al. (2011)             |
|                       | GNRs (gold nanorods)                  | *Escherichia coli* O157:H7 | 100 ag/ml | 100 ag/ml-10^3 cfu/ml | Eum et al. (2010)            |
|                       | Au-capped nanopillar plasmonic biosensor | Human immunoglobulin | 1 ng/ml   | 1 ng/ml-100 µg/ml | Saito et al. (2012)           |
|                       | Gold nano-ellipsoid arrays             | Transmembrane protein CD63 | 1 ng/ml  | 1 ng/ml-10^3 ng/ml | L v et al. (2019)             |
|                       | Gold-capped nanostructures             | IgA                      | 10 ng/µL | 10 ng/µL-500 ng/µL | Ali et al. (2018)             |
|                       | Cyclo-dienyl polymer (COP)             | Cell interleukin-6       | 10 ng/ml | 10 ng/ML-100 ng/ml | Luo et al. (2020)             |
| RIFS                  | Nanoporous thin film                  | Theophylline             | 0.05 µM   | 0.05-48 µM | Feng et al. (2016)             |
|                       | Porous thin film                      | TNF-α                    | 0.13 µg/ml | 100-1500 ng/ml | Rajeev et al. (2018)          |
|                       | Au-coated nanopore thin film          | Salicylic acid           | 0.1 µM    | 0.1-100 µM | Chen et al. (2019)             |
|                       | Au-coated nanopore thin film          | Abscisic acid and salicylic acid | 0.1 µM | 0.1-200 µM | Feng et al. (2020)            |
|                       | Au-coated nanopore thin film          | Insulin, glutamic acid decahydroxylase (GAD) insulinoma associated protein-2 (IA-2) | 0.05 U/ml | 0.1 U/ml-50 U/ml | Mao et al. (2019)             |
|                       | Au-coated nanopores                   | Gentamicin sulfate (GS) | N/A       | N/A         | Song et al. (2017)             |
| PL                    | Au-coated nanopore thin film          | Staphylococcus aureus    | 2 CFU/ml  | 0-2000 CFU/ml | Pia et al. (2020)             |
|                       | Nanoporous anodic alumina             | Cocaine                  | 0.5 µM    | 0.5 µM-1 mM | Ribes et al. (2016)           |
|                       | Nanoporous anodic alumina             | d-glucose                | 0.010 M   | 0-1200 m mo/L | Santos et al. (2013b)         |
|                       | Nanoporous anodic alumina             | l-cysteine              | 0.010 M   | 0-1200 m mo/L | Santos et al. (2013b)         |

The LOD for R6G is $10^{-11}$ M. Zhang et al. described a large-scale Ag dendrite-integrated AAO membrane used as a 3D SERS-active substrate, and advantages of these 3D structure were to generate a special overlap with intense and uniform fields and to provide a large metallic surface (Figure 5; Zhang et al., 2016).

Most of these nanostructured SERS substrates are non-transparent, limiting many SERS applications (Yan et al., 2018). Yan et al. fabricated the transparent SERS substrate based on AAO shown in Figure 6; after the first anodization process was finished, phosphoric acid could be used to etch the AAO template and remove the porous alumina layer, followed by a four-step process of anodization and etching to fabricate conical...
pores with nanotips. A SnCl$_4$ aqueous solution was then used to remove the aluminum, and the template became transparent, after which a Ag-NPs layer was sputtered onto it. Such a transparent SERS substrate can be used to examine analytes in opaque substances such as ractopamine residue on pork. That paper described detecting ractopamine over a range from $10^{-4}$ M – $10^{-8}$ M. Such measurements can directly detect chemicals in opaque media with good specificity and they have potential to measure other trace chemicals on food surfaces.

Point-of-care testing (POCT) is an important diagnostic tool with several key advantages, including rapid data availability, reduced time, small sample volume for a large test menu, and robustness in detection of various biomarkers without false-negative effects (Kim et al., 2017a). Chen and Sailor, 2011 developed the micro-array shown in Figure 4B, an AAO (2 × 2)-based SERS sensor for detecting C reactive protein, interleukin-6, serum amyloid A, and procalcitonin by modifying capture antibodies (Chen et al., 2020). The researcher first immobilized antibodies on a 2 × 2 test array, then dyed encoded core-shell SERS nanotags, Au$_{NBA}$@Ag, Au$_{4-MBA}$@Ag, Au$_{DNTB}$@Ag, and Au$_{MB}$@Ag were used as labels for detection of CRP, IL-6, SAA, and PCT, respectively, subsequently detected using a Raman spectrometer. All four of these inflammatory biomarkers can be detected over a linear dynamic range spanning at least five orders of magnitude, and the authors used different AAO pore sizes (140, 170, 250, 300, 350, and 390 nm) to detect the CRP biomarkers. Based on this experiment, and comparing with respect to SERS intensity, they found that a 350 nm AAO pore size and a 785 nm laser exhibited optimum performance. They finally compared the sensitivity of an AAO membrane to that of an NC membrane for detecting biomarkers, with results showing...
that the AAO membrane could accumulate more immune complexes and reduce non-specific absorption. This experiment illustrated that micro-array AAO-based SERS VFA can be used for multiplexed detection of inflammatory biomarkers with high sensitivity.

Surface Plasmon Resonance

Surface plasmon resonance, whose first application in 1982 was for SPR used in a biologic sensor (Liedberg et al., 1983), is based on generation of surface plasmons from an evanescent electromagnetic wave, a phenomenon that occurs when a light beam is focused on the surface of a prism coated with a thin metallic film. SPR sensors are widely used for detection of biological and chemical analytes, environmental monitoring, and medical diagnostics (Huber et al., 1999), with SPR-based biosensors exhibiting several advantages over other sensing methods. SPR exhibits excellent sensitivity either when the refractive index (RI) changes on the metal-dielectric interface or when molecular interaction occurs, and it can yield real-time kinetics information. Finally, by using defocused laser illumination and a charge-coupled device (CCD) camera as a detector, SPR can measure the intensity distribution in a large surface area with multiple sensing spots; this is called SPR imaging (SPRi).

AAO structures can be used to develop unique SPR sensing systems using localized surface plasmon resonances (LSPR). LSPR can be generated by various nanostructures, including gold nanodisks (Dahlin et al., 2009), nanoshells (Hirsch et al., 2003), nanorings (Larsson et al., 2007), and nanoholes (Rindzevicius et al., 2005) in thin films. In contrast to a SPR, a LSPR does not require a prism or a goniometer, meaning that a LSPR can be used in less complex equipment. Figure 7 depicts the principle of LSPR phenomena and optical interferometry using an antigen-antibody-conjugated AAO chip (Yeom et al., 2011). The light illuminates the sensor, and reflected light from an Au sheet and the bottom of the Al substrate will interfere by interacting with both constructive and destructive interference to form an interference wave (Huang et al., 2011). Equation 9 (Whitney et al., 2005) shows that once a target has been immobilized on the sensor, it will change the effective index of refraction and in turn the effective optical thickness, resulting in changes in the reflected wavelength.

$$\Delta \lambda_{\text{max}} = m \Delta n \left[ 1 - e^{-d/l_f} \right].$$  (9)

In Eq. 9, $\Delta \lambda_{\text{max}}$ is the wavelength shift, $m$ is the refractive index sensitivity, $\Delta n$ is the change in refractive index induced by adsorption, $d$ is the effective thickness of the layer, and $l_f$ is the characteristic length of the electromagnetic-field decay. According to Eq. 9, LSPR can measure small changes in the interfacial refractive index of the AAO surface (Kim et al., 2017b). The most commonly used method to produce AAO-based LSPR systems is to grow a layer of AAO on the surface of a thin Al film deposited on the surface of the prism.

LSPR biosensors have attracted attention over the past decade by offering high sensitivity (Amanda et al., 2004), a small footprint (Chen et al., 2009), and non-chemical labeling (Hammond et al., 2014; Kim et al., 2017c). Capability for spontaneous detection gives the LSPR potential for diagnostic and point-of-care testing (POCT) (Endo et al., 2005; Acimovic et al., 2014; Chen et al., 2015; Oh et al., 2016). While there are many high-quality LSPR reviews (Anker et al., 2008; Jonsson et al., 2008, 2011; Ringe et al., 2013; Cao et al., 2014; Estevez et al., 2014; Kim et al., 2015), in this section we focused on AAO-based LSPR biosensor.

The most common AAO-based LSPR biosensor for detecting CRP antigen was developed by Yeom et al., in 2011 (Yeom et al., 2011), who fabricated a uniform AAO substrate using two-step anodization, then deposited 5 nm Ni and 15 nm Au layers on the AAO surface. The result (Figure 8) shows that reflected spectra from the membrane is shifted in response to variation in CRP antigen concentration; the graph depicts wavelengths between 600 and 780 nm. Increasing the CRP antigen concentration
induces incremental increases in intensity, and the wavelength shifts with the reflectance spectra increasing as the log of antigen concentration, offering a large dynamic range and high sensitivity for quantitative detection of CRP antigen, with the $\lambda_{\text{max}}$ of reflectance wavelength shifting dramatically with variations in CRP antigen concentration (from 1 fg/ml to 100 $\mu$g/ml). To improve sensitivity, the group employed a sandwich assay method (Eum et al., 2010) using a GNP-labeled antibody for the sensor system (Yeom et al., 2013); the sensitivity of the sensor increased by 1.84 times and an LOD for a CRP antigen concentration of 100 ag/ml.

Saito et al. (Saito et al., 2012), developed an AAO-based LSPR biosensor to detect Human immunoglobulin. They used nanoimprint lithography (NIL) molds to fabricate two types of
AAO, then transferred the AAO to a Cyclo-olefin polymer (COP) film surface, followed by sputtering a thin layer of gold onto the structure. A uniformly distributed Au-NPs structure that could enhance the signal-to-noise ratio by reducing the nonspecific binding was fabricated. The detection limit for IgG was 1.0 ng/ml. In a further study, a microwell array and a nanopillar structure were integrated into a single substrate to enhance the device’s biosensing capability, resulting in a detection limit for anti-IgA of 10 ng/μL (Ali et al., 2018). To improve biosensor sensitivity, the same group fabricated a COP-based LSPR sensor chip with a dense concave-convex nanostructure for generating “hotspots” on the surfaces of metallic nanoparticles (MNPs) (Luo et al., 2020), with an uneven nanostructure on the rough surface of the nanopillar fabricated by plasma etching (Kondyurin et al., 2006; Luo et al., 2020; Ting et al., 2010; Vesel and Semenic, 2012). Experiments detecting the cell cytokine indicated that the refractive index sensitivity was improved by the longer plasma etching time (Beeram and Zamborini, 2011; Ding et al., 2017; Luo et al., 2020).

A low-cost AAO-base LSPR biosensor was described by Lv’s group in 2019 (Lv et al., 2019). They fabricated the nano-ellipsoid arrays combined with the microfluidic chip shown in Figure 9 to detect the anti-CD63 antibody. Different refractive index solutions (air, water, 1 M glucose, ethanol, and NaCl) were used to test the responses of the biosensor, with results indicating that the red shift of the extinction spectra was increased due to the refractive index of the sample. Different concentrations of exosomes were also detected, and the peak wavelength of the anti-CD63 antibody spectra increased as the exosome concentration increased. The detection limit was 1 ng/ml.

**Reflectometric Interference Spectroscopy**

For various AAO dimensions, geometries, and chemical compositions, AAO structures exhibit characteristic responses when they interact with light. Many studies have described applications of AAO to surface profiling (Madani-Grasset et al., 2008; Debnath et al., 2009), metrology (Maniscalco et al., 2014), optical and chemical biosensors (Brecht et al., 1995), refractive index measurements for thin films (Buron et al., 2006), and many others (Jiang and Gerhard, 2001; Kim et al., 2007; Carter et al., 2011; Kaur et al., 2019). The RIFS spectrum of AAO produces fringes with well-resolved peaks generated by the Fabry-Perot effect (Alvarez et al., 2009a; Kuncser et al., 2011; Kumeria et al., 2012), whose equation is:

\[
OT_{\text{eff}} = 2n_{\text{eff}} \cdot L \cdot \cos \theta = m \lambda,
\]

where \(n_{\text{eff}}\) is the effective refractive index of AAO, \(L\) is the pore length (Ihmels et al., 2018), and \(m\) is the order of the RIFS fringe whose maximum is located at wavelength \(\lambda\). Such peaks in the RIFS spectrum are useful for sensing because the binding molecules on the surface’s inside pores will change the effective index of refraction and in turn change the effective optical thickness, causing a shift in the number of reflected interface fringes (Alvarez et al., 2009b).

Feng et al., focused on AAO-based RIFS biosensors for detecting plant chemicals, using AAO as an aptamer-based nanopore thin film sensor for detecting theophylline in a buffer solution and in complex fluids that included plant extracts and serum samples (Feng et al., 2018). Experimental results showed that the aptamer sensor not only exhibited good specificity and selectivity, but also had reasonable reusability with a significantly improved dynamic-detection range. Using ∼1 μL plant extract or serum samples, the detection limit for theophylline was 0.05 μM. Low cost and ease of operation make this type of sensor suitable for point-of-care application in monitoring patient theophylline levels in real time. Such a biosensor also can also be used to detect tumor necrosis factor-alpha (TNF-α) in buffer solution and in complex media (simulated wound fluid) using anti-TNF-α antibodies (Rajeev et al., 2018). Based on the detection principle for the RIFS, when the TNF-α has reacted with anti-TNF-α antibodies, the effective optical thickness (EOT) of the AAO thin film will change. TNF-α detection is achieved by monitoring EOT evolution with time, with a detection limit of 0.13 μg/ml.

AAO nanopore structure also has potential for plant hormone detection. For example, plantaptamer (DNA) identification has been achieved using a AAO nanopore structure integrated within a microfluidic device (Chen et al., 2019). That paper introduced a structure-switching aptamer-based nanopore thin-film sensor developed for cost-effective, rapid,
sensitive, and simple detection of SA in both buffer and plant extracts. A high-affinity SA aptamer was identified by immobilizing the SELEX library rather than the SA and by screening the library using a structure-switching SELEX approach. This nanosensor also exhibited good selectivity with respect to SA and its common metabolites. The performance of the AAO-based aptamer biosensor was statistically indistinguishable from that of HPLC.

To rapidly and efficiently detect various plant hormones, Feng et al. (Feng et al., 2020), developed a new chip equipped with aptamer-based sensors interfaced with capillary microfluidics suitable for screening and detecting hormones in plant samples (Figure 10). Using this type of sensor, even if the hormones inside the sample are unknown, the sensor can screen or determine which type of plant hormones are in the samples. In this experiment, only an abscisic acid (ABA) aptamer and salicylic acid (SA) aptamer were functionalized on the sensor and they detected unknown samples containing ABA, SA, auxins, cytokinins, and gibberelline. The AAO-based RIFS biosensor exhibited high sensitivity, specificity, and reusability, offering a new cost-effective platform for potentially distinguishing and screening different plant hormones in raw plant samples.

Another multiplexed detection approach for detecting autoantibodies for Type 1 diabetes (T1D) panels was reported by Mao et al. (Mao et al., 2019). Their chip (Figure 11A,B) could simultaneously detect three autoantibodies in serum by functionalizing three different antigens (insulin, GAD, IA-2) on the sensors. These three autoantibodies were applied through Inlet 3, Inlet 4, and Inlet 5, so that each row had 3 sensors for use in detecting one autoantibody. Their results indicated that the optical signal increases with increased concentration of the three autoantibodies, and the detection limit for these three autoantibodies was 0.05 U/ml.

Chao et al. (Song et al., 2017), reported drug loading and release enabled by the AAO nanopore thin film and layer-by-layer (LBL) nanoassembly shown in Figure 11C–E. In this experiment, gentamicin sulfate (GS), poly (acrylic acid) (PAA), and chitosan (CHI) were applied to the Au-coated AAO thin film device, followed by a [PAA/GS/PAA/CHI] combination applied ten times, representing a total of forty layers of chemicals deposited onto the nanopore thin film surface. During the drug-release process, the sample was immersed into flowing DI water and reflectance signals were used to measure the deposition of each chemical layer and the release procedure. During the loading process, the wavelength decreased (peak blueshift) during loading of the first two layers, but once the nanopore had been filled with chemicals, the chemicals can only deposit on the AAO surface, leading to a red shift. During the release process, the wavelength exhibited a blue shift. The peak shift was a red shift rather than a blue shift, suggesting that the chemicals/drug stored inside the nanopores were initially released into the DI water. Two different sizes of nanopore are were used in this experiment, and the results showed that drug release time and released drug can readily be further increased by simply adding LBL nanoassembly steps and/or increasing nanopore size and density.

**Photoluminescence-Based AAO Biosensors**

Photoluminescence spectroscopy can be used when light energy, or photons, stimulate the emission of a photon from any matter.
When light illuminating a sample is absorbed, a process called photon excitation can occur, causing the material to jump to a higher electronic state, then release energy, and finally return back to a lower energy level (Shen et al., 2004; Santos et al., 2013b). The photoluminescence process includes both fluorescence emission and phosphorescence emission. AAO-based PL biosensors can be used to detect antibody-antigen bindings, enzyme-substrate digestions, and drug loading and release, and they have many applications in applications such as nanoreactors, drug releasing nanochips, etc. (Casanova et al., 2008; Andrew et al., 2010; Ruminski et al., 2010; Chen et al., 2011). The optical principle for an AAO-based PL sensor, the Fabri-Pérot effect, is the same as for an AAO-based RIS sensor.

Pla et al., used AAO to detect Staphylococcus aureus using the PLS method with rhodamine B, with the amount of released rhodamineB increasing with an increase in cocaine concentration. The signal representing the released rhodamine B was detected by a fluorescence spectrometer. and the author detected bacterial concentrations ranging from 0 to 2×10^3 in both PBS and clinical blood samples (Pla et al., 2020), reflecting an LOD of 2 CFU mL^-1 in PBS buffer and 5 CFU mL^-1 in blood media. Moreover, the probe demonstrated a high selectivity of S. aureus and did not respond to the presence of other Staphylococcus species. Martínez et al., used the same method to detect cocaine within concentrations ranging from 0.5 μM to 1 mM, resulting in a LOD level of 0.5 μM, with the sensor having a higher affinity for cocaine than morphine (Ribes et al., 2016).

The underlying optical principles for PLS-AAO and RIS-AAO are identical. Santos, et al. (Santos et al., 2013a), presented a comparative study of these two methods by detecting different analytes under distinct adsorption (Figure 12), using nanopore sizes for PLS-AAO and RIS-AAO of 55 ± 2 and 47 ± 2nm, respectively. Two experiments are described in this paper: 1) detection of D-glucose under nonspecific adsorption conditions, and 2) detection of L-cysteine under specific adsorption conditions, and the results showed that the PLS-AAO biosensor exhibited better performance in both experiments. The authors also summarized the main factors influencing the sensitivity of AAO-based biosensor that could explain the reason for PLS-AAO platform to be much more sensitive than the RIS-AAO platform for detection of D-glucose and L-cysteine.

**CONCLUSION**

This review paper mainly deals with optical techniques in combination with AAO platforms such as surface-Enhanced Raman Scattering (SERS), surface Plasmon Resonance (SPR), reflectometric Interference Spectroscopy (RIS), and photoluminescence Spectroscopy (PL). An AAO-based optical biosensor exhibited simple and fast operation with very good selectivity specificity, and reusability, with a detection limit lower than current lab-based equipment. It also exhibited performance statistically indistinguishable from HPLC for measuring.
concentrations of samples. AAO-based optical sensors and microfluidic chip can be combined to achieve multiplexed detection, even POCT, and we believe that AAO has huge remaining potential in many application areas such as nanotechnology, optics, medicine, and materials science.

AUTHOR CONTRIBUTIONS
SF planned this review paper, summarized the search, analyzed the results, and wrote this 485 review paper. WJ conducted the search of the relevant literature materials. All authors have 486 read and agreed to the published version of the manuscript.

FUNDING
Project supported by the Program for Innovative Teams of Outstanding Young and Middle-aged Researchers in the Higher Education Institutions of Hubei Province (Grant No. T2020014).

REFERENCES
A´cimovi´c, S. S., Ortega, M. A., Sanz, V., Berthelot, J., Garcia-Cordero, J. L., Renger, J., et al. (2014). LSPR Chip for Parallel, Rapid, and Sensitive Detection of Cancer Markers in Serum. *Nano Lett.* 14 (5), 2636–2641. doi:10.1021/nl500574n
Ali, R. A. M., Espulgar, W. V., Aoki, W., Jiang, S., Saito, M., Ueda, M., et al. (2018). One-step Nanoimprinted Hybrid Micro-/nano-structure for In Situ Protein Detection of Isolated Cell Array via Localized Surface Plasmon Resonance. *Ipn. J. Appl. Phys.* 57 (3S2), 03EC03. doi:10.7567/ijap.57.03ec03
Alkire, R. C., Gogotsi, Y., and Simon, P. (2008). *Nanostructured Materials in Electrochemistry.* John Wiley & Sons.
Altomare, M., Cha, G., and Schmuki, P. (2020). Anodiz Nanoporous Niobium Oxide Layers Grown in Pure Molten Ortho-Phosphoric Acid. *Electrochimica Acta* 344, 136158. doi:10.1016/j.electacta.2020.136158
Alvarez, S. D., Derfus, A. M., Schwartz, M. P., Bhatia, S. N., and Sailor, M. J. (2009a). The Compatibility of Hepatocytes with Chemically Modified Porous Silicon with Reference to In Vitro Biosensors. *Biomaterials* 30 (11), 26–34. doi:10.1016/j.biomaterials.2008.09.005
Alvarez, S. D., Li, C.-P., Chiang, C. E., Schuller, I. K., and Sailor, M. J. (2009b). A Label-free Porous Alumina Interferometric Immunosensor. *Acs Nano* 3 (10), 3301–3307. doi:10.1021/nn900825q
Amanda, J. H., Zou, S., George, C. S., and Richard, P. V. D. (2004). Nanoscale Optical Biosensor: Short Range Distance Dependence of the Localized Surface Plasmon Resonance of Noble Metal Nanoparticles. *J. Phys. Chem. B* 108 (22), 6961–6968. doi:10.1021/jp036261n
Andrew, J. S., Anglin, E. J., Wu, E. C., Chen, M. Y., Cheng, L., Freeman, W. R., et al. (2010). Sustained Release of a Monoclonal Antibody from Electrochemically Prepared Mesoporous Silicon Oxide. *Adv. Funct. Mater.* 20 (23), 4168–4174. doi:10.1002/adfm.201000907
Anglin, E., Cheng, L., Freeman, W., and Sailor, M. (2008). Porous Silicon in Drug Delivery Devices and Materials/. *Adv. Drug Deliv. Rev.* 60 (11), 1266–1277. doi:10.1016/j.addr.2008.03.017
Anitha, V. C., Zazpe, R., Krkal, M., Yoo, J., Sopha, H., Prikryl, J., et al. (2018). Pt Nanoparticles Decorated TiO2 Nanotubes for the Reduction of Olefins. *Appl. Mater. Today* 10, 86–92. doi:10.1016/j.jcat.2018.06.017
Anker, J. N., Hall, W. P., Lyandres, O., Shah, N. C., Zhao, J., and Van Duyne, R. P. (2008). Biosensing with Plasmonic Nanosensors. *Nat. Mater.* 7, 442–453. doi:10.1038/nmat2162
Mao, S., Feng, S., and Que, L. (2019). Detection of Autoantibodies for Type 1 Diabetes Using Label-free Optical Sensors,” in 2019 20th International Conference on Solid-State Sensors, Actuators and Microsystems & Eurosensors XXXII (TRANSDUCERS & EUROSensors XXXIII) (IEEE), 578–581.

Masuda, H., Asoh, H., Watanabe, M., Nishio, K., Nakao, M., and Tamamura, T. (2001). Square and Triangular Nanohole Array Architectures in Anodic Alumina. Adv. Mater. 13 (3), 189–192. doi:10.1002/1521-4095(200102)13:3<189::AID-ADMA189>3.0.CO;2-Z

Masuda, H., and Fukuda, K. (1995). Ordered Metal Nanohole Arrays Made by a Two-step Replication of Honeycomb Structures of Anodic Alumina. Science 268, 1466–1468. doi:10.1126/science.268.5216.1466

Nguyen, N. T., Hwang, I., Kondo, T., Yanagishita, T., Masuda, H., and Schmuki, P. (2017). Optimizing TiO2 Nanotube Morphology for Enhanced Photocatalytic H2 Evolution Using Single-Walled and Highly Ordered TiO2 Nanotubes Decorated with Dewetted Au Nanoparticles. Electrochemistry Commun. 79, 46–50. doi:10.1016/j.elecom.2017.04.016

O’Sullivan, J. P., and Wood, G. C. (1970). The Morphology and Mechanism of Formation of Porous Anodic Films on Aluminium. Proc. R. Soc. Lond. A. Math. Phys. Sci. 317 (1531), 511–543. doi:10.1098/rspa.1970.0129

Oh, B.-R., Chen, P., Nidetz, R., McHugh, W., Fu, J., Shanley, T. P., et al. (2016). Multiplexed Nanoplasmonic Temporal Profiling of T-Cell Response under Immunomodulatory Agent Exposure. ACS Sens. 1 (7), 941–948. doi:10.1021/acssensors.6b00240

Pan, S., and Rothberg, J. L. (2003). Interferometric Sensing of Biomolecular Binding Using Nanoporous Aluminium Oxide Templates. Nano Lett. 3 (6), 811–814.

Petryayeva, E., and Krull, U. J. (2011). Localized Surface Plasmon Resonance: Oxidation. J. electroanalytical Chem. 706, 146–158. doi:10.1016/j.jelechem.2011.02.005

Ramírez, G. E., Ali, N., and Fawcett, D. (2011). Progress in Nano-Engineered Nanosensors. Nanoscale 3 (11), 482–486. doi:10.1039/c1nr10355h

Rajeev, G., Xifre-Perez, E., Prieto Simon, B., Cowin, A. J., Marsal, L. F., and Scully, J. P., and Wood, G. C. (1970). The Morphology and Mechanism of Formation of Porous Anodic Films on Aluminium. Proc. R. Soc. Lond. A. Math. Phys. Sci. 317 (1531), 511–543. doi:10.1098/rspa.1970.0129

Sieber, I., Hildebrand, H., Friedrich, A., and Schmuki, P. (2005). Sensitivity of Metal Nanoparticle Surface Plasmon Resonance to the Dielectric Environment. J. Phys. Chem. B 109 (46), 21556–21565. doi:10.1021/jp054227y

Sieber, I., Hildebrand, H., Friedrich, A., and Schmuki, P. (2006). Initiation of T-Cell Response under Immunomodulatory Agent Exposure. ACS Sens. 1 (7), 941–948. doi:10.1021/acssensors.6b00240

Shen, Y., Jia, R.-P., Luo, H.-Q., Chen, X.-G., Xue, D.-S., and Hu, Z.-D. (2004). Highly Ordered Nanochannel-Array Architecture in Anodic Alumina. Appl. Phys. Lett. 71 (19), 2770–2772. doi:10.1063/1.1201208

Thompson, G. E., Furneaux, R. C., Wood, G. C., Richardson, J. A., and Goode, J. S. (1978). Nucleation and Growth of Porous Anodic Films on Aluminium. J. Phys. Chem. Res. Tokyo 91, 543. doi:10.1098/rspa.1970.0129

Tinsley-Bown, A. M., Canham, L. T., Hollings, M., Anderson, M. H., Reeves, C. L., and Tinsley-Bown, A. M. (2010). Surface Roughening of Polystyrene and Poly(methyl Methacrylate) in Ar/O2 Plasma Etching. J. Electrochem. Soc. 157 (23), 9913–9915. doi:10.1149/1.3470451

Voelcker, N. H. (2018). A Label-free Optical Biosensor Based on Nanoporous Silicon. Sensors Actuators B: Chem. 268, 1466. doi:10.1016/j.snb.2018.06.058
Wang, Y. X., Pan, Z. Y., Ho, Y. K., Xu, Y., and Du, A. J. (2001). Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms. Nucl. Instr. Methods Phys. Res. B 180 (1-4), 251–256. doi:10.1016/s0168-583x(01)00425-6

Wei, W., Macak, J. M., Shrestha, N. K., and Schmuki, P. (2009). Thick Self-Ordered Nanoporous Ta[J(sub 2)[O[sub 5] Films with Long-Range Lateral Order. J. Electrochem. Soc. 156 (6), K104. doi:10.1149/1.3116243

Whitney, A. V., Elam, J. W., Zou, S., Zinovev, A. V., Stair, P. C., Schatz, G. C., et al. (2005). Localized Surface Plasmon Resonance Nanosensor: A High-Resolution Distance-Dependence Study Using Atomic Layer Deposition. J. Phys. Chem. B 109 (43), 20522–20528. doi:10.1021/jp0540656

Willets, K. A., and Van Duyne, R. P. (2007). Localized Surface Plasmon Resonance Spectroscopy and Sensing. Annu. Rev. Phys. Chem. 58, 267–297. doi:10.1146/annurev.physchem.58.032806.104607

Xia, X. H., Ashruf, M. A., French, P. J., and Kelly, I. J. (2000). Galvanic Cell Formation in Silicon/metal Contacts: the Effect on Silicon Surface Morphology. Chem. Mater. 12 (6), 1671–1678. doi:10.1021/cm9912066

Xue, D.-J., Wang, J.-J., Wang, Y.-Q., Xin, S., Guo, Y.-G., and Wan, L.-J. (2011). Facile Synthesis of Germanium Nanocrystals and Their Application in Organic-Inorganic Hybrid Photodetectors. Adv. Mater. 23 (32), 3704–3707. doi:10.1002/adma.201101436

Yang, W., Sun, K., Chao, K., Allarbi, N. S., Li, J., and Huang, Q. (2018). Fabrication of a Novel Transparent SERS Substrate Comprised of Ag-Nanoparticle Arrays and its Application in Rapid Detection of Ractopamine on Meat. Food Anal. Methods 11 (8), 2329–2335. doi:10.1007/s12161-018-1216-z

Yang, Z., Si, S., Dai, H., and Zhang, C. (2007). Piezoelectric Urea Biosensor Based on Immobilization of Urease Onto Nanoporous Alumina Membranes. Biosens. Bioelectron. 22 (12), 3283–3287.

Yang, W., Li, Z., Lu, Z., Yu, J., Hao, Y., Man, B., et al. (2019). Graphene-Ag Nanoparticles-Cicada Wings Hybrid System for Obvious SERS Performance and DNA Molecular Detection. Opt. Express 27 (3), 3000–3013. doi:10.1364/oe.27.003000

Yeom, S.-H., Han, M.-E., Kang, B.-H., Kim, K.-J., Yuan, H., Eum, N.-S., et al. (2013). Enhancement of the Sensitivity of LSPR Based CRP Immunosensors by Au Nanoparticle Antibody Conjugation. Sensors Actuators B: Chem. 177, 376–383. doi:10.1016/j.snb.2012.10.099

Yeom, S.-H., Kim, O.-G., Kang, B.-H., Kim, K.-J., Yuan, H., Kwon, D.-H., et al. (2011). Highly Sensitive Nano-Porous Lattice Biosensor Based on Localized Surface Plasmon Resonance and Interference. Opt. Express 19 (23), 22882–22891. doi:10.1364/oe.19.022882

Yoshikawa, H., Murahashi, M., Saito, M., Jiang, S., Iga, M., and Tamiya, E. (2015). Parallelized Label-free Detection of Protein Interactions Using a Hyper-Spectral Imaging System. Anal. Methods 7 (12), 5157–5161. doi:10.1039/c5ay00738k

Yoshikawa, H., Murahashi, M., Saito, M., Jiang, S., Iga, M., and Tamiya, E. (1991). Anodic Oxide Films. London; New York: Academic Press.

Yu, H., Zhu, S., Yang, X., Wang, X., Sun, H., and Hao, M. (2013). Synthesis of Coral-like Tantalum Oxide Films via Anodization in Mixed Organic-Inorganic Electrolytes. PLoS ONE 8, e66447. doi:10.1371/journal.pone.0066447

Zhang, C. Y., Lu, Y., Zhao, B., Hao, Y. W., and Liu, Y. Q. (2016). Facile Fabrication of Ag Dendrite-Integrated Anodic Aluminum Oxide Membrane as Effective Three-Dimensional SERS Substrate. Appl. Surf. Sci. 377, 167–173. doi:10.1016/j.apsusc.2016.03.132

Zhang, J., Qu, S., Zhang, L., Tang, A., and Wang, Z. (2011). Quantitative Surface Enhanced Raman Scattering Detection Based on the “Sandwich” Structure Substrate. Spectrochimica Acta Part A: Mol. Biomol. Spectrosc. 79 (3), 623–630. doi:10.1016/j.saa.2011.03.045

Zhang, L., Macdonald, D. D., Sikora, E., and Sikora, J. (1998). On the Kinetics of Growth of Anodic Oxide Films. J. Electrochem. Soc. 145 (3), 898. doi:10.1149/1.1838364

Zhao, Y., Chu, B., Zhang, L., Zhao, F., Yan, J., Li, X., ..., and Lu, Y. (2018). Constructing Sensitive SERS Substrate with a Sandwich Structure Separated by Single Layer Graphene. Sensors Actuators B: Chem. 263, 654–642. doi:10.1016/j.snb.2018.02.037

Zheng, Q., Lee, H. J., Lee, J., Choi, W., Park, N. B., and Lee, C. (2014). Electrochromic Titania Nanotube Arrays for the Enhanced Photocatalytic Degradation of Phenol and Pharmaceutical Compounds. Chem. Eng. J. 249, 285–292. doi:10.1016/j.cej.2014.03.111

Zhou, C., Yu, Z., Yu, W., Liu, H., Zhang, H., and Guo, C. (2019). Split Apteramer-Based Detection of Adenosine Triphosphate Using Surface Enhanced Raman Spectroscopy and Two Kinds of Gold Nanoparticles. Microchimica Acta 186 (4), 251. doi:10.1007/s00604-019-3356-2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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