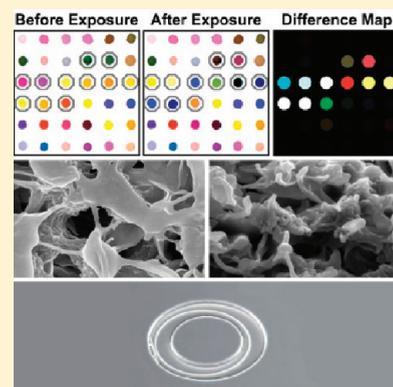


## Nanostructured Substrates for Optical Sensing

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**ABSTRACT:** Sensors that change color have the advantages of versatility, ease of use, high sensitivity, and low cost. The recent development of optically based chemical sensing platforms has increasingly employed substrates manufactured with advanced processing or fabrication techniques to provide precise control over shape and morphology of the sensor micro- and nanostructure. New sensors have resulted with improved capabilities for a number of sensing applications, including the detection of biomolecules and environmental monitoring. This Perspective focuses on recent optical sensor devices that utilize nanostructured substrates.



Over the past decade, a variety of new optical sensing modalities have been developed, catalyzing research in both fundamental and applied sciences. Current research has increasingly exploited advances in the fabrication of materials to modify and greatly enhance existing sensing techniques. Greater control over the micro- and nanostructure of materials has resulted in sensor materials with increased sensitivities, multiplexing capabilities, or both. For example, while surface plasmon resonance has been known for 25 years, advances in lithographic techniques have enabled additional control over the fabrication of nanostructures and has opened up new paradigms in probing molecular interactions due to the heightened sensitivity that these structures provide. In addition, advances in silicon microfabrication have given rise to a wide variety of new structured materials such as photonic resonators with high  $Q$  factors. As another example, colorimetric indicators were a staple in analytical chemistry long before instrumental analysis became commonplace; new structured sensor materials now incorporate colorimetric dyes, enhancing their properties and expanding their applicability. In this Perspective, we highlight a number of recent developments of structured substrates for optically based sensing, particularly involving methods that detect analytes through differences in wavelength-dependent material properties.

**Surface Plasmon Sensing Substrates.** Conventional surface plasmon resonance relies on changes in the bulk refractive index of the surrounding medium. Localized surface plasmon resonance (LSPR), in contrast, probes the local dielectric environment immediately surrounding a plasmonic nanostructure.<sup>1–4</sup> By optimizing the size and shape of nanostructures, the optical properties can be extremely sensitive to surface binding events that change the local refractive index. An assortment of structured metal substrates with well-controlled size and spacing have been employed for sensing with LSPR such as nanoholes,

nanowells, and other nanocrystalline shapes; representative structures are shown in Figure 1.

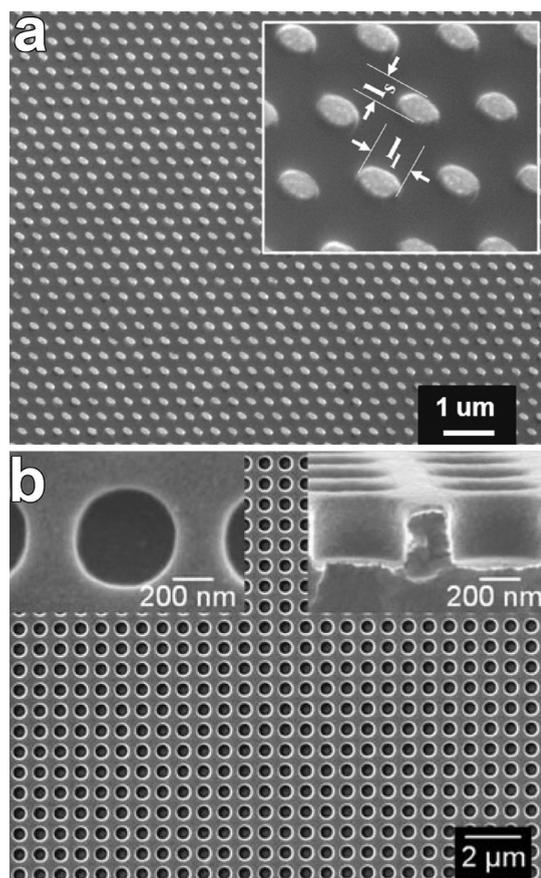
A common sensing motif in LSPR involves functionalizing the surface of the nanostructure with an antibody or an antigen and introducing a sample containing the target analyte. The specific binding of the analyte, as dictated by the selectivity of the capture agent, changes the local refractive index proximal to the nanostructure, which is then measured as a modulation in the wavelength-dependent optical properties of the nanostructure. This works effectively for a variety of antibody–antigen pairs, including gold nanoislands functionalized with rabbit immunoglobulin

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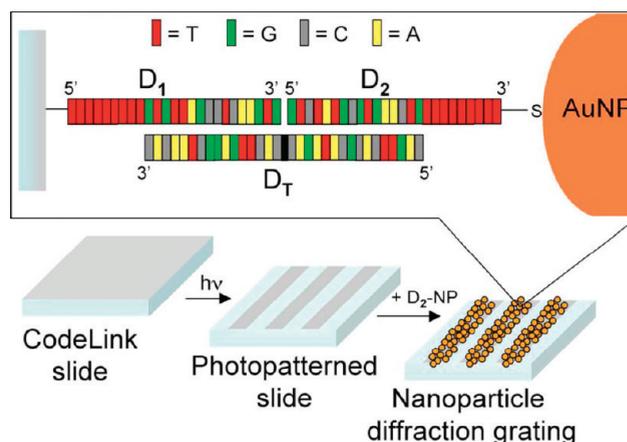
**Figure 1.** (a) Array of elliptical Au nanodisks on a glass wafer; inset shows higher magnification and the aspect ratio of the nanodisks (from ref 8). (b) Scanning electron micrographs of a nanowell plasmonic crystal (from ref 7). Left inset: Top view showing the approximate nanowell diameter. Right inset: Cross-sectional view showing the nanowell depth and continuous Au coverage on the surface.

G and human chorionic gonadotropin,<sup>5</sup> nanohole arrays functionalized with glutathione *s*-transferase,<sup>6</sup> and nanowell arrays functionalized with antioat immunoglobulin G.<sup>7</sup>

Sensitivities of antibody–antigen pairs can be increased by using sandwich assays with modified detection antibodies. Detection antibodies for prostate-specific antigen (PSA), for example, were modified with alkaline phosphatase, which catalyzed the production of insoluble precipitates that agglomerated on an elliptical nanodisk substrate.<sup>8</sup> While the PSA binding events would have been otherwise undetectable at low concentrations (below 2.8 nM) due to the low surface coverage of the antigen, the buildup of precipitate on the nanostructure itself caused a refractive index change that resulted in femtomolar detection limits of the antigen. While the addition of a secondary amplification step allows for a significant improvement in signal, this does remove the ability to monitor the binding of a target antigen in real time.

Enhanced LSPR signals have also been achieved by using nanoparticle-conjugated detection antibodies, increasing anti-biotin signals by 400%.<sup>9</sup> This phenomenon is due to local refractive index changes in combination with plasmonic coupling between the nanostructure and conjugated nanoparticle.

LSPR is capable of detecting more than antibody–antigen binding, however. Van Duyne and co-workers have developed

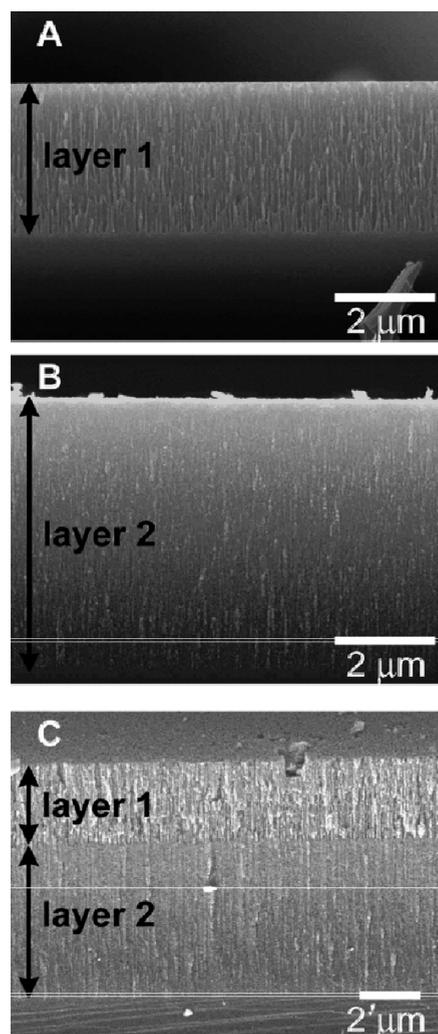


**Figure 2.** Schematic diagram of the *in situ* generated nanoparticle diffraction gratings used for detecting ssDNA. In this method, ssDNA capture probes ( $D_1$ ) are patterned into lines on a glass substrate. The addition of the ssDNA target ( $D_T$ ) does not create a measurable signal by itself. Instead, addition of gold nanoparticles modified with the ssDNA probe sequence ( $D_2$ ) results in the formation of a diffraction grating, which can be read out optically. (Reprinted with permission from ref 20. Copyright 2008, American Vacuum Society.)

triangular nanoprism sensors to monitor drug interaction with a cytochrome p450 enzyme,<sup>10</sup> to observe the conformational changes of a bound protein,<sup>11</sup> and even to directly detect adsorption of inert gases (i.e., He, Ar, N<sub>2</sub>) on nonfunctionalized surfaces.<sup>12</sup> Larson et al. have also displayed multiplexed detection of bovine serum albumin, NaCl, Coomassie blue, and liposome solutions with nanohole arrays.<sup>13</sup> Similarly, Rogers, Nuzzo, and co-workers have demonstrated that nonfunctionalized nanowell and nanopost plasmonic crystals show optical sensitivities to different alkanethiols<sup>14</sup> as well as nonspecific binding of proteins.<sup>7,15</sup>

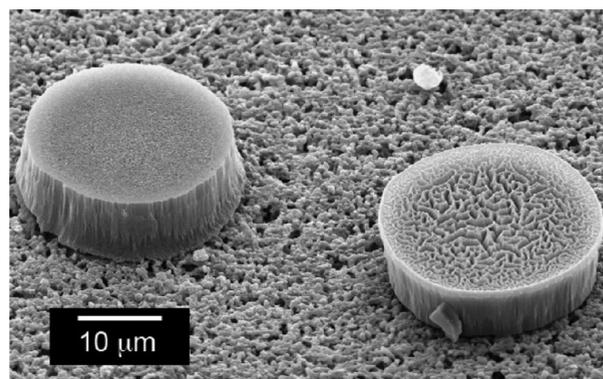
**In this Perspective, we highlight a number of recent developments of structured substrates for optically based sensing, particularly involving methods that detect analytes through differences in wavelength-dependent material properties.**

**Diffraction Grating Substrates.** Diffraction gratings are another class of optical sensors that have benefited from advanced fabrication techniques. By monitoring the change in intensity of the diffraction spots from a grating, researchers can probe interactions occurring on the surface of or within the grating material.<sup>16,17</sup> This class of sensors offers a number of advantages, including an extraordinarily simple readout, ease of fabrication, and low cost. The gratings can also be fabricated using a variety of materials, enabling the use of a wide range of functionalization schemes.



**Figure 3.** Scanning electron micrographs (secondary electron) of cross sections of porous silicon single layers with (a) large and (b) small pore diameters. (c) By varying the applied current density during the etching process, double layers can be also generated (from ref 25).

Wark et al. developed a method of optical sensing based on nanoparticle-enhanced diffraction gratings that takes advantage of the coupling of plasmons between a gold diffraction grating and gold nanoparticles.<sup>18</sup> In this method, diffraction gratings (consisting of 7  $\mu\text{m}$  wide and 45 nm thick gold lines) were lithographically defined on a glass substrate. The gratings were functionalized to present a single-stranded DNA (ssDNA) capture probe that was complementary to half of a target ssDNA. The target ssDNA was presented in solution to the sensor surface, where it was bound to the capture probe. This binding event itself was not sufficient to elicit a response from the diffraction gratings. Afterward, the surface was exposed to a solution of gold nanoparticles functionalized with a second ssDNA molecule that was complementary to the other half of the target ssDNA; upon binding to the target, the gold nanoparticles with the second ssDNA formed a sandwich pair bound to the functionalized grating. The coupling of localized surface plasmons on the gold diffraction grating surface to those of the nanoparticles resulted in a highly sensitive sensor. The gratings were used as a sensing substrate by examining the change in

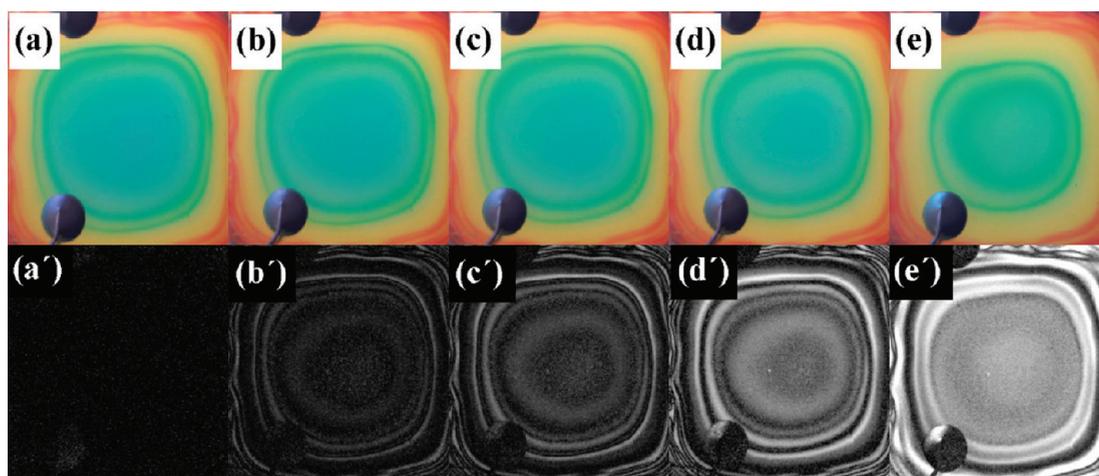


**Figure 4.** Scanning electron micrograph of porous silicon substrates used for multiplexed detection of DNA (from ref 30).

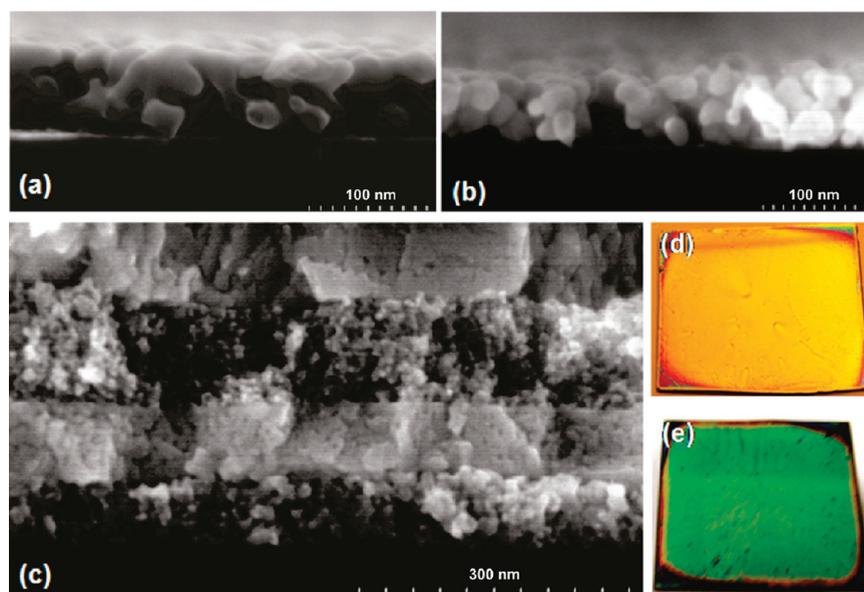
first-order diffraction efficiency that occurs upon binding of target molecules to the surface of the gratings.<sup>18</sup> This technique was further developed to incorporate enzymatic amplification steps that could lead to the incorporation of nanoparticles to the sensor surface.<sup>19</sup>

Another sensing method using diffraction gratings (shown in Figure 2) was conceived by Sendroui and Corn.<sup>20</sup> Instead of starting with a patterned metallic diffraction grating directly on the sensor substrate, the grating was assembled in situ onto 7.5  $\mu\text{m}$  lines of ssDNA capture probes (sequence  $D_1$ ) patterned onto the surface of a glass slide. Hybridization of the target sequence (sequence  $D_T$ ) alone was not sufficient to elicit a diffraction response, but when the target was introduced after preassociating with gold nanoparticles presenting a sequence partially complementary to the target (sequence  $D_2$ ), the resulting sandwich complex gave a diffraction response. By monitoring the first-order diffraction measurements with simple collimated white light, Sendroui and Corn were able to detect target DNA at concentrations as low as 10 pM. By using a HeNe laser and avalanche photodiode, they were able to minimize background light scattering and reduce their limit of detection to 10 fM.

**Photonic Crystals.** Photonic crystals are materials with periodic nanostructure regions of high and low dielectric constants that can attenuate light propagation due to conditions of constructive and destructive interference. This phenomenon can be accurately explained by Bragg's law,  $m\lambda = 2nd \sin(\theta)$ , where  $m$  is the diffraction order,  $\lambda$  is the wavelength of light,  $d$  is the lattice spacing of the material,  $n$  is the refractive index of the material, and  $\theta$  is the incident angle of light. 1D photonic crystals, also called Bragg stacks or Bragg mirrors, are popular sensing materials that change color according to refractive index changes caused by adsorption or binding events in the material.<sup>21–24</sup> Sailor and co-workers have developed 1D porous silicon photonic crystals by the electrochemical etching of crystalline silicon with hydrofluoric acid. By alternating the current during the etching process, pore densities can be controlled as a function of depth into the silicon (Figure 3).<sup>25</sup> This precise control allows for a range of porous silicon materials to be synthesized from those containing simple cylindrical pores to materials with oscillating, periodic pores. Materials containing these periodic structures are classified as a special type of 1D photonic crystal known as a Rugate filter. Rugate filter materials have been tailored by treating the surface of the pore walls with different functional groups and multiplexed for the detection of isopropanol and heptane



**Figure 5.** Optical photographs (a–e) and difference images (a'–e') of a porous silicon Bragg mirror exposed to ethanol vapor at concentrations of (a) 0, (b) 140, (c) 2000, (d) 10 000, and (e) 22 500 ppm. The difference images are multiplied by a factor of 10 to show the changed segments of color clearly. (Reprinted with permission from ref 31. Copyright 2010, Elsevier.)



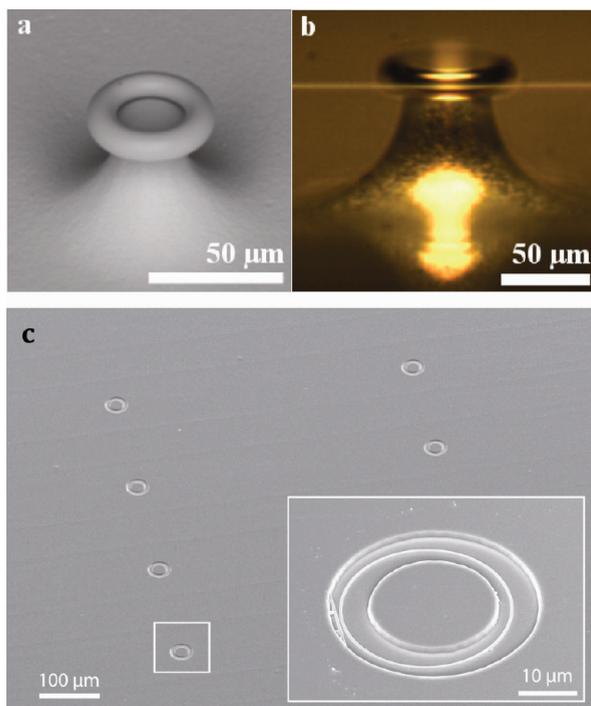
**Figure 6.** (a) SEM cross section image of a porous nanoparticle  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> thin film; (b) SEM cross section image of a porous nanoparticle ZnO thin film; (c) SEM cross section image of two double layers of a nanoparticle  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub>/WO<sub>3</sub> Bragg mirror; (d) optical photograph showing yellow reflectivity of a spin-coated, three double-layer ZnO/WO<sub>3</sub> Bragg mirror; (e) optical photograph showing green reflectivity of a spin-coated, three double-layer nanoparticle  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub>/WO<sub>3</sub> Bragg mirror (from ref 38).

vapors.<sup>26</sup> A similar type of surface functionalization was used for the detection of HF and Cl<sub>2</sub>.<sup>27</sup>

Double-stacked porous silicon materials have been used by the Sailor group to detect ethanol, heptane, toluene, and dimethyl methylphosphonate (a simulant for sarin gas).<sup>28</sup> A similar double-layered silicon material has also been used to monitor the enzymatic activity of Pepsin through the digestion of  $\alpha$ -casein.<sup>29</sup> Encoded multilayered porous silicon surfaces were also used for the multiplexed detection of DNA (Figure 4).<sup>30</sup> Because different etching currents result in characteristic reflectance properties, a combination of characteristic peaks can be encoded into a material by applying a specific current sequence to the etch process, creating a “spectral barcode” within the material.

Particular DNA capture sequences can be covalently attached to a silicon substrate with a specific spectral barcode. A mixture of target DNA is fluorescently labeled and subsequently allowed to hybridize with the silicon substrates. Monitoring the fluorescence can detect when a binding event occurs, and reflectivity measurements can determine which specific DNA sequence is fluorescing. This allows for the detection and discrimination of multiple analytes within the same sample. Lee et al. have also used multilayered porous silicon photonic crystals for the detection of a series of polar solvents, such as isopropanol, ethanol, methanol, and acetone (Figure 5).<sup>31,32</sup>

Hybrid photonic crystals have also been produced for optical detection of a variety of analytes. Míguez and co-workers have

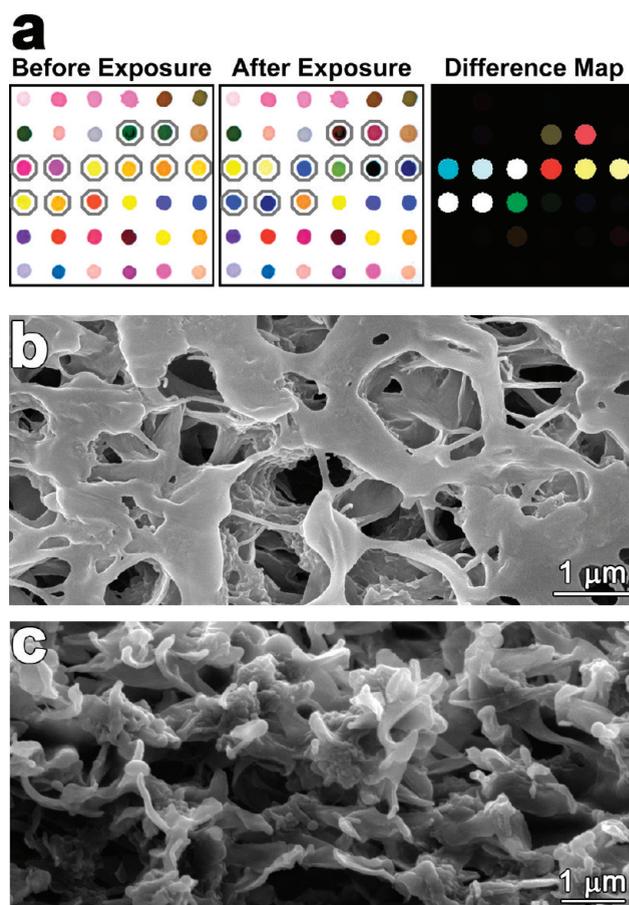


**Figure 7.** (a) Scanning electron micrograph and (b) an optical micrograph of a microtoroid photonic resonator (from ref 43; reprinted with permission, copyright 2010). A tapered fiber used to excite resonance in the microtoroid can be seen in (b) as well. (c) An array of microring resonators from ref 47 (reprinted with permission, copyright 2010). The inset shows an individual microring next to a linear waveguide, both of which have been revealed within an annular opening inside of a polymer cladding layer.

developed Bragg reflector materials based on alternating  $\text{SiO}_2$ – $\text{TiO}_2$  layers for the detection of isopropanol, water, toluene, and chlorobenzene.<sup>33,34</sup> De Stefano et al. used a porous silicon photonic crystal with amino-functionalized poly( $\epsilon$ -caprolactone) for the detection of isopropanol, ethanol, and methanol.<sup>35</sup> The polymer coating was found to protect the silicon from alkaline dissolution without adversely affecting detection limits. The Sailor group used a porous silica photonic crystal backfilled with an acrylic hydrogel for the optical detection of pH and temperature changes.<sup>36</sup>

Ozin and co-workers have developed an alternative bottom-up synthetic pathway to 1D photonic crystals using nanoparticle assemblies (Figure 6). Alternating films of mesoporous silica and titania nanoparticle films were capable of optical detection of varying pressures of toluene vapor.<sup>37</sup> Alternating  $\alpha$ - $\text{Fe}_2\text{O}_3$ / $\text{WO}_3$  nanoparticle films and  $\text{ZnO}/\text{WO}_3$  nanoparticle films were used in a similar fashion for the optical discrimination of ethanol, isopropanol, *n*-propanol, and *t*-butanol.<sup>38</sup> Additionally, alternating  $\text{SiO}_2$  and  $\text{TiO}_2$  nanoparticle layers with nine different surface functionalities have been used for the multiplexed detection and discrimination of six different volatile organic solvents and four different bacteria strains.<sup>39</sup>

**Photonic Resonators.** Another class of rationally structured sensors that take advantage of microscale lithography are photonic resonators.<sup>40,41</sup> Light is coupled into a dielectric material via the evanescent field of a neighboring optical fiber or waveguide. Light at specific wavelengths can couple into the microcavity at specific wavelengths, which are defined by a constructive

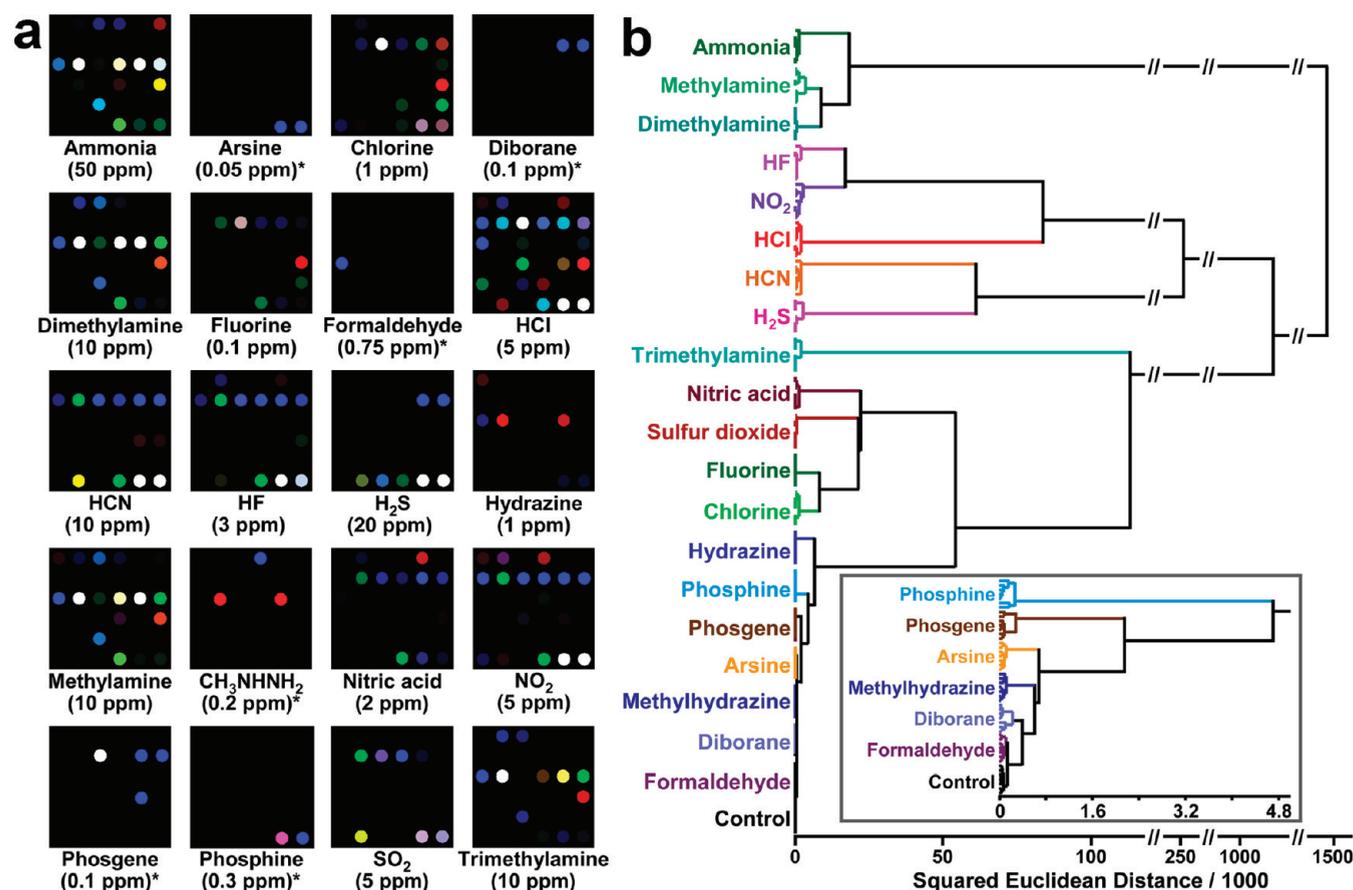


**Figure 8.** (a) Colorimetric sensor array printed on a PVDF membrane, showing the digital images before and after exposure to an analyte (in this case, ammonia at its IDLH concentration) and the color difference map; (b) SEM image of the PVDF top surface after printing; (c) SEM image of the cross section of the printed PVDF membrane. (Modified from ref 65. Reproduced by permission of The Royal Society of Chemistry, copyright 2009. <http://dx.doi.org/10.1039/B916571A>).

interference condition  $m\lambda = 2\pi r n_{\text{eff}}$ , where  $m$  is a nonzero integer,  $\lambda$  is the wavelength of incident light,  $r$  is the radius of the resonator, and  $n_{\text{eff}}$  is the effective refractive index of the optical mode. The refractive index term of the resonance condition renders these devices sensitive to binding-induced changes in the local dielectric environment, often in the form of target biomolecules binding to specific receptors (DNA, antibodies, etc.).

These sensors have been realized via microfabrication in several different geometric configurations. Notably, high-fidelity fabrication methods can allow for exceptionally high quality factor cavities, and thus, small shifts in the exceptionally spectrally narrow resonances can be easily resolved. Microtoroids (Figure 7ab) can offer exceptionally high quality factors, and the possibility of single-molecule detection has been suggested using these devices.<sup>42,43</sup> Optical interrogation of these devices, however, remains a challenge at present, and this limits their applicability in multiplexed sensor configurations.

An alternative photonic resonator is based on chip-integrated microring waveguides (Figure 7c). These structures typically feature lower-quality factors ( $Q \approx 10^5$ ) but offer key advantages in terms of fabrication and optical interrogation.<sup>44,45</sup> In fact,



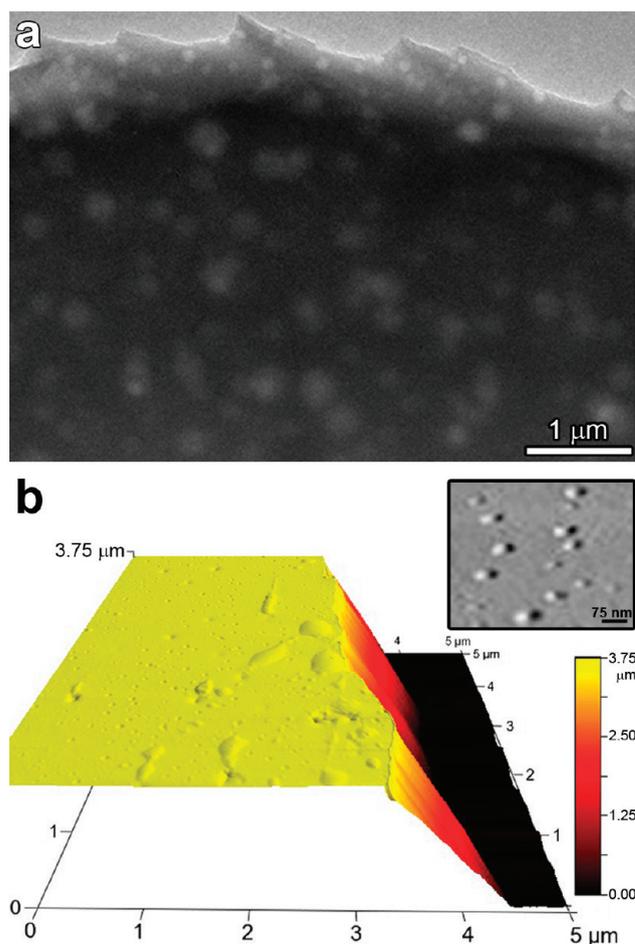
**Figure 9.** Nanoporous ormosil-based colorimetric sensor arrays. (a) Color difference maps and (b) hierarchical cluster analysis of 20 representative toxic industrial chemicals (TICs) at their permissible exposure level (PEL) concentration. For display purposes, the color ranges of these difference maps are expanded from 4 to 8 bits per color (RGB range of 4–19 expanded to 0–255), except for several weaker responding TICs that are marked with asterisks (RGB range of 2–3 expanded to 0–255) (from ref 72).

large arrays of individually addressable microrings can be easily fabricated using standard commercial semiconductor processing methods, and the lithographically controlled positioning of the linear access waveguide next to the microring greatly simplifies optical alignment. Utilizing microring resonators, Bailey and co-workers have demonstrated a wide range of sensing array applications, including the multiplexed detection of proteins,<sup>46</sup> nucleic acids,<sup>47</sup> and cytokines.<sup>48</sup> Silicon photonic wires for protein and nucleic acid detection have also been fabricated in spiral geometries that offer an increased path length while maintaining a compact footprint.<sup>49–51</sup>

**Colorimetric Sensor Substrates.** Structured substrates are also used in colorimetric detection methods (i.e., those involving chemically responsive dyes or pigments) and can be easily adapted to a variety of analytes. As discussed below, colorimetric detection methods have the advantage of being exceptionally inexpensive due to the ubiquitous nature of digital photographic imaging, which also allows them to be highly portable. Due to their rapid recent development, as well as their versatility, portability, and low-cost, the remainder of this Perspective will focus on colorimetric sensors. There has also been substantial recent colorimetric research using surface-functionalized nanoparticles where optical properties change due to the distance-dependent interactions of nanoparticle aggregates; these materials will not be reviewed here, having been thoroughly discussed elsewhere by Mirkin,<sup>52</sup> Lu,<sup>53</sup> and Rotello.<sup>54</sup>

A central requirement of all colorimetric sensors is analyte access to the chromophores. This can be met with semiliquid films of highly plasticized polymers containing dissolved indicators, but it is often better served by the use of high-porosity membranes as nanostructured supports. Porosity on the nanometer scale is critical for rapid exposure of colorimetric indicators to the environment containing potential analytes.<sup>55</sup> One may even argue that litmus paper is the predecessor to all sensors with structured substrates, given the microfibrillar nature of cellulose paper. More recently, fibrous membranes made from other polymers have found important applications for colorimetric sensors. PVDF (polyvinylidene difluoride, i.e.,  $-(\text{CH}_2\text{CF}_2)_n-$ ) has been found to be particularly effective for a variety of biochemical applications (e.g., Western blots) due to its high purity, chemical inertness, and ease of fabrication. Membranes of PVDF are made by floating a solution of the polymer dissolved in dimethylformamide or methyl ethyl ketone on a water trough; the fibrous membrane is formed on the water surface as the organic solvent diffuses into the water.

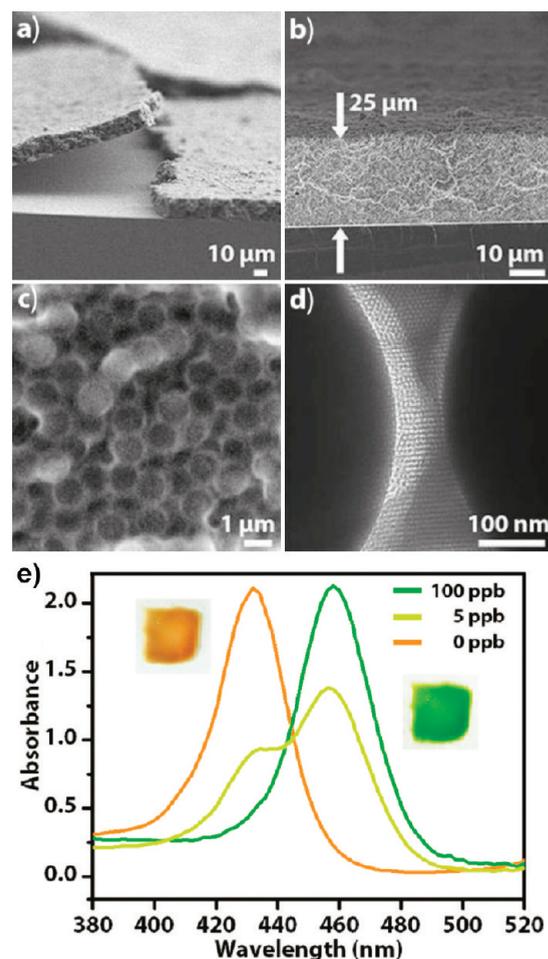
Over the past few years, a general approach to an “optoelectronic nose” was developed that used a diverse range of chemically responsive dyes deposited on high surface area PVDF membranes.<sup>55–64</sup> This approach uses disposable colorimetric sensor array with selected chemically responsive dyes in four classes, (1) dyes containing metal ions (e.g., metalloporphyrins) that respond to Lewis basicity (i.e., electron pair donation, metal



**Figure 10.** (a) Transmission electron micrograph (TEM) of printed porous pigment that was then removed from the polymer substrate and placed on a TEM grid. The 50–200 nm features show the porosity created in these ormosil xerogel spots, which are  $\sim 4 \mu\text{m}$  thick and 1 mm in diameter. (b) An AFM micrograph in perspective showing the height of the porous pigment at the spot center compared to the base height of the PET as revealed by a scrape from a blade. The inset shows an enlargement of the surface pores ( $<100 \text{ nm}$ ). (Modified from ref 69. Reproduced by permission of The Royal Society of Chemistry, copyright 2011. <http://dx.doi.org/10.1039/C0NR00963F>).

ion ligation), (2) pH indicators that respond to Brønsted acidity/basicity (i.e., proton acidity and hydrogen bonding), (3) dyes with large permanent dipoles (e.g., vapo-chromic or solvatochromic dyes) that respond to local polarity, and (4) metal salts that participate in redox reactions. This colorimetric sensor array, therefore, is responsive to the chemical reactivity of analytes rather than to their effects on the secondary physical properties (e.g., mass, conductivity, adsorption, etc.) normally used by other electronic nose techniques. The colorimetric sensor array is simply digitally imaged before and after exposure, and a difference map (red minus red, green minus green, blue minus blue) is generated (Figure 8a). As discussed below, the difference map is a unique molecular fingerprint for each odorant or mixture of odorants at a given concentration.

Printing of the chemically responsive dyes might have been problematic in altering the nanostructure of the membrane. The dye formulations, however, did not clog the pores or damage the PVDF morphology upon printing, as shown by scanning electron



**Figure 11.** (a) SEM image showing an overview of the composite film of mesoporous silica spheres in a mesoporous silica framework (from ref 90). (b) Cross-sectional SEM of the composite film. (c) SEM showing the composite structure of spheres within the silica matrix. (d) TEM revealing the mesoporous structure in the silica matrix used to embed the spheres. (e) UV-vis absorption spectra of the composite exposed to solutions containing the indicated concentrations of  $\text{Cd}^{2+}$  ions. The insets show digital photographs of the sensing materials as synthesized (left) and in a 20 ppb  $\text{Cd}^{2+}$  solution (right).

micrographs of printed (Figure 8bc) and nonprinted areas of the membrane.<sup>65</sup> Printing of the arrays on PVDF did not alter the porosity of the membrane in any way or damage or dissolve the PVDF membrane, and the microstructure of the membrane was completely unaffected.

In general, ordinary pigments (i.e., insoluble colorants) cannot be used as sensors for the simple reason that analytes can interact only with the very external monolayer of the colorant. If the pigment is created so that it has a very high microporosity, however, then analytes can gain access to the internal colorant centers. Such nanoporous pigments have generally been synthesized using various colorimetric indicators doped into organically modified silicas (ormosils) for an assortment of sensing applications.<sup>66–68</sup> These materials circumvent complex processing steps by simply allowing an amorphous silica matrix to form around the indicator molecules, effectively trapping them within the solid as condensation occurs, while allowing access of the chromophore to environmental analytes.

The Suslick group has used these sol–gel materials to develop printable colorimetric sensor arrays based on chemically responsive nanoporous pigments.<sup>65</sup> By using inks made from ormosil suspensions containing chemically responsive dyes, they are able to print arrays onto nearly any nonporous surface. By combining differently doped porous pigments into one array, the composite response of the immobilized semispecific indicators to environmental changes can be used to provide a “molecular fingerprint” unique to the analyte, in much the same way that the olfactory system works. The molecular fingerprint is used to visually differentiate similar analytes, and the high dimensionality allows for the facile discrimination among diverse analytes (Figure 9).

The nanoporous ormosil materials are prepared by acid-catalyzed hydrolysis of solutions containing commercially available silane precursors (e.g., tetraethoxysilane (TEOS), methyltriethoxysilane (MTEOS), phenethyltrimethoxysilane, and octyltriethoxysilane (octyl-TEOS)) and dissolved in low-volatility solvents (e.g., methoxyethanol or diethylene glycol dimethyl ether) that serve as porogens on the nanometer scale. After hydrolysis, the chemically responsive indicators are added to the sol–gel solutions, printed on a polymer or glass surface, and allowed to form a porous xerogel.<sup>69</sup> After curing, the resulting porous pigment is ~1 mm in diameter and ~4 μm thick and consists of 50–200 nm pores throughout the material (Figure 10). Arrays of these porous pigments have been used for the detection of toxic industrial gases at ppb concentrations,<sup>70–72</sup> complex odorant mixtures (e.g., coffee aromas),<sup>73</sup> and sugars and artificial sweeteners in aqueous solutions.<sup>74,75</sup>

As noted earlier, high porosity on the nanometer scale is critical for rapid exposure of colorimetric indicators to the environment containing potential analytes. To this end, the development of periodic mesoporous silica materials has also proved of use for some colorimetric sensors. Silica has a number of advantages as a host material for colorimetric probes including optical transparency, relative inertness to both gases and liquids, good stability over a wide range of pHs, and high surface areas. Highly ordered mesoporous aluminosilica materials are typically synthesized using structure-directing surfactant templates, such as CTAB (cetyltrimethylammonium bromide) or triblock copolymers. These sacrificial templates form columnar micelles that direct silica condensation, resulting in the formation of highly periodic and highly tunable porous materials.<sup>76–78</sup> There are also a few downsides to using highly ordered mesoporous materials for colorimetric sensing applications; the sacrificial templates are relatively expensive, and the synthesis is made more difficult by the washing or calcination needed for template removal, which complicates colorimetric indicator incorporation and generally precludes easy preparation of sensor arrays.

After template removal, the resulting mesostructured silicas can be functionalized or doped with reactive chromophores for colorimetric sensing, and such materials have recently been used for metal ion sensing especially, but also for a range of liquid- and gas-phase organics. Jung and co-workers have developed mesoporous silica-based colorimetric sensors for the detection of Cu<sup>2+</sup> and Hg<sup>2+</sup> cations based on covalently tethered chromophores.<sup>79,80</sup> Similarly, El Safty et al. have demonstrated Co<sup>2+</sup>, Cu<sup>2+</sup>, and Hg<sup>2+</sup> detection using electrostatically immobilized indicators.<sup>81–83</sup> Martínez-Mañez and co-workers have recently reported five different mesoporous silica-based sensors used in a multiplexed system for the detection and discrimination of 12 biologically relevant anions (e.g., glutamate, ADP, ATP) at physiological pH.<sup>84</sup> This group has also recently produced

Hg<sup>2+</sup> and pyrophosphate sensors using immobilized squaraine dyes<sup>85,86</sup> in addition to a size-selective amine sensor.<sup>87</sup> Johnson and co-workers have used phenyl-containing silica materials further functionalized with porphyrin indicators for the detection of hydrocarbons such as benzene, toluene, cyclohexane, and hexane.<sup>88,89</sup> Li and Stein developed a hierarchical material where mesoporous silica spheres containing immobilized tetra(1-methyl-4-pyridyl)porphyrin were entrapped in a periodic mesoporous silica skeleton that was capable of detecting Cd<sup>2+</sup> ions at low ppb concentrations (Figure 11).<sup>90</sup> This two-stage approach could allow for the embedding of mesoporous spheres containing functionalities that may not otherwise be compatible with the host silica material.

**An assortment of optically based chemical sensing techniques have benefited from the use of micro- and nanostructured substrates, resulting in devices with improved detection performance.**

An assortment of optically based chemical sensing techniques have benefited from the use of micro- and nanostructured substrates, resulting in devices with improved detection performance. Most such sensors have been developed for the detection of a single analyte, particularly in bioassays utilizing antibody–antigen pairs, while multiplexed systems are generally in an earlier stage of implementation. Substrate specificity remains a challenge, particularly for low-level detection of analytes in the complex milieu that biofluids generally contain. The alternative method of chemical specificity from pattern recognition of sensor arrays has proven especially useful in environmental analysis in both gas- and liquid-phase analysis.

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