

Deep Learning Image Analysis of Nanoplasmonic Sensors: Toward Medical Breath Monitoring

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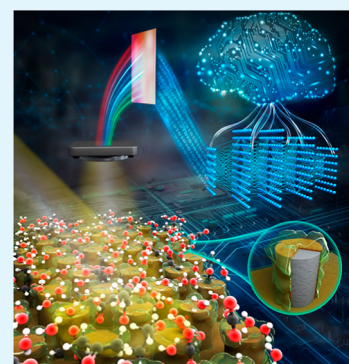


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ABSTRACT: Sensing biomarkers in exhaled breath offers a potentially portable, cost-effective, and noninvasive strategy for disease diagnosis screening and monitoring, while high sensitivity, wide sensing range, and target specificity are critical challenges. We demonstrate a deep learning-assisted plasmonic sensing platform that can detect and quantify gas-phase biomarkers in breath-related backgrounds of varying complexity. The sensing interface consisted of Au/SiO₂ nanopillars covered with a 15 nm metal–organic framework. A small camera was utilized to capture the plasmonic sensing responses as images, which were subjected to deep learning signal processing. The approach has been demonstrated at a classification accuracy of 95 to 98% for the diabetic ketosis marker acetone within a concentration range of 0.5–80 $\mu\text{mol/mol}$. The reported work provides a thorough exploration of single-sensor capabilities and sets the basis for more advanced utilization of artificial intelligence in sensing applications.



KEYWORDS: plasmonic sensing, nanofabrication, breath sensing, deep learning, chemical sensing

INTRODUCTION

Nanoplasmonics is a research area of growing importance that has increasingly contributed to enabling capabilities for developing cost-effective biomedical diagnostics. Much of the success has been in solution-phase detection, where lock-and-key binding creates readily detectable changes in interfacial optical properties.^{1–7} Gas-phase plasmonic studies are much less common.^{8–10} However, the advantages of plasmonic devices^{1,3–5,11–16} such as rapid response speed, high sensitivity, miniature size, and the capability for remote measurement by using an optical spectrometer/camera/photodetector outside the sampling chamber offer enormous possibilities for a broader range of gas-phase applications, one of which is the expanding need for noninvasive medical breath analysis and monitoring.^{10,17–20}

In recent years, the interest in breath analysis for screening and diagnosing certain diseases has progressed due to advanced detection methods and new analytical technologies.^{17,19,21–28} By studying biomarkers, for example, various volatile organic compounds (VOCs) and other volatile small molecules, researchers are identifying targets for noninvasive disease diagnostics in exhaled human breath. The volatile small molecules in exhaled breath, although at combined concentrations of less than 1%, comprise over 1000 compounds that include biomarkers for potential pathologies, such as diabetes, lung cancer, asthma, chronic obstructive pulmonary disease, and others.^{17,21–23,29} Mass spectrometry-based studies for VOC biomarkers have been reported,^{21–23,30} but there remains a significant need for research directed toward the development of smaller, easy-to-use, and cost-effective breath analysis

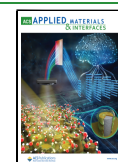
devices. Salient examples of prior efforts include studies of chemiresistor devices,^{31,32} metal–oxide–semiconductor (MOS)-based sensors,^{19,24} arrays of nanoparticle and nanotube-sensing elements,²⁵ polymer-based sensors,^{26,33} quartz crystal microbalances acoustic sensors,³⁴ and so forth.³⁵ While all have demonstrated utility in detecting and quantifying biomarkers in human breath, an ongoing challenge for the field is to develop methods that permit both adequate analyte sensitivity and discrimination in rather complex mixtures at the same time. Because gas-phase sensing does not typically offer the lock-and-key target monitoring methodology that solution-phase biosensing employs, the challenge is especially difficult.

Our approach involves gas-phase sensing enabled by an optimized metal–organic framework (MOF)/plasmonic interface, camera-based image acquisition, and deep learning signal processing. We demonstrate how enhanced levels of analyte sensitivity and selectivity are realized in complex breath-related backgrounds by combining these technical components. Specifically, the plasmonic platform consists of nanopillar structures (SiO₂ pillars with Au coating) designed to have an enlarged interconnection area between the metal and dielectric materials in order to generate stronger localized surface

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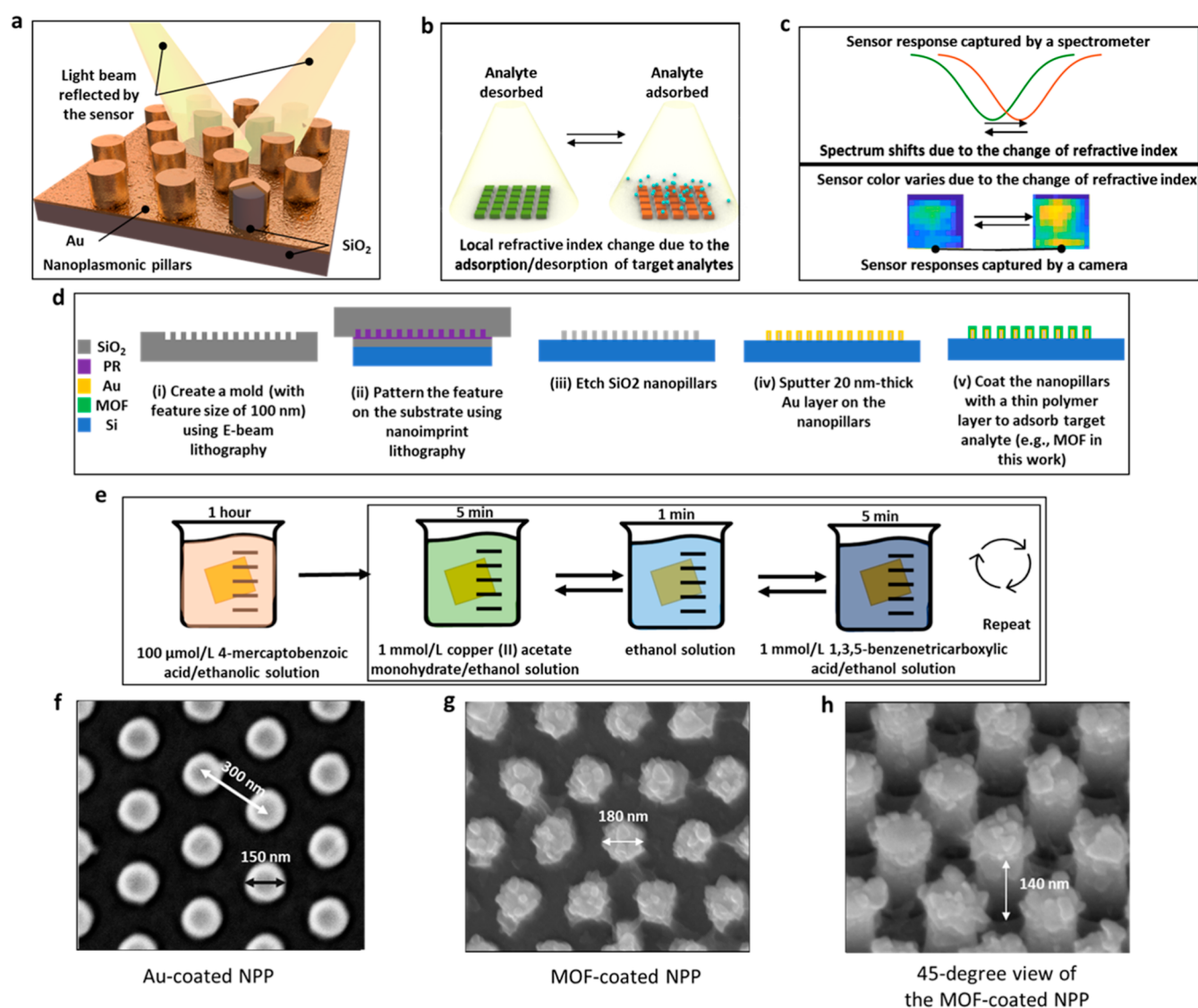


Figure 1. | Design and fabrication of NPPs for gas sensing. (a) 3-D schematic illustration of a portion of a NPP array. Each SiO_2 nanopillar has a diameter of 100 nm and is coated with (5 nm Cr + 20 nm Au). (b,c) Sensing mechanism: LSPR is excited when light interacts with the nanopillars, which can be observed by measuring the optical spectrum (top inset in (c)) or the color (bottom inset in (c)) of the sensing platform. When analytes are adsorbed by the sensing platform, the local refractive index changes slightly and cause a spectrum shift, as well as a color change. (d) Fabrication flowchart of NPPs with gold coating. (e) Schematic of MOF synthesis flow. SEM images showing top views of (f) Au-coated nanopillars with a diameter of 150 nm and a period of 300 nm (center-to-center distance), and (g) nanopillars with 15 nm-thick MOF coating. (h) SEM image showing a 45° view of nanopillars with MOF coating.

plasmon resonance (LSPR) signals when interacting with incident light, and hence higher sensitivity. We exploited a nanoimprint lithography (NIL)-based fabrication process with a reusable mold to transfer the nanostructured patterns onto the substrate, providing a universal method to save time, lower cost, and also yield high-quality fabrication outcomes. A conformal MOF film served to separate, transport, and locate gas-phase molecules at Au plasmonic “hot spots” of the nanopillar array. The optical responses of the plasmonic platform during testing were monitored by a complementary MOS (CMOS) camera, which eliminates the need to use a high-cost measurement device—for example, a spectrometer—in recording responses to the test environments. The camera-acquired responses can be represented as digital images and provide high-dimensional signals [in red, green, and blue (RGB) channels] to help discriminate the target analyte from a complex background. A deep learning neural network model,

named SensingNet, was specially developed to intelligently analyze the image responses of the plasmonic sensing platform without using any other information. It is worth noting that this work was carried out using a single, unmodulated plasmonic sensor, which shows the power of using deep learning analysis approaches to extend the capabilities of a single sensor as compared to utilizing the data richness generated from sensor arrays or modulated sensors.

To investigate the performance capabilities of the developed platform/approach relevant to an existing clinical need, we examined breath acetone sensing as a noninvasive diabetic ketosis monitor. Breath acetone, one of the three ketone bodies [acetoacetate, beta-hydroxybutyrate (BHB), and acetone], has statistically significant correlations with the other two ketone bodies and is linked with metabolic derangements seen in diabetes and other ketosis-related situations.^{36–40} Ketone measurement can provide warnings

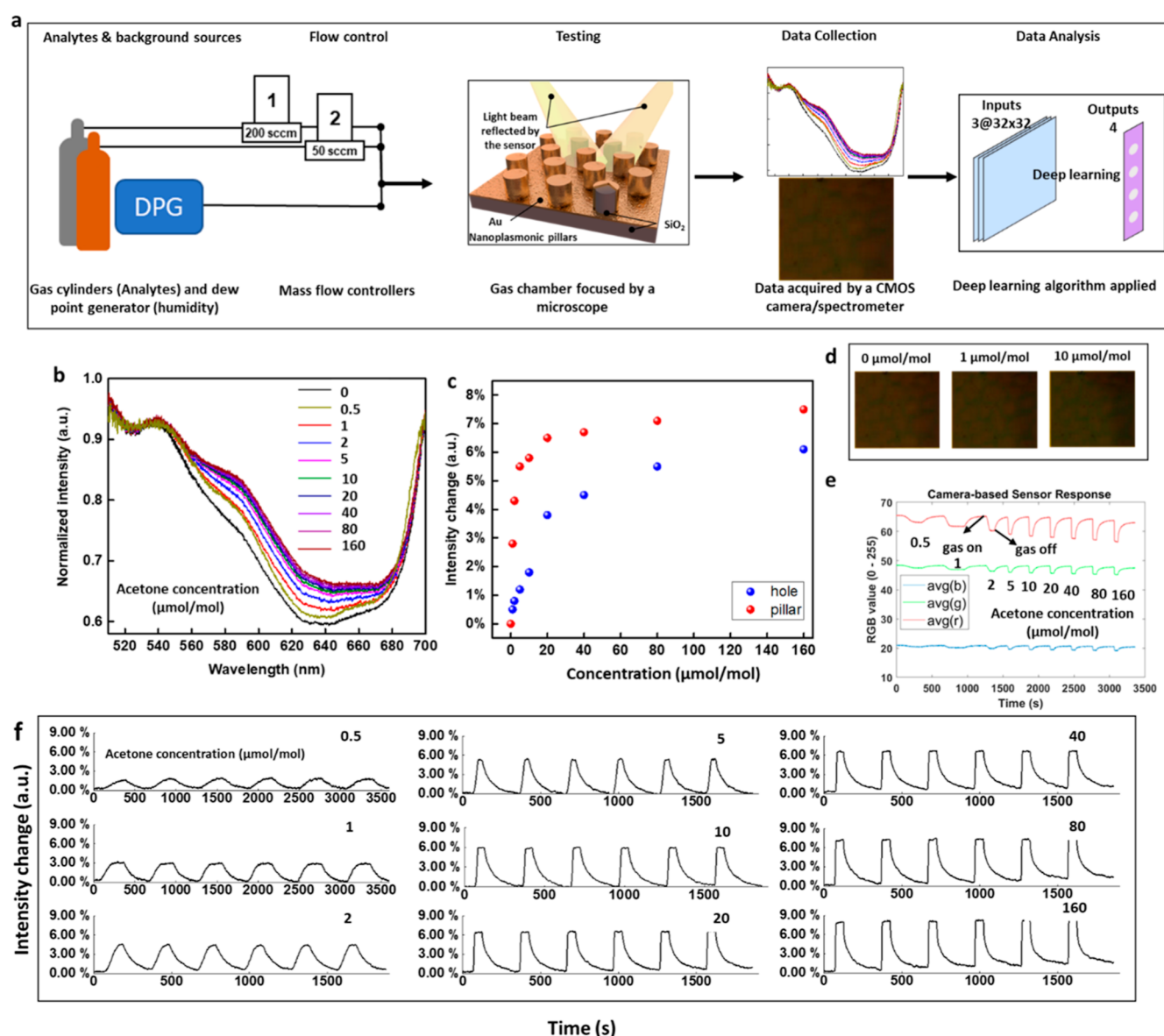


Figure 2. Experimental results for plasmonic acetone sensor tested with a target analyte (acetone). (a) Schematic diagram of gas sensing measurement and analysis procedures. (b) Spectra of an NPP sensor coated with 15 layers of the Cu-BTC MOF, acquired under exposures to varying acetone concentrations [from 0.5 to 160 $\mu\text{mol/mol}$ (ppm)] combined with dry air. (c) Comparison of responses from the new NPP sensor and a previously reported NHA sensor.⁹ (d) Examples of sensor responses acquired by a CMOS camera under different acetone concentrations in dry air. The color variation can be recognized by the eye. (e) Clearer view of the camera-based sensor response plotted as RGB values in a time series. (f) Stability verification with six cycles of continuous testing for each acetone concentration. Note that nominal acetone concentrations were used in this figure. (See also concentration values reported in Table 1 of the Materials and Methods section.)

of diabetic ketosis or ketoacidosis, a life-threatening metabolic disorder that occurs with insulin deficiency or during stress, such as intercurrent illness or surgery. The concentration of acetone in exhaled breath is less than 2 $\mu\text{mol/mol}$ (ppm), and the blood BHB is less than 0.6 mmol/L for nondiabetic ketoacidosis conditions. In diabetic ketoacidosis, the concentration of breath acetone is higher than 40 $\mu\text{mol/mol}$ (ppm), and the blood BHB is higher than 3.0 mmol/L.³⁷

In this work, we conformally coated the Au nanopillar plasmonic surface with a Cu-1,3,5-benzenetricarboxylate (Cu-BTC) MOF to effectively adsorb and detect the marker acetone under varying concentrations (from 0.5 to 160 $\mu\text{mol/mol}$). The target acetone was presented within either dry air or simulated human breath background (air with 80% relative humidity at 23 °C balanced with 2.8% CO_2). A classification

accuracy of $98.8 \pm 0.1\%$ was achieved for all of the different cases we investigated. In addition, more complex breath specimens were simulated by varying both CO_2 concentrations and relative humidity, and a classification accuracy of $95.1 \pm 0.2\%$ was achieved in these more dynamic conditions for the developed AI-assisted plasmonic sensing system. We also illustrate how a unique cost function can be applied to transfer the mispredictions to their nearby classes to achieve those high-risk classification accuracies, which is essential for the development of practical medical devices.

The reported results demonstrate the operation of a plasmonic image sensor and associated deep learning signal processing to address challenges in identifying and quantifying a low-concentration analyte in a complex gas-phase background. We believe that this work will provide valuable

guidance for future studies toward next-generation AI-enhanced sensing/plasmonic-based research. While the testing results on acetone in simulated breath are presented as an example to prove the feasibility of the technology, we believe that the methodology can also be applied for a broader range of applications, such as analyzing other breath biomarkers,^{21–23,29} improving the operation of condensed-phase plasmonic biosensors,^{1,5,41} and expanding to other applications such as plasmonic nanoreactors,¹² high-resolution hyperspectral imaging,³ and forth.

■ RESULTS AND DISCUSSION

Design of NPPs and the Associated Sensing Mechanism. In this work, we developed a unique nanopillar structure to form the plasmonic surface. As shown in Figure 1a, each nanopillar has a SiO₂ pillar coated with gold. The diameter and height of the SiO₂ pillars are both 100 nm and the thickness of the gold coating film is 20 nm (with a 5 nm Cr adhesion layer). The distance between each pillar is 300 nm (center-to-center). This plasmonic surface is fabricated on a SiO₂-on-silicon substrate. The design offers a very high interconnection area between the metal layer and the dielectric region, thus generating more substantive LSPR signals when interacting with incident light.

As indicated above, the incident photons within certain resonant frequencies (or wavelengths) are absorbed/scattered and reflected by the plasmonic surface. Consequently, an intensity dip can be observed in the waveform recorded by a spectrometer when measuring the reflected light. Next, when there are any analytes such as gas molecules or biological molecules that attach close to or otherwise interact with the plasmonic surface, the local refractive index and the resonant frequency will slightly change and lead to a spectrum shift in the waveform of the reflected light detected by the spectrometer (as demonstrated in Figure 1c). The conventional plasmonic sensing mechanism is based on this frequency characteristic.

In this work, we also exploited another sensing approach based on the measurement and analysis of the color change of the plasmonic surface. Similar to the frequency shift characteristic, the surface color change is also due to the change of local refractive index and shift of resonant frequency when analytes are attached to the plasmonic surface^{10,18} (as illustrated in Figure 1b,c). A low-cost, small-size camera module can be used to acquire images of the plasmonic sensor surface as an alternative to spectrometer-based measurements. The sensor surface images (RGB values) are then analyzed with signal processing methods. In this work, a deep learning neural network model is developed to intelligently predict the sensing results in a complex background, that is, simulated human breath. To optimize the prediction accuracy, the neural network model is specifically designed for use with the reported plasmonic sensor.

Fabrication and Characterization of Nanoplasmonic Pillars. Figure 1d schematically illustrates the fabrication process used in this work for the Au-coated nanoplasmonic pillars (NPPs). Figure 1e shows the synthesis flow used to generate the MOF coating on the NPP surface. Note that nanostructured surfaces are normally patterned by using electron beam (e-beam) lithography. However, e-beam lithography is slow, costly, low in area coverage, and only compatible with limited substrate materials. To develop a cost-effective and universal nanosensor fabrication technique (over

a large surface area, on different and even flexible substrate materials), we exploited the NIL technique^{42,43} in this study. A detailed description of the fabrication process and MOF synthesis are included in the Materials and Methods section.

Figure 1f,g shows SEM images of the top views of part of the fabricated NPPs without and with a MOF coating. As indicated, the Au-coated nanopillars are accurately fabricated into a circular shape with a diameter of 150 nm and a period of 300 nm (center-to-center distance). After MOF coating, the diameter of nanopillars increased to 180 nm (and the 300 nm period remained the same). Figure 1h shows a SEM image taken to show the 45° view of the fabricated nanopillars with MOF coating, which have a height of 140 nm.

Experimental Testing of the NPP Sensing Platform.

Figure 2a shows components of the gas sensing measurement system used in this work for the testing of the NPP sensing platform. A detailed description of the testing system is included in the Materials and Methods section.

The experimental testing protocol consists of three parts. Part I is testing an NPP sensor coated with 15 layers of Cu-BTC MOFs under acetone balanced with dry air. Figure 2b,c,f demonstrate the testing results with acetone concentrations varied from 0.5 to 160 $\mu\text{mol/mol}$ (ppm). Figure 2b plots the responses of the NPP sensor, showing that the spectral change of the reflected light varies with different wavelengths and under different acetone concentrations.

Figure 2f provides a more explicit analysis in the time domain to demonstrate the peak intensity (around 630 nm) changes as the acetone concentrations are varied over time [i.e., increased from 2.1 to 7.6% with acetone concentration increased from 0.5 to 160 $\mu\text{mol/mol}$ (ppm)]. Figure 2c shows the performance comparison between the new NPP sensor in this work with a previously reported nanohole array (NHA) sensor.⁹ Improved performance is obtained with the NPP sensor throughout a wide range of acetone concentrations, especially with a larger improvement (4 to 5 times) in the low concentration range [<10 $\mu\text{mol/mol}$ (ppm)]. Figure 2d,e demonstrates the sensor responses captured by a complementary MOS (CMOS) camera. Figure 2d shows some of the acquired images (sensor responses) when testing with different concentrations of acetone. The color variation between the images can be recognized by visual inspection (i.e., color depth of the sensor surface increased with acetone concentration), which recalls the wavelength shift in the visible range as shown in Figure 2b. Figure 2e plots the color change in the time domain and shows the color variation as the acetone concentrations changed more clearly. It is also noticed that the color variation in the red channel is larger than those in the green and blue channels. This is because the developed NPP sensing platform has a resonance wavelength at around 630 nm (Figure 2b), which shows red color. Figure 2f also presents results for stability testing of the NPP sensor, which were conducted with six successive cycles for each acetone concentration. This testing result confirms the stable and consistent performance of the NPP sensor from a low concentration of 0.5 $\mu\text{mol/mol}$ (ppm) to a relatively high concentration of 160 $\mu\text{mol/mol}$ (ppm). This verifies the NPP sensor's sensitivity and detection range could meet the requirement for breath acetone detection applications. All tests were carried out using a single NPP sensor coated with the Cu-BTC MOF.

Next, in Part II, we tested the influence of the two major chemical constituents in human breath, that is, CO₂ and H₂O.

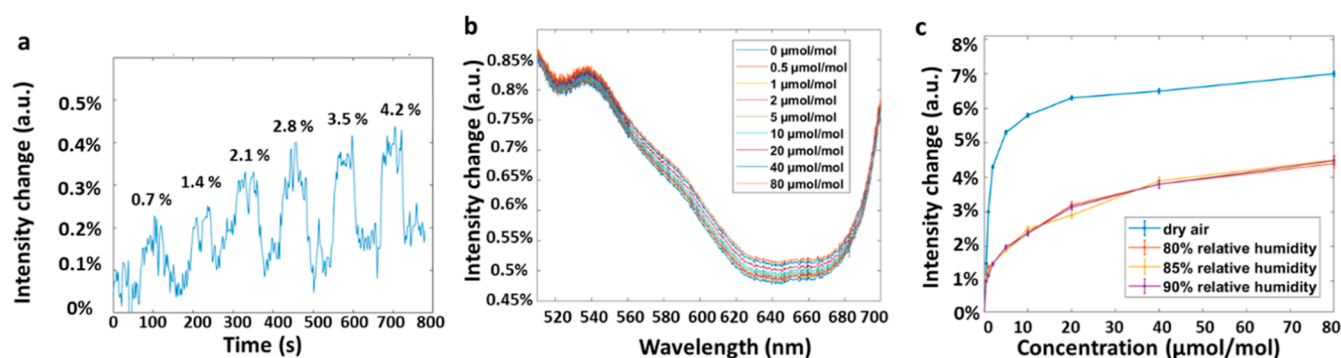


Figure 3. | Experimental results for plasmonic acetone sensor tested with interfering backgrounds. (a) Testing results for the NPP sensor under exposures to varying CO₂ concentrations combined with dry air. (b) Spectra for testing NPPs at various concentrations of acetone with 80% relative humidity at 23 °C. (c) Sensor response at various concentrations of acetone when testing under dry air and with 80/85/90% relative humidity at 23 °C, respectively. The error bar shows the standard deviation of five different experiments. Note that nominal acetone concentrations were used in this figure (see also concentration values reported in Table 1 of the Materials and Methods section).

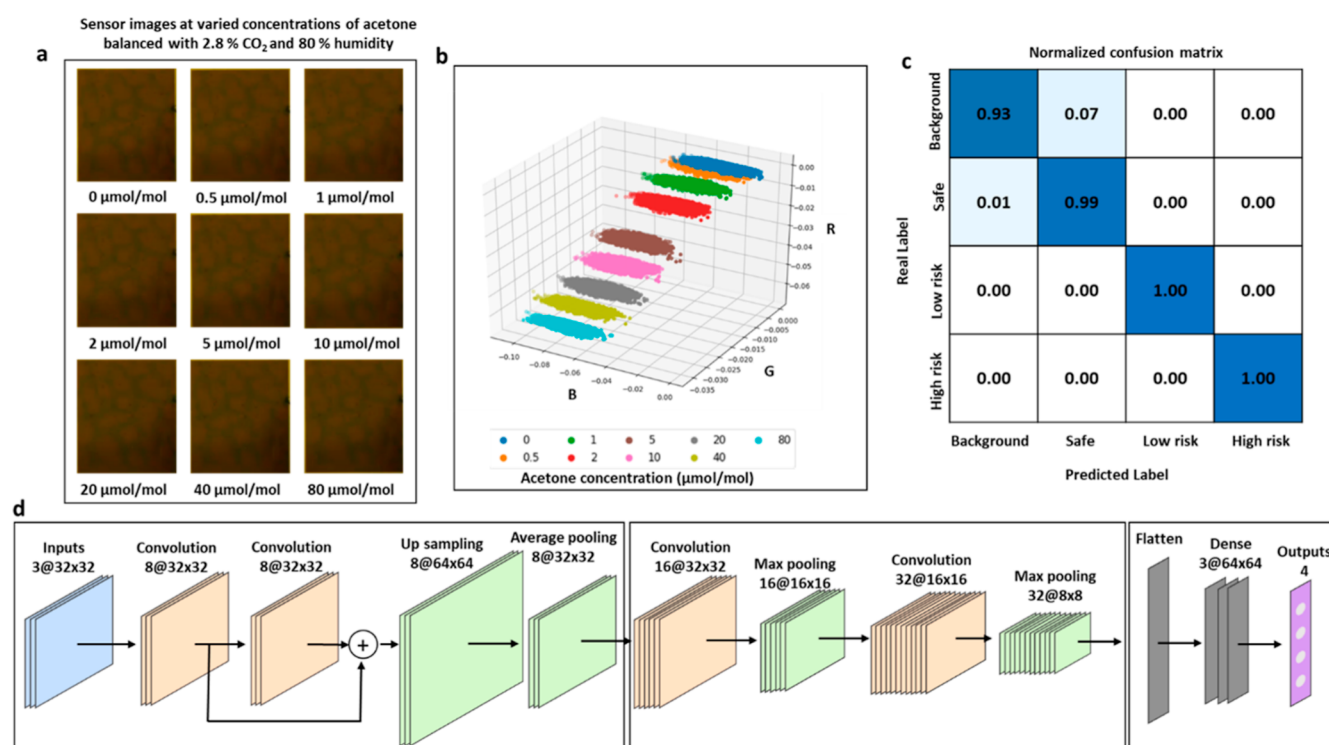


Figure 4. Experimental results for the plasmonic acetone sensor tested with the target analyte in a complex background. (a) Camera-captured images showing the change of NPP surface color under different acetone concentrations combined with a simulated breath background (air with 80% relative humidity at 23 °C balanced with 2.8% CO₂ by volume). (b) Normalized RGB value changes of the NPP images under varying acetone concentrations (from 0.5 to 80 μmol/mol (ppm)) combined with a simulated breath background. (c) Normalized confusion matrix of the cross-validation result from SensingNet. The overall accuracy is 98.8 ± 0.1%. (d) Architecture of SensingNet. The number of output parameters of each layer is represented as $k@n \times n$, where k is the number of filters/layers and $n \times n$ is the dimension of each output matrix. Note that nominal acetone concentrations were used in this figure. (See also concentration values reported in Table 1 of the Materials and Methods section.)

Figure 3a shows the testing results of the NPP sensor under varying CO₂ concentrations combined with dry air. In this test, the concentration of CO₂ varies from 0.7 to 4.2%, which approximates the common range of CO₂ in human breath.^{44,45} According to the results, the intensity change (NPP sensor's response to CO₂) varies from 0.2 to 0.4%, which is 10 to 15 times lower than the changes under acetone shown in Figure 2c,f. The potential interference of CO₂ concentration variation is relatively low when testing acetone samples ≤20 ppm but may affect the testing accuracy when testing acetone samples >20 ppm as the sensor response varies less in this range. To

examine the interference of relative humidity, the NPP sensor was tested at varying concentrations of acetone [0.5 to 80 μmol/mol (ppm)], balanced with an air of different relative humidities [80, 85, and 90% at laboratory ambient temperature (≈23 °C)]. Testing results under the three different relative humidities are presented in Figure 3b,c. According to the results, the NPP sensor's response to the varying concentrations of acetone is from 1.2 to 4.5% with slight variance, which is similar under the three different humidity levels. Note that these responses of the sensor to acetone are lower in humid conditions by ≈40% as compared with the sensing

responses in dry air. Prior reports have indicated that the Cu-MOF can adsorb acetone and humidity.^{46,47} When sensing biomarkers in human breath, the concentration of relative humidity is 10,000 times higher than the concentration of the biomarkers, acetone in this work. The MOF-coated sensor relies upon adsorption/desorption processes. When sensing under a background with high relative humidity, most of the available sites are occupied by water molecules, and thus, less acetone, which must compete with the water molecules, can be adsorbed by the MOF. Therefore, the sensor response to acetone in a background with humidity is much lower than the response observed in dry air. We will discuss approaches to analyze the response data with interference from humidity in order to monitor low-concentration acetone in later sections.

In Part III, we tested the sensor responses with various concentrations of acetone in a more complex background, that is, “simulated human breath”, by mixing acetone with a background of air and 2.8% CO₂ at an 80% relative humidity at laboratory ambient temperature (≈ 23 °C). The initial testing results in Part I and II have already shown that both CO₂ and H₂O would have some effect on the sensing responses when detecting acetone in a simulated human breath. For more complex and dynamic backgrounds, they will have a bigger negative impact and make it more difficult to predict the actual concentration level of acetone when the signal variations are more subtle. It is difficult to accurately predict the acetone concentration in this case by simply observing the change of the spectral peak intensity. Therefore, in this part, we analyzed the sensor responses by studying the variation of RGB values monitored by a CMOS camera. The RGB value is an alternative representation of the intensities in a range of different wavelengths. Thus, it can provide sensing responses in three different channels, that is, RGB, and holds the potential to enable a low-cost and portable device for breath acetone analysis. Figure 4a shows nine pictures of an NPP sensor taken under different acetone concentrations (from 0 to 80 $\mu\text{mol/mol}$) combined with simulated breath (air with 80% relative humidity at 23 °C balanced with 2.8% CO₂). Note that the color depth of the sensor surface increased very slightly with the acetone concentration, which is different from the obvious depth variation shown in Figure 2d. This is also evidence that detection in a complex background is more challenging than in dry air and thus needs more advanced analytical techniques. Next, Figure 4b presents a much clearer representation of the color-change characteristic by plotting averages of the RGB values extracted from the NPP surface images under varying acetone concentrations (from 0 to 80 $\mu\text{mol/mol}$) in our synthesized breath. According to the results, the higher concentration of acetone leads to a more significant change for each color. It is noticed that the red color has the most significant response to acetone and the blue color has the least because the response peak (about 630 nm) of the sensing platform is located in the red channel range (see Figure 2e).

Deep Learning-Assisted Signal Processing. To thoroughly study the correlations between the sensor responses (RGB values) with various concentrations of acetone and other interfering analytes, a deep learning neural network model named SensingNet was developed in this work to intelligently analyze the change of RGB values in each sensor image and accurately predict the NPP sensing results. Deep learning neural networks have been developed and applied to address challenges in many areas.^{48–51}

We employed the Part III testing data on the simulated human breath (e.g., Figure 4b) in an effort to demonstrate the feasibility of the deep learning-assisted signal processing method. Over 100,000 data were collected from 9 different concentrations of acetone balanced with simulated human breath. The data were labeled into several different classes based on the concentration of acetone: background (0 $\mu\text{mol/mol}$), safe (≤ 5 $\mu\text{mol/mol}$), low risk (≤ 40 $\mu\text{mol/mol}$), and high risk (> 40 $\mu\text{mol/mol}$).^{36–40} 80% of the data were used for training, 10% were used for testing, and 10% were used for cross-validation.

Before developing SensingNet, we first trained the dataset with some classic models, including LeNet,⁵² ResNet,⁵³ VGG,⁵⁴ and so forth,^{55,56} using the built-in API from TensorFlow⁵⁷ (Supporting Information, Table S1). These models were either overfitted or did not converge for the training because they were designed for classic image recognition, such as recognition of writings from images, classification of cats and dogs, and so forth. These models look for specific edges/features in the images to classify images. However, for the imaged responses of plasmonic sensors, no such features can be used because the pattern/feature of the plasmonic sensor does not change during the measurement; instead, the color variation (RGB values) contains the information that can be used effectively. During the training process, these state-of-art models look for “features” arising at some residuals or uneven spots and use them to classify each case. As a result, it leads to overfitting or nonconvergence because these “features” are not consistent information that correlates with the sensing responses. Based on these findings, we developed a neural network model, SensingNet, which can be specifically used for plasmonic sensors. We also note that it might be possible to use an approach based simply upon the changes in the average intensities of the RGB channels using dimensionality reduction (e.g., PCA and LDA) in conjunction with a classifier like *k*-nearest neighbors. However, the accuracy was relatively low (test accuracy around 90%). The tests using dimensionality reduction are described in more detail in the Supporting Information.

Figure 4c demonstrates the architecture of SensingNet. A detailed description of SensingNet’s design, functions, and training is included in the Materials and Methods section. As shown in Figure 4d, the cross-validation accuracy of SensingNet on the sensing data in simulated human breath (air with 80% relative humidity at 23 °C balanced with 2.8% CO₂) is $98.8 \pm 0.1\%$, which meets its design purpose as a very compelling signal processing method for the next-generation plasmonic sensing. Note that the RGB values in the sensing data for simulated human breath are clustered based on the concentration of acetone (as shown in Figure 4b), which makes it relatively simple for SensingNet to analyze and predict accurately. To further improve and test SensingNet, we put our NPP sensor into a more complicated testing background with higher complexity than the original synthesized breath.

Optimization of SensingNet with Higher Levels of Background Complexity. Next, we collected more data on new simulated human breath samples with finer acetone concentration increments and slight variations of CO₂ and relative humidity, which more closely approximates conditions for monitoring in real human breath applications. Specifically, acetone concentrations varied at finer increments such as 0, 0.5, 1, 2, 2.25, 2.5, ... 10, 11, ... 80 $\mu\text{mol/mol}$. In the meantime, CO₂ was varied from 2.1 to 3.5% (which covers the largest

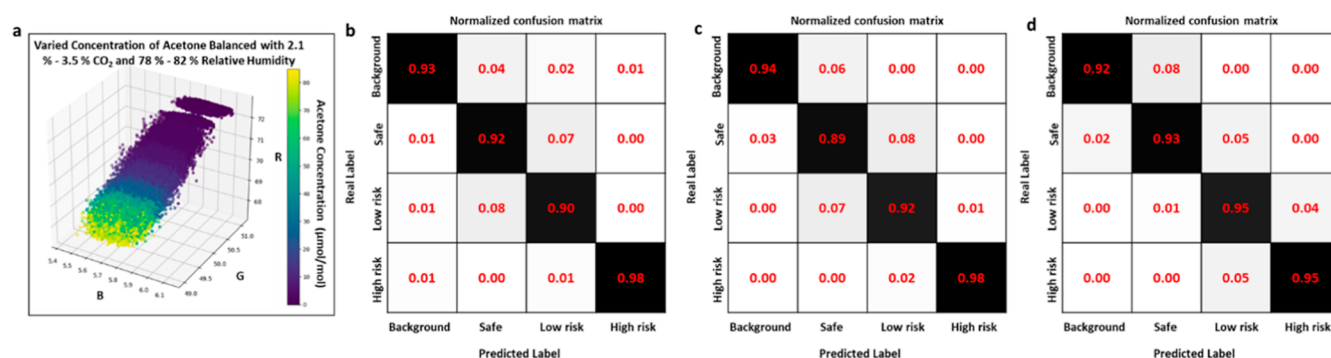


Figure 5. Deep learning analysis on more complex simulated human breath including varied concentrations of both acetone and background interferents. (a) RGB plots of the sensing data collected from testing with the more complex simulated human breath. (b–d) Confusion matrices of different loss functions: (b) without additional penalty; (c) additional penalties added between background and high risk (eq 1); (d) additional penalties added between background and high risk, and between safe and low risk.

response to CO₂ shown in Figure 3a), and the relative humidity was varied from 78 to 82% for the new simulated human breath.

Figure 5a shows an RGB plot for the new data set where we have a total of 200,000 data points collected from NPP sensor testing under different acetone concentrations combined with a new type of simulated human breath with concentration variations. Comparison with Figure 4b makes it clear that the sensing data in the more complicated simulated breath are no longer spatially well separated and thus become much more difficult to process and analyze. We retrained the system with the whole dataset (300,000 data points) including simulated human breath with both fixed and changing interferences. As shown in Figure 5b, the overall cross-validation accuracy of SensingNet, after training with new data, is $95.1 \pm 0.2\%$. Although slightly decreased from $98.8 \pm 0.1\%$, this result verifies SensingNet's solid capability for analyzing and predicting the NPP-based acetone detection in a much more complex background.

The confusion matrix shown in Figure 5b also indicates where the mispredictions occur. It is noticed that there is a small amount of misprediction (about 1%) between high risk and background, which could cause some issues in real applications. In order to minimize the misprediction between the unwanted classes, that is, high risk and background in this work, while keeping the overall accuracy of the model, we invoked a customized cost function to add additional penalties to the misprediction of specific classes.

$$J = \frac{1}{m} \sum_{i=1}^m (-y \log(\hat{y}) + \beta(y_k \log(1 - \hat{y}_L) + y_L \log(1 - \hat{y}_k))) \quad (1)$$

In eq 1, J stands for the cost function, m is the number of data in a minibatch. $\sum_{i=1}^m (-y \log(\hat{y}))$ is the standard form of cross-entropy, where y is the real label and $\hat{y}$ is the predicted label. In the second part, y_k and y_L stand for the two classes where additional penalties for misprediction will be added. Finally, β is the factor to control the number of penalties added to the model. In this work, we obtained the optimized performance by setting the β to 0.006. The overall accuracy remains $95.1 \pm 0.2\%$, and the model eliminates the misprediction between background and high risk (Figure 5c). If we keep adding penalties between safe and low risk, then the mispredictions are controlled between low risk and high risk,

and the overall accuracy is $94.4 \pm 0.2\%$ (Figure 5d), which could be a relatively safe model for practical medical applications. One can choose whether, and where, to apply eq 1 based on the application and dataset. Note that eq 1 is a classification transfer approach rather than a false-positive/false-negative optimizer. For preferentially biasing against either false positives or false negatives, other approaches would need to be applied.

CONCLUSIONS

We have described a nanopillar-based plasmonic sensing platform as well as a deep learning algorithm (SensingNet) and have shown the feasibility of predicting risk levels relevant to diabetic ketosis or ketoacidosis by training the system with simulated human breath. Increasingly complicated testing conditions were utilized to expand the selectivity and sensitivity of the deep learning-assisted plasmonic sensing system. The system, which employs only one NPP sensor, can reach 95 to 98% accuracy when predicting the risk levels of diabetic ketosis or ketoacidosis based on acetone concentrations in simulated human breath with different complexities. The signal processing methods described in this work can be generalized for use with other types of sensing platforms and to improve performance for different applications, including a range of chemical/biochemical applications.

Specifically, in this work, numerical studies were applied to develop a Au-coated SiO₂ NPP sensing platform to provide LSPR measurements sensitive enough to be used in breath acetone detection. The optimal dimension of the NPP structures was studied by sweeping the dimensional parameters in multiphysics simulations. A nanoimprinting-based fabrication process was developed to fabricate the sensing platforms in a reproducible and cost-effective way. The sensing platform was coated with 15 layers of a Cu-BTC MOF and tested first for its response to acetone from 0.5 to 160 μmol/mol in dry air. We demonstrated that sensing responses can be acquired by using a spectrometer or a CMOS camera, the latter providing the feasibility to make a portable and low-cost device. The sensing platform was also tested in a variety of simulated human breath conditions, that is, a mixture of 0.5 to 80 μmol/mol acetone, in air with 2.1 to 3.5% CO₂, and 78 to 82% relative humidity at 23 °C. By applying a deep learning model (SensingNet) specifically designed for plasmonic sensors and camera-acquired sensor responses, we were able to predict the risk levels of diabetic ketosis or ketoacidosis at

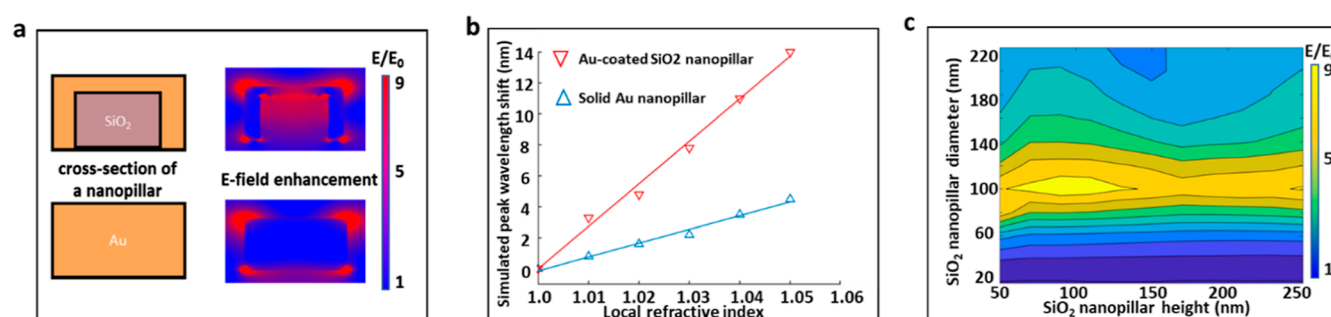


Figure 6. FDTD simulation of NPPs. (a) Comparison of the simulated E-field enhancement between a Au-coated SiO₂ nanopillar (this work) and a solid Au nanopillar. The Au-coated SiO₂ nanopillar has more interconnections between metal and dielectric materials so that larger LSPR signals can be generated to improve the sensing performance. (b) Simulated wavelength shift when the local refractive index changes from 1 to 1.05. The Au-coated SiO₂ nanopillar configuration shows a 3× stronger sensitivity than the solid Au pillar structure. (c) Contour map of the E-field enhancement at various diameters and heights of the nanopillars.

95% accuracy, without knowing other information, using just the single-sensor data. A customized loss function was also developed to minimize the false-positive/negative predictions by adding additional training penalties to the mispredictions between some specific output classes, which is critical for the future development of any practical medical devices.

MATERIALS AND METHODS

Localized Surface Plasmon Resonance. LSPR is a phenomenon in which incident light is trapped within metallic nanoparticles or nanostructures with smaller dimensions than the wavelength of the input light. An oscillating electric field is generated near the nanoparticles' surface, which causes conduction electrons to oscillate coherently at a certain resonant frequency, and this leads to a maximum optical absorption at that resonant frequency. The LSPR and the resonant frequency are determined by a number of factors such as the density of electrons, the effective electron mass, the shape and material of the interfacial nanostructure, the size and volume of the charge distribution, and so forth. These factors can be designed for specific applications, such as chemical/biochemical sensing.

Finite-Difference Time-Domain Simulation of Nanoplasmonic Pillars. Figure 1a schematically shows the 3-dimensional (3-D) model structure examined using the finite-difference time-domain (FDTD) simulation tool. In addition to the Au-coated SiO₂ nanopillar structure, we also modeled and simulated a conventional Au nanopillar structure for comparison. The two structures have the same dimensions (150 nm diameter, where the diameter of SiO₂ was set to 100 nm) and the same incident light source. The only difference is the nanopillar's material. According to the simulation results shown in Figure 6a, the Au-coated SiO₂ nanopillar generates a larger amount of oscillating electric fields around the gold coating film, which is consistent with the expectations and justifies the plasmonic design used in this work. In contrast, the conventional Au pillar only has oscillating electric fields near the top corners and bottom interface, although the intensities of the oscillating electric fields are close in the two designs.

In another comparison, we swept the local refractive indices of both plasmonic surfaces (Au-coated SiO₂ nanopillar vs conventional Au nanopillar) to simulate and compare the shift of peak wavelengths. In this simulation, sweeping refractive indices is done to simulate different analytes being attached to the plasmonic surface, and the amount of peak wavelength shift is an indication of the adsorbate sensitivity of the plasmonic sensor. According to the simulation results shown in Figure 6b, the Au-coated SiO₂ nanopillar design has a 3 times stronger sensitivity than the conventional Au nanopillar structure.

We also swept the height and diameter of the Au-coated SiO₂ nanopillar separately in another simulation and plotted the corresponding electric field intensities under the varied dimensions in a contour map in Figure 6c. According to the simulation result, we

found one of the optimal dimensions is 100 nm in height and 100 nm in diameter for the SiO₂ pillar with the thickness of the Au layer kept at 25 nm. These dimensions were adapted as the parameters selected for our fabrication work. (Note that in the fabrication, we deposited 5 nm of Cr between the SiO₂ layer and the Au layer for better adhesion, and the Au layer was then set to 20 nm.)

Fabrication of Nanoplasmonic Pillars. As shown in Figure 1d, the first step is to fabricate a mold with nanoholes (inverse of the nanopillars) with a diameter of 100 nm and thickness of 150 nm. The mold is produced via the following process steps: pattern 100 nm circles on a SiO₂ substrate using e-beam lithography; deposit and lift-off 10 nm-thick Cr for protection; etch 150 nm into the SiO₂ layer for the holes using reactive ion etching (RIE). The mold is formed for NIL and can be used multiple times to save time and lower the fabrication cost. Note: the depth of nanoholes in the mold is determined by the thickness of the NIL resist and the height of the designed nanopillars. One can adjust the SiO₂ RIE etching time to get different depths of the holes in the mold for other applications and processes.

After fabricating the mold, the nanopillar patterns are printed to another Si/SiO₂ substrate using the NIL technique (step ii in Figure 1d). The next step is to clean the remaining photoresist and etch the SiO₂ pillars using RIE. Then, a 5 nm-thick Cr layer and a 20 nm-thick Au coating are deposited around the SiO₂ nanopillars using DC sputtering to finalize the NPPs.

Detailed recipes for each step are as follows. We used thermal oxide wafers with 300 nm SiO₂ on a 500 μm Si wafer purchased from Graphene Supermarket.⁵⁷ The substrate was spin-coated with NXR-1025 photoresist⁵⁷ at 5000 rpm and baked for 5 min at 105 °C. Then, the mold was positioned on top of the substrate and imprinted at 120 °C and 1379 kPa (200 psi) using an NX-2000 nanoimprinter.⁵⁷ After that, the residual photoresist on the imprinted substrate was cleaned using an Unaxis 790 RIE machine with O₂ plasma etching.⁵⁷ Note that the thickness of the residual layer depends on the thickness of the photoresist and the dimension of the features on the mold. We recommend analyzing the cross-section of a nanoimprinted sample using SEM to measure the thickness of the residual layer and estimate the O₂ etching time required. It is essential to clean the residual layer while maintaining the imprinted features. Then, we applied RIE (Unaxis 790)⁵⁷ with CHF₃ to etch the nanopillars. Finally, 5 nm Cr and 20 nm Au were coated on the etched platforms using DC sputtering (Denton Vacuum Discovery 550).⁵⁷ The fabricated sensing platforms were coated with the Cu-BTC MOF using the methods described below for the porous membrane used for breath acetone detection in this work. (Other thin-layer functional materials can be used for different purposes.) LSPR usually extends 10 to 30 nm^{9,58} from the surface of the nanostructures. Therefore, we recommend controlling the thickness of the coating material in that range for the best performance of LSPR-based plasmonic sensors.

Synthesis and Function of MOFs. MOFs have emerged as promising materials for selective gas adsorption and separation due to

their distinct advantages over other traditional porous materials (e.g., activated carbon and zeolite), including high surface area, adjustable pore size, uniformly distributed metal centers, and tunable functionalities.^{58,59} Our previous study has shown that Cu-1,3,5-benzenetricarboxylate (Cu-BTC) MOF-coated plasmonic sensing platforms can assist in the detection of acetone at various concentrations from 500 nmol/mol to 320 μ mol/mol.⁹ In this work, we functionalized the fabricated NPP platform with 15 layers of Cu-BTC MOFs to effectively adsorb and detect the target analytes. Figure 1e demonstrates the synthesis flow (modified from previous works^{9,59}) used to generate the MOF coating on our NPP surface. As shown in the Figure 1e schematics, the Au-coated sensors were submerged in a self-assembling monolayer solution (100 μ mol/L 4-mercaptobenzoic acid/ethanolic solution) for 1 h. Then, we repeated the following process 15 times to coat the Cu-BTC MOF: dip the sensor in a 1 mmol/L copper(II) acetate monohydrate/ethanol solution for 5 min and rinse in ethanol for 1 min; then dip into a 1 mmol/L 1,3,5-benzenetricarboxylic acid/ethanol solution for 5 min with 1 min ethanol rinse. Note: 15 layers of MOF coating is the optimized thickness for the LSPR platforms based on our previous study⁹ because LSPR enhancement extends to a certain distance (usually <30 nm) from the surface of the nanoscale features. Figure 1g,h illustrates part of the MOF-coated NPPs. The diameter of the NPPs was expanded to 180 nm due to the MOF coating and the height was expanded to 140 nm accordingly. Figure S2 (Supporting Information) shows the X-ray photoelectron spectroscopy (XPS) results, which characterize material aspects of the growth of a Cu-BTC MOF on a plasmonic platform specifically used for XPS analysis that was prepared to be equivalent to the plasmonic platform used in the optical sensing measurements.^{9,60,61}

Setup of the Gas Sensing Measurement System. As indicated in the schematic diagram in Figure 2a, the experiment system consisted of gas cylinders, a gas-mixing manifold and control system, mass flow controllers, an optical microscope, and a sealed gas chamber with the NPP sensor held inside. Specifically, the sealed gas chamber was placed on the microscope and the NPP sensor inside the chamber was focused using a 5 $\times$ objective lens (numerical aperture: 0.10) through a glass window on top of the chamber. The incident light (12 V, 100 W, tungsten halogen bulb) focused on the sensing platform is reflected back to the objective lens. We used two different types of equipment to capture the sensing signals, that is, a spectrometer and a CMOS camera, corresponding to the two sensing approaches that have been discussed in the previous sections. Specifically, the spectrometer was connected to the microscope by a fiber optical cable to collect spectra of the reflected light. The CMOS camera was mounted at one of the eyepiece positions of the microscope to capture the images of the sensing platform. In both modes, the data (spectroscopic or imaging) were saved for analysis.

In this work, a custom gas manifold system was used to produce different testing conditions. As shown in Figure 2a, compressed gases were mixed with dry zero-air and humidified zero-air (through a dew-point generator) at specific ratios to generate different testing cases. Two acetone cylinders were used, that is, 500 μ mol/mol acetone/dry air and 2000 μ mol/mol acetone/dry air. The total combined flow rate for all gases to the sensor chamber was targeted to be 2000 standard cm³/min (sccm) or less (depending upon desired analyte concentrations), and the maximum flow rate for acetone/air was controlled at 50 sccm. We report and use acetone concentration values at nominal levels in Figures 2–4, but a subsequent review indicated that there are minor deviations in the delivered acetone concentrations owing to bias from the certified values of the commercial gas cylinder contents and corrections in flow rates for CO₂. Table 1 summarizes the delivered acetone concentrations and associated uncertainty estimates.

In simulated breath backgrounds, acetone samples ≤ 10 μ mol/mol were generated using the 500 μ mol/mol acetone/air cylinder, while acetone concentrations >10 μ mol/mol were generated using the other acetone cylinder. Tests in the dry air background exclusively used the 500 μ mol/mol acetone/air cylinder. Various concentrations of CO₂ in the test cases were generated by mixing pure CO₂ with the test flow.

Table 1. Bias-Corrected Acetone Concentrations during Testing under Varied Backgrounds, Including Dry Air and Simulated Breath^a

nominal (μ mol/mol)	delivered (μ mol/mol)
0.5	0.5 $\pm$ 0.1
1	1.0 $\pm$ 0.1
2	2.0 $\pm$ 0.1
5	5.1 $\pm$ 0.1
10	10.2 $\pm$ 0.2
20	20.9 $\pm$ 0.7
40	41.9 $\pm$ 1.4
80	83.7 $\pm$ 3.1
160	162 $\pm$ 12

^aEstimated uncertainties ($\pm x$, $k = 1$) include those associated with flow rates and commercial cylinder concentration uncertainties, as well as variations from flow rate settings for the different background conditions.⁶² Note that the nominal 160 μ mol/mol concentration was tested only in a dry air background.

While the gas flow from a cylinder was turned off, the same volume of dry air was added to the system to keep the overall testing environment stable, including the total flow rate, CO₂, and relative humidity concentrations. We set the temperature at the dew-point generator at 22 $^{\circ}$ C and balanced it with dry air to generate the desired humidity level. In the Part II testing described in the Results and Discussion section, we tested acetone at various concentrations at 80, 85, and 90% relative humidity at laboratory ambient temperature (≈ 23 $^{\circ}$ C) to study the impact of moisture in the testing. Note that relative humidity levels presented in this work are for the laboratory ambient temperature. In the Part III testing, simulated human breath samples were created by mixing various concentrations of acetone with 2.8% CO₂ by volume in air at 80% relative humidity. Note that the relative humidity in exhaled human breath is usually saturated due to the temperature difference between the human body and the environment. In this initial work, we used 80% relative humidity to ensure better control of testing cases; transfer learning technologies can be applied to study breath samples with saturated humidity in real applications. Note that other methodologies may also need to be applied to achieve the desired outcome.

Later, we generated more complex testing cases to explore the limit of the plasmonic sensing system and the deep learning-based signal processing algorithm. Specifically, various concentrations of acetone with finer concentration increments were mixed with additional randomly varied CO₂ (2.1 to 3.5% by volume) and relative humidity (78 to 82%). The range of fluctuations for CO₂ and relative humidity was chosen based on the sensor response and human breath analysis reports in the literature.^{9,44,45,63,64}

Design, Training, and Testing of SensingNet. Figure 4d shows the architecture of SensingNet. The model consists of three main blocks. The first block applies blurring filters to remove any unusual pixels by averaging the pixel values with their neighbors. The second block picks the most sensitive areas from each image, and the third block predicts the final results. The first block has two convolution layers, a residual bridge, an upsampling layer, and an average pooling layer. The purpose of the first block is to eliminate any uneven pixels. An ideal sensing image should have uniform RGB values for each pixel on the same sensor. However, during the measurement, due to the distributed nature of the light source, the presence of fabrication-related contamination, and some adhered small particles, there can be an uneven distribution of the colors (RGB of the pixels). Depending on the level of unevenness, the sensing analysis may need to apply different levels of blur filters. Therefore, we used two convolution layers with a residual block to let the system pick the optimal blur-filtering process for each case. The upsampling layer doubled the pixels by adding a new pixel between every two pixels (the new pixel value is the average number of its neighbors). Then, the image size is reduced back by an average pooling layer. The up-sampling and

average pooling further helps to remove any uneven pixels of the input images. The second block consists of two groups of convolution layers and max-pooling layers; the number of filters is doubled as the size of outputs is reduced. The difference in color for each class is further enhanced, and the most sensitive pixels are automatically selected for better classification. For this work, we determined that two groups of convolution layers and max-pooling layers give the highest accuracy. In the case of a more extensive dataset or for different applications, it may be necessary to reduce or increase the layers to reach optimized performance. Finally, in the third block, the flattened data were sent to a few dense layers to make the final decision. We reach our best performance with three dense layers (with 64 filters/layer); it may again be necessary to adjust the number of layers and filters here to reach the optimized results for other applications.

In this work, we used a cost-effective CMOS camera (AmScope MD500⁵⁷) to monitor the sensor response through platform image capture. A more portable camera module such as a smartphone camera can also be used to measure the sensor response, based on our testing. This indicates that the system can be designed with small, cost-effective electronic modules as a portable device for daily usage. The acquired data (images) were first preprocessed by cropping the sensing area from the whole images, calculating the averaged RGB values, saving the cropped images, and storing the averaged RGB values, image paths, and the corresponding labels, including acetone concentration, relative humidity level, and so forth in a CSV file. These steps were processed by using Python⁵⁷ and open-source packages such as OpenCV,⁶⁵ pandas,⁶⁶ NumPy,⁶⁷ and so forth. While training the deep learning models, some information, such as interfering analytes' concentrations, CO₂ levels, relative humidity levels, etc., were kept unknown for the system to set up a testing environment close to real-world applications. Over 200,000 new data were captured and labeled. The images were labeled with the corrected acetone concentrations (see Table 1). 80% of the total data (including the 100,000 from the previous section and the 200,000 newly collected data) were used for training, while 10% were for testing and 10% were for cross-validation. TensorFlow⁵⁷ was used to build, train, and test the model (SensingNet) in this work. All the data were normalized before training/testing. The dimension of the input layers was resized to $3 \times 32 \times 32$ in order to reduce the number of parameters and speed up the training process. For each convolutional layer, the size of the filters was set as 3×3 , strides were set as 1, padding was set as True. The number of filters was set as 8 in the first convolutional layer and then doubled as the output size reduced (max-pooling) each time. For each dense layer, the dropout rate was set as 0.5 to prevent overfitting. The other hyperparameters were set as follows: the activation function was "relu" for all hidden layers and "softmax" for the output layer; the mini-batch size was set as 256; the optimizer was set as "adam"; the loss function was set as "CategoricalCrossentropy"/eq 1; "Accuracy" was used as the evaluating metrics during training since the data were evenly split for each class (i.e., background, safe, low risk, and high risk). Other hyperparameters were kept as default values in TensorFlow. The training process converged in 50 to 100 epochs depending on the size of the data. In this work, a confusion matrix was plotted after each cross-validation to verify the performance of the model such as accuracy for each class, number of mispredictions, false positive/negative rates, and so forth. The process was repeated until the optimal performance was reached. The output of the deep learning-based algorithm is described in the Results and Discussion section.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsami.2c11153>.

Sensing response analysis using PCA, LDA, and other CNN models and XPS analysis of the Cu-BTC MOF-coated NPP sensor (PDF)

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Notes

The authors declare no competing financial interest.

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