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Enabling point-of-need chemical detection by miniaturizing ion-trap mass spectrometry

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A B S T R A C T

There exists a wide-ranging need to provide both qualitative and quantitative chemical information in near-real time outside of the laboratory environment. In response to this need, efforts in recent years have focused on the transition of laboratory-based instruments for chemical analysis into field-portable forms. Of the many techniques for chemical analysis, mass spectrometry has been an active area for miniaturization efforts due to the quality of chemical information the technique can provide and its ability to operate either stand-alone or coupled with additional analytical techniques. In this mini-review, we provide an overview of what we term 'point-of-need' chemical measurements and summarize the various means by which they can be generated. We then transition to focus exclusively on the application of mass spectrometry and specifically on the miniaturization of ion-trap mass analyzers to enable this class of measurements. Examples are provided that demonstrate how this technology has been developed and used within the point-of-need application space.

1. Introduction

Chemical information is often most advantageous when it is generated quickly at the point-of-need and used to guide a decision-making process to a beneficial result. *In situ* chemical detection is often tied to the end goal of hazard protection whether the hazard posed is from harmful chemicals or pathogens. Common examples include a hazmat team identifying unknown chemicals at an industrial or clandestine laboratory site or a soldier on the battlefield assessing potential threats such as explosives or chemical warfare agents. The desire for point-of-need chemical detection is expanding beyond these conventional applications into areas such as rapid diagnostics (e.g. rapid COVID tests) and bio-manufacturing where monitoring the health and progress of fermentation processes in real-time directly impacts the yield of therapeutic agents.

There are several approaches to sensing chemicals at the point-of-need. Targeted, single to few analyte detection systems such as lateral flow assays [1,2], colorimetric reagent-based sensors [3,4], and various electrochemical-based sensors [5] are quite common. These sensors can provide semi- to highly selective measurement solutions in a compact package with detection levels sufficient to provide early warning or detect-to-protect levels of safety. Scaling these detectors to address multiple analytes simultaneously requires bundling many individual sensors together within the same package. While it is possible to extend this approach for several analytes, it quickly becomes prohibitive considering the breadth and diversity of chemical targets.

The elucidation of the mechanism for mammalian olfaction in the 1990s [6] gave rise to the sensing concept of an 'electronic' or 'artificial' nose, where arrays of non-specific chemical transducers were bundled together and the pattern response across the array, rather than any single sensor, was used to elucidate a chemical's identity [7–10]. In principle, by processing the aggregate array response across a diverse training set of chemicals, these systems can identify many more analytes than there are individual sensors in the array, thus addressing the challenges associated with scalability in the single sensor-single analyte approach. Combinatorial sensor response models were initially developed using chemometric methods which have given way in recent years to machine learning techniques [11]. While a few detection systems utilizing this approach have crossed over into the commercial realm they have not found widespread use, largely owing to challenges with long-term response stability and reproducibility, and unpredictable behavior with complex samples containing multiple chemical species.

Another approach to facilitate chemical detection and/or identification at the point-of-need has focused on the miniaturization of laboratory-grade instruments for chemical analysis [12]. This top-down approach has the benefit of leveraging decades of understanding of how these instruments perform in the laboratory and the types of chemical information they can provide. Raman, FTIR, NIR, and X-ray fluorescence spectroscopy are all examples of laboratory-grade analytical techniques that have undergone reductions in size, weight, and power (SWaP) to the

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point where field portability and even hand-held operation is possible. Recent years have also seen the transition of Gas Chromatography-Mass Spectrometry (GC-MS) [13–15] and stand-alone mass spectrometry [16, 17] into field transportable and hand-held form factors, respectively. These systems have been commercially available since the mid-1990s from a number of instrument vendors and have been used to address a wide range of field detection scenarios [13,18,19]. Microfluidic platforms [20–24] and their more integrated counterpart micro-total analysis systems [25,26] have been an active source of development for over two decades now and have also been adopted commercially.

In order to move chemical detection techniques out of the laboratory and into environments where the operating conditions are much more variable, samples are much less controlled, and users are focused on simplicity and ease of use, several requirements must be met. The devices should be rugged, battery powered, capable of operating at the extremes of environmental conditions, require little to no sample preparation, and provide results quickly and clearly. As a result, the transition from laboratory-grade instruments to smaller, more mobile platforms typically require trade-offs in capability and/or performance to meet these portability requirements. No single technique has evolved in a manner that meets all the requirements, however for those that have come close, the commercial markets have materialized. In the remainder of this review, we focus on the miniaturization and development of ion-trap mass spectrometry into smaller, more ruggedized forms capable of providing rapid chemical detection at the point where it is needed. We provide a brief survey of the different types of mass analyzers with a focus on miniaturization. We then discuss the rationale for utilizing ion-trap based mass analyzers for miniaturization, along with the development of this platform into low SWaP form factors and provide a few examples of applications where these devices have found use along with some current avenues of research.

2. Miniaturization of mass analyzers

The long-running desire to adapt mass spectrometry instrumentation to make chemical measurements at the point-of-need comes as little surprise. Its speed, sensitivity, selectivity, and ability to interface with a variety of separation methods has led to mass spectrometry becoming the workhorse instrument for a wide range of applications from elemental analysis to studying large biomolecules in complex samples. Nearly all the common mass analyzers have, at one point or another, been the subject of miniaturization efforts. Mass analyzers range in complexity and analytical figures of merit but their differences in vacuum requirements are most relevant for miniaturization efforts as the vacuum system is almost always the largest contributor to the instrument's SWaP.

The vacuum requirements for every mass analyzer are reduced by shrinking the physical dimensions of the mass analyzer itself, albeit to different degrees. In instruments where it is desirable to have essentially zero ion-neutral collisions occur during analysis, reducing the distance ions must travel leads to a shorter allowable mean free path (i.e. higher pressure), such as time-of-flight and sector mass analyzers, but with a cost in resolution and/or sensitivity. Efforts to miniaturize TOF analyzers has yielded a steady reduction in size all the way down to a 5 cm flight path TOF with a resolving power of 330 [27]. Sector mass analyzers in the Mattauch-Herzog geometry have the additional benefit of needing only static fields and can use permanent magnets that draw no power. Early miniaturized sectors with flight paths of tens of centimeters, while impressive for their time, resulted in instruments in the 20 kg range, [28]. More recently, very small MEMS-based sectors are being developed that retain resolving powers over 100 with <2 cm flight paths [29]. Surprisingly, efforts have even been made to miniaturize a fourier transform ion cyclotron resonance (FT-ICR), the mass analyzer requiring the most stringent vacuum conditions by several orders of magnitude. This effort resulted in a large suitcase-sized instrument with an impressive resolving power over 1000 [30,31], though further reductions in size seem unlikely.

Quadrupole mass filters (QMF) are relatively pressure tolerant at 10^{-4}–10^{-5} Torr when compared to the previously discussed mass analyzers, and again, even higher pressures are tolerated as the ion flight path is reduced through miniaturization. While QMF's fairly high-power electronics scale favorably with size, maintaining the alignment tolerances needed for current commercial quadrupole rods is an already tall order that is even more challenging with miniaturization. MEMS and other advanced manufacturing techniques have allowed the miniaturization and commercialization of the QMF in recent years [32–34] although turbo pumping systems are still required. A commercially available residual gas analyzer has been developed which uses 1.27 cm long rods with an inscribed radius, r_o, of 0.33 mm [35]. Resolution was fairly constant up to 10 mTorr (~250X higher than full-scale QMFs). However, sensitivity saw a steep drop off with a 50% reduction at 2–3 mTorr due to increased ion-neutral collisions scattering ions before they reached the detector. Similar size analyzers have also been made using the precision of MEMS-based fabrication to aid in rod alignment [36]. In addition to their other merits, arrays of alternating rods can form many parallel mass analyzers operating in concert, helping to mitigate the loss in sensitivity observed upon miniaturization [37].

3. Miniaturizing ion-trap mass analyzers

There remain two significant issues common to miniaturizing the mass analyzers discussed above. First, in each case, their resolution is intrinsically dependent on the length of the ion flight path, presenting an unfavorable relationship to miniaturization. Second, none of these miniaturized instruments have reduced their vacuum requirements enough to eliminate the need for turbomolecular pumps. Eliminating these heavy, high power, and fragile pumps is vital for a durable and low-cost system suitable for field use. Radio frequency (RF) ion traps are the path towards overcoming both issues. In addition to less stringent machining and alignment tolerances, ion trap theory does not tie spectral resolution of an ion trap to the trap dimensions. Traditional ion traps also operate at 10^{-3} Torr, already ~100X the pressure of the next best mass analyzer. For these reasons the majority of miniaturization efforts have focused on ion traps, and to that end, many successful miniaturized traps have been developed and operated. Conventionally shaped ion traps with radii down to 500 μm have been made with traditional machining and down to tens of microns and below with microfabrication [38–40]. As with linear quadrupoles, parallel arrays of these traps can offset sensitivity losses arising from trap miniaturization. Ion traps containing toroidally-shaped trap electrodes have also been miniaturized [41,42]. Additional trap geometries that have been miniaturized include the rectilinear ion trap developed by the Cooks group [43], albeit while still relying on turbo pumps to maintain relatively low pressures.

A clear tradeoff between buffer gas pressure and spectral resolution is predicted by prior theoretical work. Early studies by Goeringer, et al. [44] predicted a linear increase in spectral peak widths (Δm/m) with increasing pressure (P) given by Eq. (1) below:

$$\frac{\Delta m}{m} \propto \frac{P}{\Omega_{RF}} = \frac{4\sqrt{3}}{\Omega_{RF}\tau} \tag{1}$$

where Ω_{RF} is the trap's RF drive frequency and τ is the resonant ion motion relaxation time due to ion neutral collisions. More recent work by Xu et al. [45] also predicted a linear dependence of peak width vs pressure and their model produced peak widths (fwhm) of 9.5 m/z at 250 mTorr of air buffer gas pressure in a rectilinear trap. This implies peak widths ca. 40 m/z at pressures greater than 1 Torr, the pressure regime needed for elimination of turbo pumps. This estimation assumed a constant RF drive frequency similar to traditional laboratory-based systems (~1 MHz), but as can be seen in Eq. (1) scaling the RF frequency higher is predicted to offset the peak broadening as the pressure

is raised. By operating traps in the 6–9 MHz range at 1.2 Torr, Ramsey et al. has demonstrated peak FWHM of ~1.0 m/z and ~4.5 m/z in both helium [46] and ambient air [47], respectively. Theoretical work by Arnold [48], that incorporates the mass of the buffer gas, agrees well with these data. This peak width vs pressure relationship has been validated all the way up to 60 MHz [49], producing ~1 m/z wide peaks in 1 Torr ambient air. This strategy of high pressure and high frequency operation has now been employed in commercial systems, resulting in the first mass spectrometers in truly handheld form factors.

4. Mass spectrometry at high pressures

The first commercially available mass spectrometer operating at high pressure was released by 908 Devices (Boston, MA) in 2014—the M908—and was focused on addressing the detection needs of the safety and security/first responder market. The device incorporates a miniaturized ion trap with critical dimensions in the hundreds of microns range capable of analyzing ions in the 50–400 Da range. A continuous inlet flow of approximately 2 sccm and ion trap pressure >1 torr is serviced by a compact scroll pump, roughly 2 cubic inches in volume. The core of the M908 – a pod containing the entire mass analyzer (ionizer, ion trap, and detector) – is easily replaceable which enables the user to swap in a new one quickly in the event it becomes contaminated. The M908 has a positive mode glow discharge (GD) ionization source compatible with the instrument's operating pressure. The M908 weighs 4.2 pounds, including a lithium ion battery supplying power for 2.5–4 h depending on the mode of operation. The unit is equipped with a small inlet pump that facilitates continuous analysis of ambient air samples, and it also houses a thermal desorbing unit that enables discrete analysis of condensed phase materials from a collection swab. The M908 performs a full mass scan at 2 Hz and compares the resulting mass spectra to a database of common toxic industrial chemicals, chemical warfare agents, select drugs of abuse, and various precursor chemicals. If a library match is detected by the algorithms, an alarm is displayed to the user along with information about the hazards associated with the particular alarm. Since the device was built for use by first responders, the automated detection/matching algorithms eliminate the need for any advanced technical knowledge or skills on the part of the operator. Detection limits for the M908 were in the low ppm range for vapors and the single microgram range for solids and liquids, depending on the chemical.

The M908 was followed up with the release of the MX908 in 2017, a second generation micro ion-trap device that is also focused on the point-of-need chemical detection requirements of first responders in the field forensics market. The MX908 is slightly larger than its predecessor, weighs in at 9.5 pounds including battery, and can operate continuously for 3–5 h on its internal Li-Ion battery. Both the M908 and the MX908 use similarly designed ion-trap mass analyzers, however the MX908 utilizes corona needle based atmospheric pressure chemical ionization (APCI) as its ionization source. This type of ionization source generates reagent ions from ambient air which then proceed to ionize analytes via ion-molecule reactions [50–52] The higher ionization efficiency at atmospheric pressure, due to higher collision rates, along with higher inlet flow (~6 standard cubic centimeters per minute (sccm)) led to a significant improvement in sensitivity, with detection limits 100–1000x lower than the M908. The MX908 also generates both positive and negative mode mass spectra in real-time with rapid switching of the source polarity. The MX908 also employs in-source collision-induced-dissociation (CID), whereby the full mass-spectral response for the compound of interest is evaluated, and then select electromagnetic (EM) fields are energized to cleave the ions into daughter ions. The resulting series of ions at their respective dissociation energies provides far greater statistical confidence in the evaluated mass-spectral response. The MX908 currently performs this type of analysis automatically without guidance from the operator. An example of the discriminating ability of CID is shown in Figure 1 below where two isobaric compounds, VX and Russian VX (RVX), are distinguished from one another by deliberately breaking them into fragments of different masses using two collision energies, a process which takes about a hundred milliseconds in the device Figure 1.

The added selectivity provided by CID [46] in the MX908 has significantly expanded the range of targets to hundreds of different compounds across threat classes including drugs of abuse, explosives, chemical warfare agents, precursors and industrial chemicals. By combining CID with advanced algorithms, the MX908 can alert the user to derivatives of fentanyl that are not currently in its library based on similarities in fragmentation patterns. The MX908 is also able to address wide range of sample phases via interchangeable front-end modules that are optimized for the collection and analysis of vapors and aerosols in ambient air or condensed-phase analytes via swab thermal desorption.

5. Point-of-need bioprocessing applications

Point-of-need analyzers are also widely used in bioprocessing laboratories. With cell culture growth cycles ranges from several days to several weeks, rapid feedback in analytics is critical for high throughput experiments. Mass spectrometry in the process development space has generally been limited to central laboratory settings where complicated systems are run by highly trained users. Turnaround times on the order of days to weeks are common given the need to package, transport, and analyze samples at a separate location. Ideally, a simplified analyzer would be run next to a bioreactor and the data would be analyzed by a user who has limited knowledge of the measurement technology but requires the information it provides quickly so that process conditions can be adjusted. These analyzers must be robust, simple to use, self-calibrating, and require little to no data interpretation; functioning as a black 'answer' box. They should be compatible with a regulated laboratory environment and standard laboratory IT security including the 21 CFR Part 11 compliance checklist.

Key aspects of the bioprocessing application are raw materials analysis and analyzing metabolites in fresh and spent media samples. Differences between batches of media samples is a concern for cell culture scientists and engineers due to the culture-to-culture variability they can induce. Fast and accurate methods to analyze these samples are needed to ensure they meet acceptance criteria. Understanding metabolite changes during a cell culture experiment are used to understand growth patterns and optimize for product quality attributes and yield. They are also essential for accurate modeling of the bioreactor process and scaling reactor volumes.

The Rebel, also from 908 Devices, was launched in 2019 as a spent media analyzer with the capability to quantitate 32 metabolites including amino acids, biogenic amines, dipeptides, and B vitamins. The device combines a microfluidic capillary electrophoresis (CE) chip and electrospray ionization (ESI) with a microscale ion trap MS in a single, desktop computer sized form-factor. The fully integrated design of the Rebel also bundles the vacuum pump, autosampler, and reagent handling within the single enclosure. The CE-ESI-MS operation at high pressure has been covered in detail in previous publications [53,54], but a brief overview will be discussed. The Rebel samples are diluted a minimum of 10x in a diluent that includes internal standards used for quantitation. The Rebel CE chip, diluted media samples, and BGE are loaded into the device after which all sample manipulation is performed by an integrated autosampler. A pressure-based sample injection is used to load approximately 4 nL of sample into the chip separation channel where analytes are separated by electric fields applied to the chip wells. The analytes are detected via ESI by the MS detector, which consists of a microscale ion trap running over a mass range from 75 to 300 m/z. The entire process of loading and analyzing a single sample takes 7 min including all fluidic operations and quantitative analysis by the automated algorithms. Only 3.5 min is actually spent on the analytical separation and analysis.

The image plot Figure 2 shows CE migration time on the x-axis, m/z

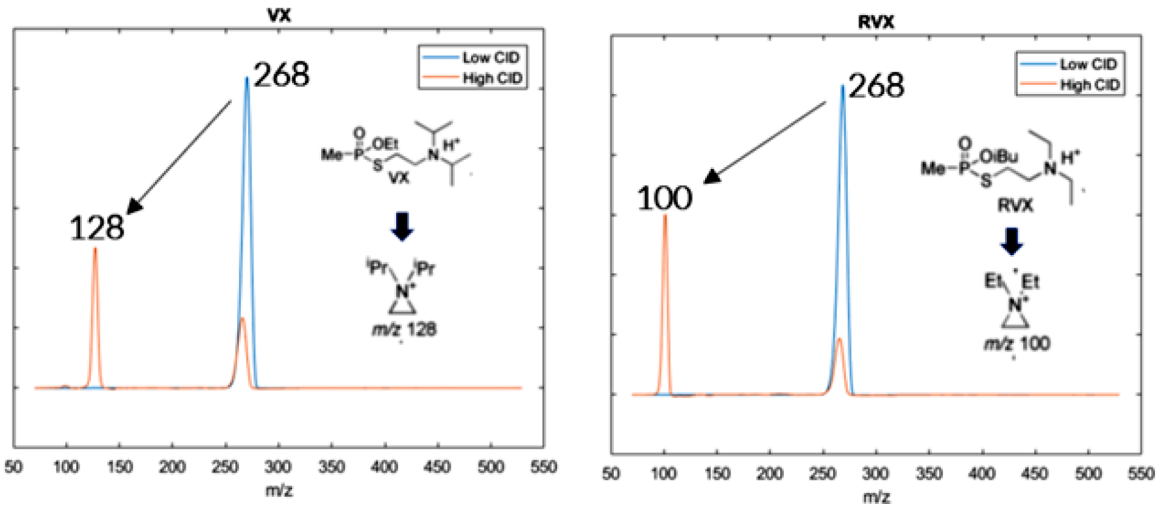

Fig. 1. MS of VX (Left) and RVX (Right) from an ion trap MS operating above 1 torr. Blue traces, under low-CID energy conditions (25 V), show identical mass spectra for these isomers. Red traces, using high-CID energy (70 V), fragment ions tend to dominate the resulting mass spectrum.

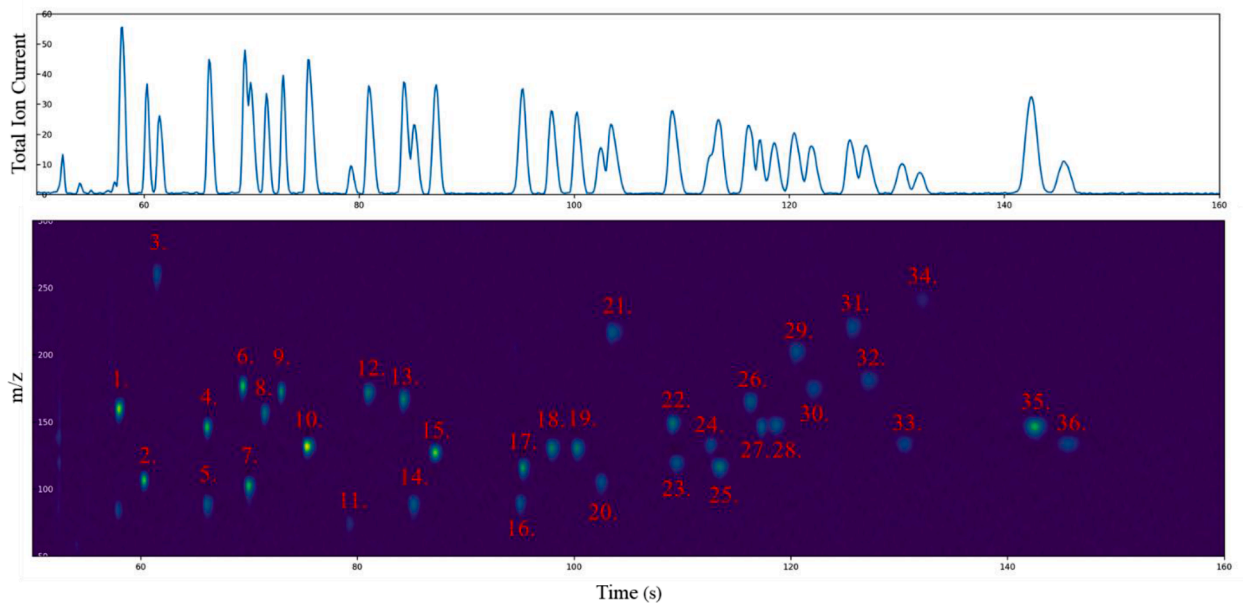

Fig. 2. Top – Total ion current vs. time of a CE-MS trace on Rebel demonstrating the separation of 31 analytes in just over 2.5 min. Bottom - Image plot demonstrating additional analyte separation via the mass (m/z) axis. Analyte identities in the image plot are as follows: 1-Homolysine, 2-Choline, 3-Vitamin B1, 4-B-Alanine, 5-Lysine, 6-Arginine, 7-GABA, 8-Histidine, 9-Methylhistidine, 10-Pip, 11-Glycine, 12-Vitamin B6-OH, 13-Vitamin B6-Oxo, 14-Alanine, 15-Nicotinamide, 16-Sarcosine, 17-Valine, 18-Isoleucine, 19-Leucine, 20-Serine, 21-Alanyl-Glutamine, 22-Methionine, 23-Threonine, 25-Proline, 26-Phenylalanine, 27-Glutamine, 28-Glutamic Acid, 29-Tryptophan, 30-Citrulline, 31-5F-Trp, 32-Tyrosine, 33-Aspartic Acid, 34-Cystine, 35-Me-Asp, 36-Hydroxyproline.

on the y-axis, and signal intensity of the mass spectra as the color intensity. The four internal standards were analyzed at 50 uM concentrations while all other species were detected at 25 uM. The 32 components currently analyzed by the Rebel include 19 of the 20 common amino acids excluding cysteine, 4 B Vitamins (pyridoxine, pyridoxal, thiamine, and nicotinamide), 2 dipeptides l-Alanyl- l-glutamine and cystine), and 7 biogenic amines (B-alanine, aminisobutyric acid, choline, citrulline, hydroxyproline, methylhistidine, and sarcosine).

As the platform develops and matures the target list should expand to cover more metabolites of interest that are present in bioreactors. Nucleic acids, other biogenic amines, and an expanded range of di- and tri- peptides are all within reach of this platform. Additional Rebel library expansion could be possible through derivatization of neutral and negatively charged species in solution to convert them to positive ions. Further opportunities for library expansion would be possible using a negative mode separation and ESI. The HPMS detector has already been proven as a dipolar mass analyzer through the MX908 applications.

6. Future directions

Miniaturized ion-trap mass spectrometers operating at high pressure will continue to advance in their analytical capability while simultaneously progressing towards smaller form factors. Ion-trap mass analyzers in general offer several unique scan modes that can translate into improved performance for point-of-need applications. For example, resonant ion ejection from the trap using axial RF scans [44] offers the potential for lower power consumption and increased mass resolution. Targeted ion isolation/fragmentation techniques such as MS-MS or Stored Waveform Inverse Fourier Transform (SWIFT) [55] operation

offer the possibility of qualitative analysis with even greater specificity. As the devices continue to evolve so too will the application space. Bioprocessing applications that are currently at-line will trend toward more fully integrated 'in-line' systems, where the need for a user to collect and input samples into the device is removed, further lowering the operational burden. There is also a large application space focused on the processing of human biological samples whether for toxicological purposes, for example screening biofluids for drugs of abuse, or for diagnostic purposes such as tracking biomarkers associated with a disease state. Technological advancements in commodity electronics, computing, algorithms, and long-range wireless communications will set the stage for more ubiquitous chemical sensing platforms [56], whether they be deployed as environmental monitoring systems or as feedback systems controlling and adjusting manufacturing processes on the fly. Finally, the high-fidelity chemical detection enabled by miniaturized ion-traps will undoubtedly play a role at the robotic interface, providing machines and unmanned vehicles [58] with virtual olfaction [57] such that remote chemical detection with little to no direct human engagement downrange is possible.

Declaration of Competing Interest

None.

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