

Accelerated Colorimetric Gas Sensors with Emerging Robotic Laboratories

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Abstract: Chemical sensing refers to the detection and identification of chemical substances by converting chemical or physical properties of molecular or ionic species (i.e., analytes) into analytical signals. Recently, the emerging robotic laboratories, or self-driving labs, have played a crucial role by efficiently exploring a vast design space of the chemical gas sensors with the Design-Build-Test-Learn (DBTL) developing cycle, enhancing the experiment efficiency and consistency as well as tackling complex multivariable optimization. This integration allows for rapid and effective optimization of chemical sensing materials, paving the way for fast and on-demand development and deployment of new materials to application.

Keywords: Colorimetric sensor arrays, Bayesian optimization, Volatile Organic Compounds (VOCs), High-dimensional data analysis, Design-Build-Test-Learn (DBTL) methodology.

1. Introduction

New sensor technologies often face the challenge of balancing sensitivity and robustness. As sensitivity increases, a sensor's durability typically decreases due to poisoning during real-world use. Aging is particularly problematic for reusable sensor arrays. The electronic nose, or chemical sensor array, utilizes pattern recognition techniques to identify gases, relying on a library of patterns that must accurately represent the sensors' responses at the time of application. If sensor responses drift, these libraries can quickly become obsolete. One solution is to develop disposable sensors, decoupling the conflicting demands of sensitivity and robustness.

Gas colorimetric sensors based on chemo-responsive colorants probe the chemical reactivity of analytes rather than their physical properties. Unlike the traditional lock-and-key model, the chemical olfaction system uses pattern recognition from the combined responses of many olfactory receptors, allowing for broad chemical identification.

Challenges remain in ensuring consistent and reproducible responses for accurate predictions of unknown analytes, essential for enhancing the applicability of chemical sensors in environmental monitoring and safety applications.[1]

Traditional methods, such as trial-and-error and one-variable-at-a-time methods, has advanced sensor development but are severely limited when dealing with high-dimensional design spaces, such as limited sample sizes, poor reproducibility, and high labor intensity. This often results in unexplored areas and suboptimal solutions. Recent advancements in autonomous robotic laboratories, using closed-loop design-build-test-learn (DBTL) methodologies and artificial intelligence, provide

effective solutions. These systems can efficiently perform numerous experiments and analyze data to achieve rapid global optimization. However, real-world applications often require the simultaneous optimization of multiple objectives, rather than just a single one.

This article primarily reviews methods for accelerating the development of colorimetric gas sensors using robotic laboratories and discusses their potential applications.

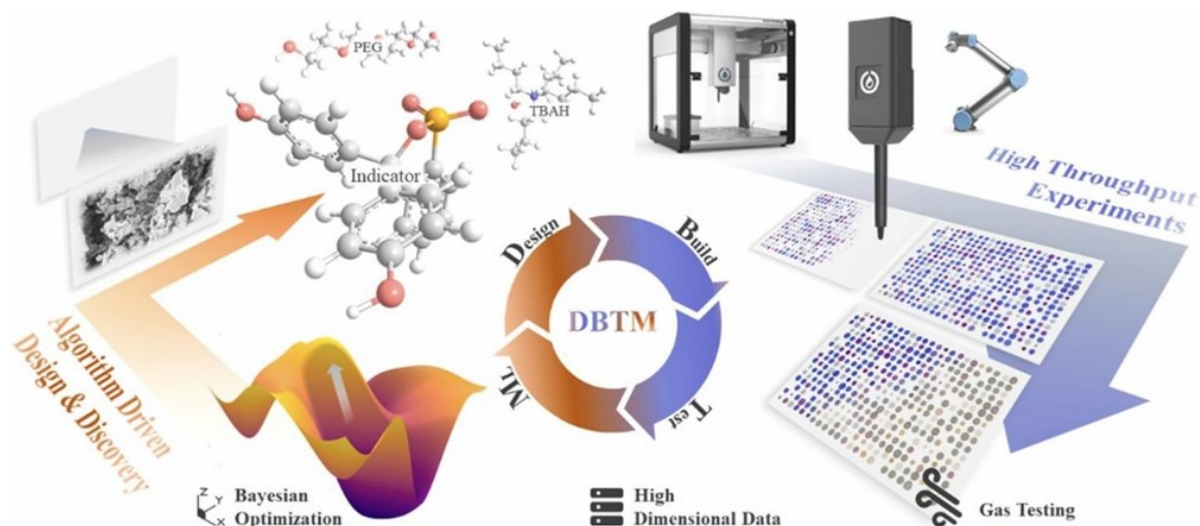


Figure 1: DBTM

Schematic of the iterative Design–Build–Test–Machine learning (DBTM) process supported by a high-throughput algorithm-drive autonomous system (HAAS) includes four steps: design, build, test, and machine learning. The Opentrons liquid handler supports the build process for synthesizing and preparing sensing units at high efficiency and repeatability. The high-throughput gas testing platform supports the test process for collecting data from up to 384 sensing units simultaneously. Machine learning is driven by our multi-target Bayesian optimization (BO) based on the collected data. Combined with machine learning and researchers' expertise, we design dosing combinations for exploration during the next iteration.

2. Success Story of Chemical Sensor Arrays

Sensor arrays typically include diverse sensors to enhance signal interactions, improving both sensitivity and chemical selectivity. These stronger interactions enable a broader range of chemical interactions beyond simple physical absorption, allowing for the identification of highly similar compounds and complex mixtures. An optimal optical sensor array combines colorimetric or fluorometric elements with diverse specificities and a range of chemical interactions. The matrix holding these dyes can further improve selectivity by altering the local environment or immobilizing the dye in a confined space, such as with molecularly imprinted polymers. Chemical sensor arrays excel in selectivity due to their ability to probe chemical properties, generating high-dimensional data that cannot be simplified into just a few coordinates. For instance, volatile organic compounds (VOCs) like amines, carboxylic acids, and thiols cause notable color changes when interacting with metalloporphyrin sensors. This type of sensor array can detect a broad spectrum of compounds, including alcohols, amines, aldehydes, and more, even at sub-parts per million levels without interference from humidity fluctuations. Its high-dimensional data allow for effective discrimination among complex mixtures without requiring component-specific analysis. Moreover, these sensor arrays maintain stability and reproducibility, with responses unaffected by temperature, humidity changes, or common interferences. Additionally, the colorimetric sensor arrays can be tuned to be

less sensitive to changes in humidity or temperature over a substantial range. The sensor array has shown excellent stability and reproducibility, with the response being independent of fluctuations in relative humidity and the presence of various common gaseous or liquid interference.

2.1. Volatile Organic Compounds

Initially developed by Rakow, Suslick, and collaborators, these arrays use metalloporphyrins to visually identify and differentiate a wide range of organic compounds, including alcohols, amines, ethers, aldehydes, and thiols. By inducing color changes through chemical adsorption, they achieve high sensitivity down to parts per million, unaffected by humidity. Recent advancements have expanded their capability to detect structurally similar analytes, with specific indicators for aldehydes and ketones, demonstrating low detection limits and excellent discrimination. These developments make colorimetric sensor arrays valuable tools in chemical analysis and environmental monitoring.

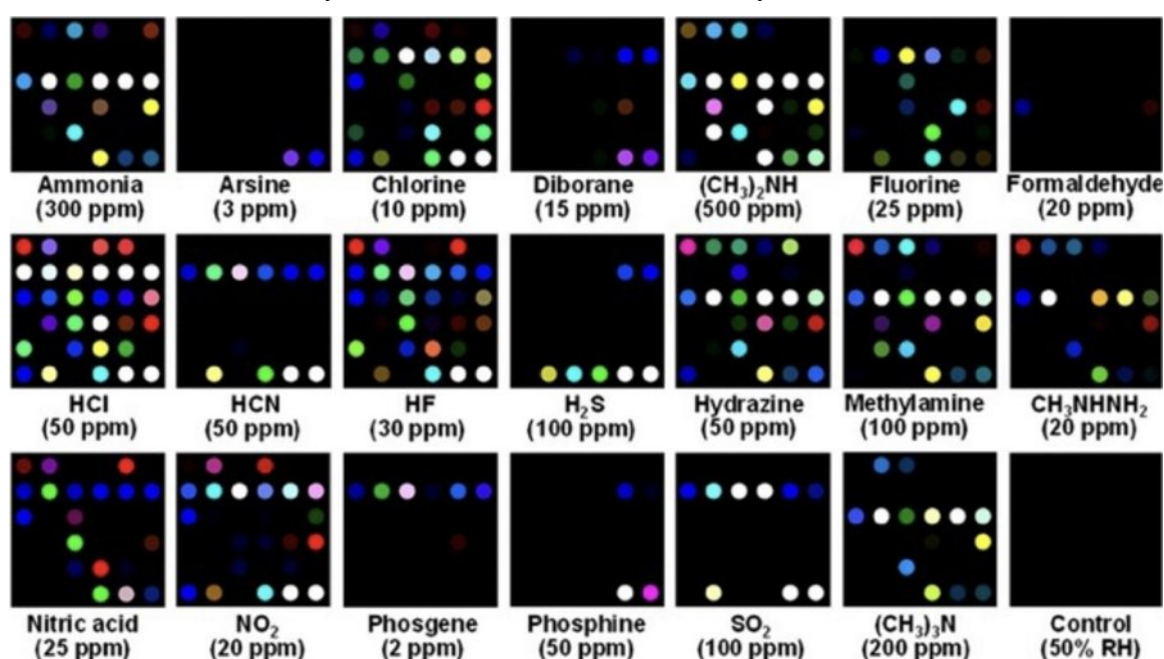


Figure 2: Color difference maps of 20 representative TICs at their IDLH.

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2.2. Toxic Industrial chemicals

Toxic industrial chemicals (TICs) are hazardous due to their reactivity and toxic effects on biological systems, such as enzyme inhibition (e.g., HCN inhibiting cytochrome c oxidase) and pulmonary damage (e.g., HCl, HF). Rapid detection and quantification of TICs are critical in chemical workplaces and during industrial emergencies. Current detection methods, including GC/MS, IMS, and electronic noses, have limitations like high cost and limited portability.

Colorimetric sensor arrays offer a promising solution by integrating chemically responsive indicators. Suslick et al. pioneered nanoporous sol-gel and plasticized pigment arrays, achieving high sensitivity and discrimination among 20 TICs, often detecting below 100 ppb. These arrays show rapid identification at both IDLH and PEL concentrations, with minimal errors and consistent performance despite environmental changes. Ongoing research focuses on developing specialized arrays for detecting TICs at varying concentrations, enhancing industrial safety and emergency response capabilities.[2]

All experiments were performed in septuplicate; no confusion or errors in clustering were observed in 147 trials. Reproduced from ref 175. Copyright 2010 American Chemical Society in figure3.

2.3. Aqueous Analytes

Aqueous analytes, dissolved or suspended in water, are often detected by measuring properties like pH, ion concentration, or the presence of specific substances. Colorimetric sensors detect volatile solute vapors in water using hydrophobic membranes and encapsulated dyes. Zhang et al. developed a sensor array that detects organic compounds at concentrations below 1 μM , visible to the naked eye. For heavy metal ions, Feng et al. created a sensor array using nanoporous pigments to detect ions like Hg^{2+} , Pb^{2+} , and Cd^{2+} at levels compliant with wastewater standards. Sensor et al. demonstrated a gold nanoparticle array that identifies metal ions like Pb^{2+} and Fe^{3+} with low detection limits of 2 μM and 10 μM . Additionally, Park and Lim integrated these arrays into paper-based microfluidics for detecting antioxidants in tea products. These advancements highlight the versatility of colorimetric sensor arrays in detecting heavy metals, pesticides, and antioxidants for environmental and food safety applications.[3]

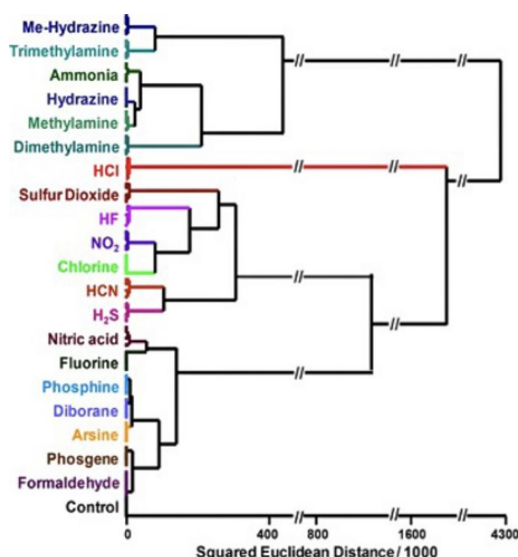


Figure 3: HCA dendrogram for 20 TICs at IDLH concentrations and a control.

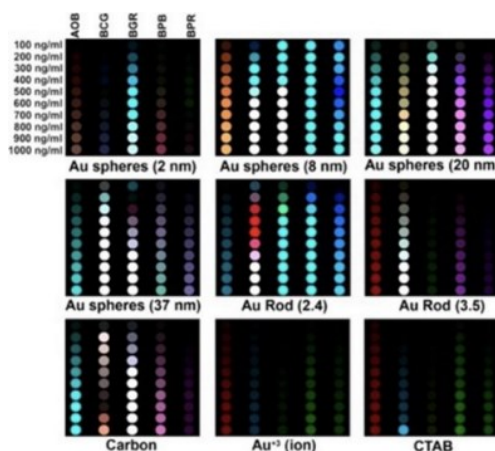


Figure 4

Color difference profiles of five sensor dyes after interaction with various NPs at different concentrations. For display purposes, difference maps were generated by subtraction of the solution absorbance before exposure from that after exposure in response to various NPs, carbon nanospheres, and precursor controls with three selected wavelengths (i.e., 480, 590, and 620 nm) assigned to RGB values; at each of these three wavelengths, absorbances from 0 to 0.484 optical density were mapped linearly to 0–255 in RGB values. Reproduced from ref 370. Copyright 2016 American Chemical Society in figure4.

2.4. Explosive

Recent advancements in explosives detection focus on optical and array-based sensors. While optical methods face challenges compared to techniques like ion mobility spectrometry, fluorescent detection of nitro-based explosives shows promise. Array sensors have made progress in detecting peroxide-based and homemade explosives by identifying specific chemical signatures. Tools like multicolor quantum dots and microfluidic paper-based devices (μ PADs) allow sensitive detection, such as μ PADs detecting TATP vapor at 2 ppb. However, ensuring consistent sensor array printing quality remains a challenge, critical for reliable detection in practical security applications. Research is ongoing to improve sensitivity and accuracy.

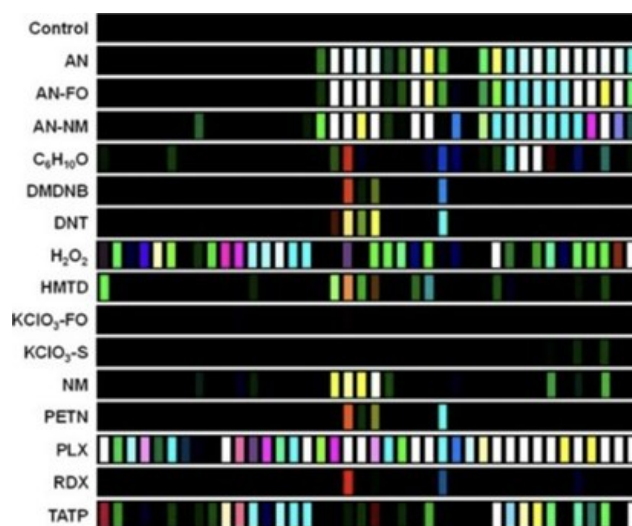


Figure 5: Copyright 2016 Royal Society of Chemistry.

Color difference maps of the 40-element linearized colorimetric sensor array with bar spots showing signal-to-noise ratios of 16 explosives, related analytes, and the control. Reproduced with permission from ref 32 in figure5.

2.5. Accelerants and Post-combustion Residues

Chemical sensor arrays have significantly improved in detecting accelerants like gasoline, diesel, and kerosene used in arson cases. Traditional colorimetric sensors struggle with low sensitivity to inert gases and hydrocarbons commonly found in accelerants. A pre-oxidation technique was developed to address this issue by exposing vaporized hydrocarbons to a strong oxidant, generating more reactive products like aldehydes and ketones. This pre-oxidation step enhances sensor responses, allowing precise discrimination between different types of petroleum products, including various gasoline grades based on octane ratings. The sensor arrays are effective before and after combustion, making them valuable for identifying accelerants in forensic investigations. These arrays are highly

sensitive, capable of detecting trace amounts of substances below 1% of their saturated vapor pressures from a library of 20 automotive fuels and control samples. They also show distinct response patterns between burned and unburned hydrocarbon samples, with unburned samples producing more complex responses due to evaporation and weak detection of combustion byproducts like CO₂. These advancements have practical applications in forensic science, environmental monitoring, and product analysis, where precise identification of hydrocarbon emissions is crucial.[4]

3. Emergence of Robotics

Chemical gas sensors are widely applicable across various fields, but optimizing sensor recipes and combining different sensors requires significant R&D efforts. Manually adjusting numerous variables for multiple goals is both labor-intensive and prone to errors. The advent of robotics labs, which increase experimental throughput and use data-driven algorithms, has introduced a new method for chemical and material development: the Design-Build-Test-Learn (DBTL) approach. This method improves efficiency, reduces labor, and ensures repeatability. A high-throughput strategy enhances the build and test stages, while machine learning algorithms analyze large datasets to design better sensor units in subsequent iterations.

In chemical sensor development, significant progress has been achieved through lab automation and DBTL. This allows simultaneous optimization of multiple sensor units, each tailored to specific concentration ranges, resulting in sensor arrays that provide a broad detection range and high sensitivity. Although setting up robotic labs for chemical synthesis and material characterization requires extensive engineering and financial investment, automating chemical sensor preparation and testing offers a more cost-effective solution. Automation typically involves using a commercial liquid handler for chemical solution preparation and a gas testing chamber with a camera for data collection, reducing complexity and cost, making it an attractive option for accelerating sensor innovation. [5]

Another critical component behind DBTL methodology is the optimization algorithm that drives the automated lab. One of the most widely used algorithm is Bayesian optimization algorithm, which is a group of black-box optimization algorithms. Unlike ordinary machine learning algorithms that tries to train a model mapping input parameters to outputs, the Bayesian optimization algorithms suggest the most promising parameters that could yield preferred targets given current collection of the data. The suggested parameters are prompted to the robotic lab and get experiment feedback of the actual target output to include in the collected data for next round suggestion. In other words, the Bayesian optimization was used iteratively with robotic experiments aiming to find the global optimum for the target. There are many out-of-box tools or software for carrying out efficient Bayesian optimizations.

The high-throughput strategy and aid of global optimization algorithm allowed researchers to obtain the optima more efficiently and robustly. Around 5 rounds of optimization iteration conducted within a week was reported to discover fully reversible and fast responsive chemical sensors for carbon dioxide. This successful demonstration of the DBTM approach showed the advantages of sensor optimization in multi-dimensional space. It minimizes labor compared with the traditional manual experimental method.[6]

4. Environmental monitoring

4.1. Air Quality Monitoring

Colorimetric gas sensors are widely used for monitoring air quality, particularly in detecting harmful gases like nitrogen dioxide (NO₂) and carbon dioxide (CO₂). These sensors function by changing color in the presence of specific gases, which can be observed directly without requiring sophisticated instrumentation. For example, in urban areas with high levels of vehicular emissions, colorimetric

sensors detect NO_2 , a common pollutant from car exhausts. The sensor contains a dye that reacts with NO_2 , leading to a visible color change. This allows for quick and real-time monitoring of air pollution levels. The simplicity and low cost of these sensors make them ideal for deployment in dense urban settings where continuous air quality monitoring is essential .[7]

4.2. Water Quality Testing

In water quality management, colorimetric sensors are used to detect the presence of heavy metals like lead (Pb) and mercury (Hg). These metals are highly toxic, even at low concentrations, and can contaminate water sources through industrial discharge or natural leaching. The colorimetric sensors work by incorporating a reagent that binds to the metal ions, causing a color shift that indicates the presence and concentration of the metal in the water. These sensors are particularly valuable in remote or underdeveloped regions where access to advanced laboratory facilities is limited. For instance, in situ testing with portable colorimetric sensors allows for immediate assessment of water safety, enabling quick decision-making to protect public health .[8]

4.3. Industrial Emissions Monitoring

Industries often emit various hazardous gases as byproducts of manufacturing processes. Monitoring these emissions is crucial to ensure compliance with environmental regulations and to protect both the environment and human health. Colorimetric gas sensors are employed in these settings to detect gases such as sulfur dioxide (SO_2) and ammonia (NH_3), which are common in industries like chemical manufacturing and agriculture. The sensors are designed to change color when exposed to specific gases, providing a straightforward method to assess the concentration of pollutants. This allows for continuous monitoring and helps industries maintain safe emission levels. The sensors are valued for their sensitivity and the ability to detect even trace amounts of harmful gases.[9]

5. Food

5.1. Monitoring Meat Freshness

Colorimetric sensors are extensively used to monitor the freshness of meat products like fish, pork, chicken, and beef. These sensors are designed to detect volatile organic compounds (VOCs) that are released during the spoilage process. As meat begins to spoil, it emits gases such as ammonia, hydrogen sulfide, and trimethylamine, which are indicative of microbial growth and protein degradation.

The sensors typically consist of a series of dye molecules that undergo a chemical reaction when exposed to these VOCs, leading to a visible color change. For instance, when trimethylamine, a compound released during the spoilage of fish, interacts with the sensor, it triggers a color shift from yellow to purple. This color change can be captured using a smartphone or a digital camera, and the intensity of the color shift can be analyzed to determine the level of freshness or spoilage. This method provides a rapid, non-invasive way to assess meat quality in real-time, helping to reduce food waste and ensure consumer safety [10]

5.2. Rapid Food Safety Screening

Gold-nanoparticle-based colorimetric sensors have become increasingly popular for the rapid screening of food safety issues, particularly in detecting hazardous substances like pesticides, toxins, and antibiotic residues in agricultural products. These sensors utilize gold nanoparticles because of their unique optical properties, which cause a noticeable color change when they aggregate in the presence of specific analytes. For example, in the detection of pesticide residues on fruits and

vegetables, the sensor changes color from red to blue when the nanoparticles aggregate upon binding with the pesticide molecules. This visible color change can be easily detected by the naked eye or with simple optical devices, providing a quick and reliable method for assessing food safety. Such sensors are particularly valuable in the field, where they can be used to perform on-site testing without the need for complex laboratory equipment.[11]

5.3. Detection of Chemical Hazards in Food

Colorimetric sensors are also employed to detect various chemical hazards, including heavy metals like lead and cadmium, antibiotic residues, and other toxic substances in food products. These sensors utilize nanomaterials or specific reagents that react with target chemicals, leading to a color change that can be easily observed. For instance, in the presence of lead, a common contaminant in certain foods, the sensor changes from one color to another, indicating contamination. This application is particularly important in environments where food safety standards are critical, such as in the processing of baby food or in areas where industrial contamination is a concern. These sensors offer a cost-effective and rapid method for ensuring that food products are free from harmful chemicals, thereby protecting public health .[12]

6. Extended applications

The key to DBTL's success is algorithm application. Researchers must identify essential parameters as the search space and the target(s) they wish to optimize. If multiple targets are involved, empirical preferences should be embedded in the target functions, or Pareto front techniques used.

When designing parameter space, knowledge of known relationships or chemical reactions can accelerate optimization. XXX developed a hypothesis-guided DBTL (H-DBTL) method using robots to expand the search space dimensions and achieve better global optimization. Based on the hypothesis that the chemical reactions relied on acid-base color changes, the exploration dimensions were reduced from 19 to 6 by introducing pKa as a parameter, improving optimization for ODT, PEL, and IDLH intervals. This demonstrated the H-DBTL methodology's strength in high-dimensional search space optimization.

More advanced principles for gas sensors can broaden applications, but also complicate the design space. Therefore, chemical descriptors should be further explored for more chemical mechanisms, aiding multi-target optimization with knowledge-aware algorithms.[13]

Along with the collected data, we can also apply data analysis tools for observation of discovery of scientific laws from statistical perspectives. In one sense, this could avoid biases of limited experiments; in another sense, the newly discovered or verified scientific laws could provide additional knowledge of high-throughput experimentation.

To push the method into tackling more complicated optimization problem, the array optimization can also be conducted with the same philosophy of combining high-throughput experiments and algorithms. Based upon the large amount of collected data, we can include the

Also, combined with natural language processing (NLP), the DBTL approach can be further enhanced. Researchers can obtain more hypotheses efficiently and accelerate the entire process of sensor development. With the fast development of large-language models, AI agent can automatically collect and read research articles, summarize critical chemical reaction components, and propose the design of the parameter space or search space for the researchers to review. [14]

7. Conclusion

In the past decade, chemical sensing has rapidly advanced in both sensing materials and analytical techniques, especially in array-based optical sensing. These arrays, using chemically diverse dyes or

biological receptors combined with chemometric analysis, can discriminate structurally similar analytes and mixtures. Unlike the lock-and-key recognition used in biological systems, sensor arrays utilize pattern recognition of cross-reactive sensors for specificity. This method enables sensitive and reliable fingerprinting of single compounds and complex mixtures. However, array-based sensing cannot provide detailed component-by-component analysis of mixtures and faces challenges in practical applications. Advances in portable, low-noise, and accurate optical instrumentation are addressing these challenges, moving towards real-world use. Develop more selective methods to "activate" analytes, especially in the presence of significant concentrations of interferents, to improve the sensing capability of current sensor arrays. Advance portable, low-noise, and accurate optical instrumentation capable of onboard and real-time analysis to meet real-world application needs. Enhance chemometric analysis of high-dimensional data to provide new methods for the optimal use of high-dimensional sensor arrays. Improve array-based assays to accurately predict the identity of unknown analytes and effectively eliminate disturbances from possible interferents.

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