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# Automated and robotic sample delivery systems for mass spectrometry and ion-mobility spectrometry

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Mass spectrometry (MS) and ion-mobility spectrometry (IMS) are two complementary tools enabling atomic and molecular analysis. While MS provides mass-to-charge ratio values and fragmentation patterns facilitating molecular identification, IMS enables rapid separation of chemical species by size. The two techniques are often combined to benefit from the advantages offered by both. To match the needs of contemporary research and industrial activities, these techniques have been upgraded by integrating them with automated and robotic sample delivery systems. Automation eliminates or decreases human labor involved in sample handling. It also allows for high-throughput analysis, thus increasing productivity. This is especially important considering the capital cost of MS. The common approaches to automation involve the use of autosamplers, flow-injection analysis systems, microfluidics, and robotics. In this perspective, we highlight single-cell analysis as a prominent application area of automated MS methods.

## Introduction

Automation has become a buzzword across STEM fields in the 21st century, reflecting both widespread interest and diverse interpretations. It is also a notable trend in modern chemical science and engineering. Interestingly, the word “automat” and its derivatives have different meanings around the world. In English, it signifies a type of self-service restaurants, which used to be popular in major US cities in the beginning of the 20th century,<sup>1</sup> while in some other languages related terms refer, more generally, to other automatic devices such as vending machines, gambling machines, or even, colloquially, automatic transmissions or ATMs. On the other hand, the word “robot” is derived from the Czech noun “robota” (“forced labor”), and it first appeared in the play titled “Rossum’s Universal Robots” by Karel Čapek from 1920.<sup>2</sup> Later, in the 1939 New York World’s Fair, the Westinghouse Electric Corporation presented a humanoid robot called “Elektro”, which could walk, talk, and even smoke cigarettes.<sup>3</sup> Invented by George Devol, Unimate holds the distinction of being the earliest industrial robot ever created.<sup>4</sup> It functioned as a hydraulic manipulator arm engineered to carry out repetitive manufacturing tasks. Automakers employed it to streamline operations like metalworking and welding. The International Union of Pure and Applied Chemistry defines automation as “mechanization with process control, where process means a sequence of manipulations”.<sup>5</sup> In practice, however, the term is applied much more broadly in common usage. Further discussion provides an overview of efforts to integrate broadly defined automated and

robotized systems with mainstream analytical platforms such as mass spectrometry (MS) and ion-mobility spectrometry (IMS). The examples and references highlighted here are intended to illustrate key developments, rather than to exhaustively cover the field.

## Mass spectrometry

MS is a key tool used for identification and quantification of elements and compounds.<sup>6–9</sup> It enables ultrasensitive analysis of organic molecules.<sup>10</sup> Mass spectrometers consist of three main blocks: ion source, mass analyzer, and detector. Considering a variety of potential applications, the ion source is the component that determines a mass spectrometer’s flexibility and usability. Frequently used ion sources include: electron ionization, chemical ionization, atmospheric pressure chemical ionization, electrospray ionization (ESI), and matrix-assisted laser desorption/ionization (MALDI).<sup>7</sup> Efficient formation of gaseous ions and their transmission to the mass analyzer is essential for achieving high sensitivity. For example, ESI enables transferring analytes from the liquid phase to the gas phase, generating charged species.<sup>11,12</sup> Ion sources are often interfaced with other analytical devices to expedite the analysis of many samples and enable analysis of matrix-rich samples. Some MS interfaces are simplistic (*e.g.*, a tubing connecting two components), while others are complex, and incorporate many elements (*e.g.*, transmission lines, transducers, or elements of robotics).

## Ion-mobility spectrometry

Ion-mobility measurements were pioneered by John Zeleny in the end of the 19th century.<sup>13</sup> He demonstrated that the velocity

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of atomic ions traveling through a gas-filled tube (utilizing air, oxygen, nitrogen, and carbon dioxide) under the influence of a weak electric field varied depending on both the type of gas and the ion.<sup>14</sup> He noted that the observed velocity difference in two ions can be due to an inequality in the size of the two ions.<sup>13</sup> Currently, there exist several types of IMS techniques: drift tube IMS (DT-IMS), travelling wave IMS (TWIMS), trapped IMS (TIMS), field asymmetric IMS (FAIMS), and differential mobility analyzer (DMA) IMS. DT-IMS—often regarded as the classic IMS model—is valued for its simplicity, straightforward operation, and capacity to directly measure ion mobility and calculate collision cross-section (CCS).<sup>15</sup>

Although standalone IMS systems are very convenient and downscalable, combining IMS with MS has significantly expanded the resolution of chemical analysis.<sup>15</sup> The complementary separation processes in both the ion mobility and mass dimensions offer remarkable improvements in selectivity and sensitivity.<sup>15</sup> In the early days, ion mobility-mass spectrometry (IM-MS) instruments were primarily custom-built in academic laboratories. Wider adoption as a routine analytical tool began in 2006 with the launch of the Waters Synapt HDMS, the first widely available commercial IM-MS platform. Following the success of this commercial implementation, other instrument manufacturers quickly developed their own IM-MS systems, incorporating different ion mobility separation techniques to enhance the selectivity of MS, especially for analyzing complex mixtures.<sup>15</sup> Most recently, two high-performance IMS platforms have been developed: cyclic IMS<sup>16</sup> and structures for lossless ion manipulations (SLIM).<sup>17</sup> These techniques are based on the general concept of TWIMS. They achieve high-resolution separations due to the very long ion migration pathlengths, which are in the order of tens of meters.<sup>18</sup> Because some IMS separations can be accomplished on a millisecond timescale, they can also be easily integrated into traditional gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) workflows.<sup>15</sup> Ion mobility introduces an additional layer of separation to LC-MS-based untargeted metabolomics.<sup>19</sup> The developments in IM-MS have enhanced metabolite annotation by providing an additional conditional molecular descriptor: CCS, thereby increasing confidence in identification.<sup>20</sup> An ion-mobility CCS atlas has been created for metabolite annotation.<sup>21</sup>

Despite its potential, the complexity of ion-mobility-resolved metabolomics data poses significant challenges for processing, thus limiting its broader adoption. Advanced computational tools now facilitate the distinction of co-eluted metabolite isomers that exhibit subtle variations in chromatographic and ion-mobility dimensions.<sup>19</sup> It is appealing to further develop coupling of IMS with sample preparation and separation systems, to enhance metabolomic analyses.

### Our perspective

In this perspective, we discuss approaches to automation, highlighting single-cell analysis as a key area that increasingly benefits from automated workflows. Furthermore, we categorize two key areas that define how robotics are currently applied

in modern online MS and IM-MS workflows: sample preparation and sample delivery. Here, robotic sample preparation systems refer to automated platforms that use robotics in sample preparation and subsequent delivery to MS or IM-MS, while robotic sample delivery systems refer to automated platforms that utilize robotics for sample handling and direct delivery to MS or IM-MS without multistep sample preparation. We highlight and discuss robotic systems for sample preparation and delivery, providing representative examples of their application in MS and IM-MS analytical workflows. Advancements in technologies such as artificial intelligence (AI) continue to drive the evolution of analytical methods. Although still in their early stages, other robotic applications—including those integrating AI—are also discussed later on.

## Automation

### Automated flow injection-based techniques

Conventional direct infusion ESI-MS measurements are conducted by filling a glass syringe with the sample, fixing the syringe in a syringe pump holder, attaching sample flow line to the syringe tip, and starting the pump. However, this mode of operation requires many manual operations, is time consuming, and does not enable high-throughput sampling. Therefore, other ways of sample introduction are used to increase sample throughput, and—in some cases—collect analytes from surfaces. Flow-based analytical techniques have been pivotal in streamlining sample handling and delivery in MS workflows. The concept originated from flow injection analysis (FIA), which was introduced in the 1970s by Růžička and Hansen.<sup>22,23</sup> FIA enabled the generation of reproducible transient signals by precise and controlled injection of a defined volume of the sample into a flowing carrier stream.<sup>22–24</sup> While conceptually distinct from segmented flow analysis introduced by Skeggs in the 1950s—which used discrete sample zones for clinical assays—FIA laid the foundation for contemporary flow-based methods.<sup>25–27</sup> Over time, its development can be described in three generations, reflecting the evolution from classical FIA to sequential injection analysis (SIA) and, subsequently, to bead injection-lab-on-valve (LOV) systems.<sup>24,28,29</sup>

Flow techniques, such as FIA, SIA, or multisyringe flow injection analysis (MSFIA), permit controlled and reproducible handling of liquid samples.<sup>26,30</sup> The flow techniques use valves, tubing, columns, phase separators, or even multiple syringes<sup>30</sup> to manipulate the flow of liquids, merging segments of liquids,<sup>30</sup> and extraction processes.<sup>26</sup> They have been used as a strategy to automate microextraction techniques.<sup>26</sup> SIA was also used for dispersive liquid-liquid microextraction (DLLME) on a commercial FIALab 3500 system connected to a fiber-optic charge-coupled device for detection.<sup>31</sup> Other modifications incorporated a syringe as a DLLME extraction vessel (in-syringe DLLME).<sup>32–35</sup> Direct infusion sample delivery to ESI-MS can also be “automated” allowing for the control of sample concentration,<sup>36</sup> optimization of sample flow rate,<sup>37,38</sup> or switching modifier vapors in the ionization region.<sup>39</sup>

It has been argued, however, that the use of flow systems does not necessarily imply automation.<sup>30</sup> Rather, automation is



characterized by the utilization of a computerized control system that incorporates a feedback loop.<sup>30</sup> Therefore, while the attempts discussed above may have addressed several analytical challenges, it is important to note that they may not be strictly classified as “automated” because they were either not computerized or lacked a feedback loop.<sup>30</sup> Although classical FIA is not inherently automated, as it can be performed manually using simple pumps, modern implementations often utilize LC autosamplers and computer-controlled pumps to deliver sample plugs directly to the mass spectrometer. In these setups, FIA effectively becomes automated, enabling precise, reproducible, and high-throughput operation. This approach is commonly applied on existing LC-MS systems by bypassing the chromatographic column, allowing rapid sample delivery into the ion source.<sup>40–43</sup> Coupling FIA to a drift tube IM-MS (DTIM-MS) has also been demonstrated using this approach.<sup>44</sup> While it does not fully replace conventional LC-MS, FIA—combined with tandem MS—provides a practical, high-throughput alternative for screening applications.

### Microfluidic systems for automated sample delivery

Microfluidics uses micrometer-scale channels to manipulate below nanoliter volumes of fluid.<sup>45,46</sup> The fluid flow, whether pressure- or electrically driven, is highly controlled and typically characterized by laminar behavior.<sup>45,46</sup> Microfluidics streamlines complex workflows by supporting multiplexed, automated control and sample processing within a single integrated system.<sup>47–49</sup> The automated control is mostly achieved through the use of electronic circuits, particularly, transistor-based analog and digital circuit designs.<sup>50</sup> The sample processing steps include droplet sorting and isolation, cell lysis, protein digestion, sample cleanup, and sample deposition. Microfluidic approaches, such as continuous-flow systems,<sup>51</sup> microchip electrophoresis,<sup>52–54</sup> centrifugal,<sup>51</sup> digital,<sup>51,55,56</sup> droplet,<sup>57,58</sup> and paper<sup>59,60</sup> microfluidics, have been coupled with MS. Direct coupling can be challenging due to differences in geometry, pressure, phase, wettability, and electric current.<sup>55,61</sup> This was particularly evident in attempts to integrate continuous flow systems with MALDI and matrix-free laser desorption/ionization,<sup>62</sup> as well as multi-phase or discrete flow systems with spray ionization techniques.<sup>55</sup> Developments in droplet microfluidics have progressed significantly. Key focus areas include droplet generation and manipulation, integration into chip-based systems, improved resolution and sensitivity, applications in microscale and molecular technologies, and interfacing with MS.<sup>53–55,61</sup>

Consequently, efforts have focused on developing interfaces that enable online analysis. The most common type is the continuous flow microfluidics system, which is pressure-driven,<sup>51</sup> whereas microchip electrophoresis is also a continuous flow system, but the flow is driven by an electric field.<sup>51</sup> Microchip electrophoresis evolved from the miniaturization of capillary electrophoresis (CE).<sup>52</sup> Centrifugal microfluidics is primarily used for automated, controlled sample preparation by using centrifugal forces to move fluids radially outward from the center of a disc.<sup>51</sup> These continuous flow regime

microfluidics have been employed in microchip electrophoresis-IMS,<sup>63</sup> chip-electrochromatography-IMS,<sup>64</sup> and in centrifugal microfluidics integrated with probe ESI-MS to enable automated, time-controlled sample processing.<sup>65</sup>

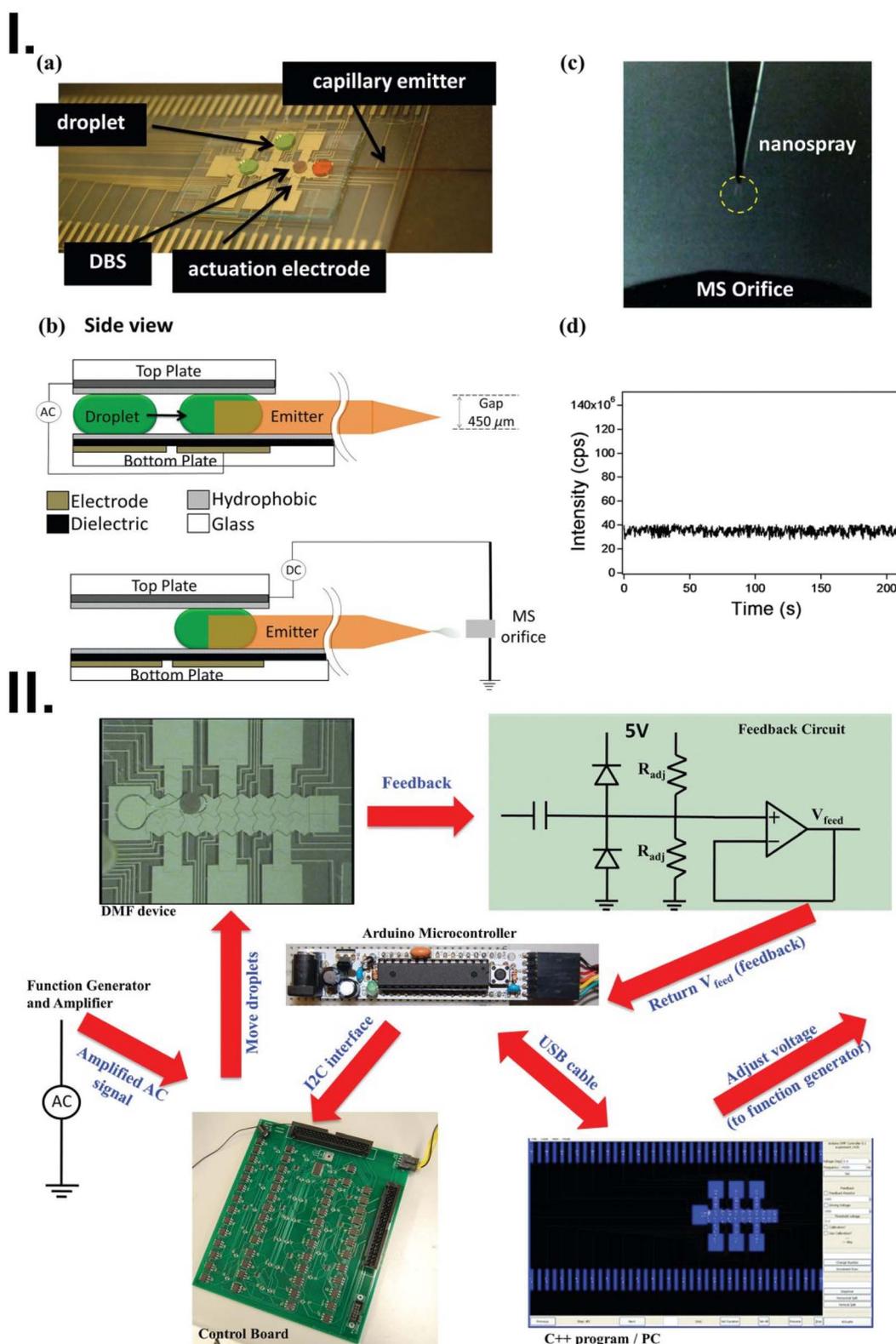
Continuous-flow systems are commonly used in perfusion or separation-based experiments,<sup>65</sup> as well as in sample preparation workflows<sup>66–68</sup> and lab-on-chip devices.<sup>69,70</sup> They facilitate the delivery of minute sample volumes to microarrays or MALDI plates, thereby enabling automated workflows.<sup>71,72</sup> Automation permitted tuning of culture conditions for real-time measurements by incorporating a culture chamber/chip, multiplexed chips, and a control device equipped with valves and software.<sup>48,49</sup> Furthermore, chip-based and capillary-based microfluidics have been integrated to simplify the setup of nanospray desorption electrospray ionization (DESI) mass spectrometry imaging (MSI),<sup>73,74</sup> and to streamline the interfacing and assembly of chip-based supercritical fluid chromatography (SFC) with MS<sup>75,76</sup> and IMS.<sup>77</sup>

Compartmentalization involves physically isolating samples into discrete volumes, reducing interference and cross-contamination.<sup>46,78,79</sup> This enables spatially confined reactions<sup>79</sup> and parallelized assays to improve throughput.<sup>79</sup> Compartmentalization is achieved through several methods, such as by closing channels with valves, typically implemented using multilayer elastic chips with control channels;<sup>79,80</sup> by isolating samples in micro/nanowells;<sup>58,80</sup> or by generating water-in-oil droplets.<sup>45,46,79–82</sup> The Fluidigm C1 system is a microfluidic chip-based automated commercial system that uses a compartmentalized microfluidic approach. In the C1 system, single cells are captured and isolated into discrete reaction chambers within integrated fluidic circuits (IFCs).<sup>83</sup> It is an electrically and pneumatically operated desktop instrument with built-in vacuum pump to position IFCs.<sup>83</sup> While not interfaced with MS, it has been used to automate entire molecular biology workflows (*e.g.*, cell capture, lysis) for single cell genomics.<sup>80,84,85</sup>

### Microfluidic platforms interfaced with MS

Interfacing droplet microfluidics with MS was considered challenging because the sub-microliter monodisperse bubbles or droplets of a dispersed gas or liquid are created in a continuous flow of immiscible carrier/mobile liquid,<sup>45,82,86</sup> on- or off-chip.<sup>72,82,86</sup> The carrier/mobile liquid of the microdroplet-encapsulated analyte generally contains halogens and surfactants for droplet stability but these may cause instability of the Taylor cone and contamination of the mass spectrometer.<sup>82,86–88</sup> Coupling strategies have involved isolating the droplets from the carrier flow prior to ionization and diverting the carrier flow to waste.<sup>86</sup> For example, Fidalgo *et al.* used fluorescence screening to trigger application of voltage that merges the droplet with a sheath liquid, thereby isolating the droplet.<sup>87</sup> However, this process causes dispersion of the droplet contents.<sup>87</sup> Furthermore, Küster *et al.* automated the deposition of aqueous droplets onto microarrays of hydrophilic spots within hydrophobic coating by using an optical detection system for real-time differentiation of droplet deposition.<sup>57</sup> In another variation, Gasilova *et al.* isolated individual droplets





**Fig. 1** DMF-nESI-MS with an impedance-based feedback control system. (I) DMF-nESI-MS interfaced by (a) a capillary emitter and a 40-pin connector for automated droplet control with (b) application of AC electric potentials to actuate the droplets and DC electric potentials to generate a nanoelectrospray. (c) Spray generated. (d) Total ion count. (II) The impedance-based feedback control system. DBS refers to dried blood spot. Adapted with permission from S. C. C. Shih, H. Yang, M. J. Jebrael, R. Fobel, N. McIntosh, O. Y. Al-Dirbashi, P. Chakraborty and A. R. Wheeler, Dried blood spot analysis by digital microfluidics coupled to nanoelectrospray ionization mass spectrometry, *Anal. Chem.*, 2012, **84**, 3731–3738. Copyright 2012 American Chemical Society.



from segmented flow *via* an on-chip spyhole, applying high-voltage pulses beneath to enable electrostatic-spray ionization of aqueous droplets.<sup>89</sup> This enabled direct coupling to MS with minimized sample dilution and improved analytical sensitivity.<sup>89</sup> Alternatively, the segmented flow is simply directly infused into the MS,<sup>81,86,90</sup> but with limitations of spray voltage and accumulation of carrier liquid at the spray tip.<sup>86</sup> Both limitations can be addressed as explored by Belder's group<sup>91</sup> and Kennedy's group.<sup>92–95</sup> In another instance, the flexibility of a droplet microfluidic chip interface using a stainless steel ESI capillary was demonstrated by coupling to three commercially available mass spectrometers—Orbitrap, DTIM quadrupole time-of-flight (Q-TOF), and TWIMS Q-TOF mass spectrometers.<sup>88</sup>

Unlike conventional droplet microfluidics, the so-called digital microfluidics (DMF) controls discrete droplets that are not confined in fluidic channels, using an array of patterned electrodes, and performs a finite set of operations.<sup>51,55,56</sup> These operations include droplet generation, merging, reagent addition, and splitting, at ambient pressure,<sup>51,55,56</sup> as well as coupling solid-phase microextraction (SPME) with high-performance liquid chromatography (HPLC)-MS.<sup>96</sup> Similar to droplet microfluidics, there were challenges in online coupling of DMF with MS, particularly in the efficient transfer of droplets to the ESI source. This is because droplets on a DMF device are unconfined and at ambient pressure, requiring pressure-assisted delivery and, at times, additional sample processing before MS analysis.<sup>55,61</sup> With advances over the years, DMF systems have been directly coupled to MS in various ways, such as DMF-MS interfaced by Venturi easy ambient sonic-spray ionization,<sup>97</sup> DMF with MALDI-MS for multiplexed sample preparation,<sup>47</sup> with ESI-MS interfaced by a microfluidic eductor,<sup>55</sup> with HPLC-MS directly autosampling from a 3D-printed manifold,<sup>98</sup> with nanoESI-MS interfaced by a specially fitted nanoESI emitter,<sup>99</sup> and a folded polyimide nanoESI emitter.<sup>100</sup> For example, Shih *et al.* demonstrated automated dried blood spot analysis using DMF with nanoESI-MS (Fig. 1I), employing a feedback-controlled system (Fig. 1II).<sup>99</sup> The system enabled precise droplet handling and on-chip processing entirely without manual intervention, significantly advancing rapid and reliable bioanalytical workflows.<sup>99</sup> A more recent approach for coupling DMF with MS eliminates the use of transfer capillaries and rather employs a microspray hole in the chip top plate.<sup>61</sup>

### Automated platforms for single-cell analysis

The ability to analyze individual cells has long been regarded as a Holy Grail of analytical science. Single-cell omics investigates cellular heterogeneity from structural, functional, environmental, or genetic variations,<sup>101–107</sup> and requires high sensitivity, high throughput, and a broad coverage of analytes.<sup>103,108</sup> In this context, automation reduces operator variability, increases throughput and reproducibility, improves cell sorting and targeting, and addresses several limitations, thereby broadening the scope of analysis in single-cell workflows. These limitations include cell clustering and random positioning of cells in a flow,

resulting in an overlap of output (peaks),<sup>53,108</sup> preservation of the cells' native metabolic state,<sup>108</sup> post-lysis degradation of analytes,<sup>108</sup> and sample injection volume scaling.<sup>108,109</sup>

### High-throughput single-cell analysis

High-throughput approaches, such as MALDI and laser-ablation ESI (LAESI), as well as flow cytometry using droplet extraction combined with pulsed direct current ESI (pulsed-DC-ESI) have been adapted for single-cell analysis, enabling automated workflows.<sup>110–115</sup> MALDI faces limitations due to specialized sample preparation requirements, including cell extraction and mixing the extract with the matrix, as well as its operation under vacuum conditions, both of which hinder its applicability for *in situ* studies.<sup>106,108</sup> In contrast, LAESI allows for ambient ionization.<sup>105</sup> However, early LAESI applications had limited spatial resolution<sup>108</sup> and manual cell targeting,<sup>113</sup> which have undergone significant improvements over the years. Earlier attempts to adapt MALDI, LAESI, and pulsed-DC-ESI for automated single-cell analysis included, respectively, the microarrays for mass spectrometry (MAMS) platform,<sup>102,116–119</sup> a fiber-based LAESI ion mobility-mass spectrometry (f-LAESI-IM-MS) integrated with a feedback-controlled autofocus system,<sup>105</sup> and an MS system integrated with real-time visual feedback and robotic micromanipulation.<sup>115</sup> Application of MAMS involves aliquoting of cells into hydrophilic spots surrounded by a hydrophobic coating, which is followed by MALDI matrix application, and MALDI-MS scan. Automation of the f-LAESI-IM-MS enabled minimal sample preparation, preserved spatial information for metabolite mapping, supported robust statistical analysis of cellular heterogeneity, and increased throughput by approximately 13-fold compared to earlier semi-automated approaches.<sup>105</sup> The automation by MAMS and f-LAESI-IM-MS requires specialized instrumentation and expertise that are financially and technically demanding, limiting accessibility.

### Challenges in achieving true single-cell resolution

Despite the progress, the reported approaches challenge the fidelity of single-cell analysis, as defined by the term “single-cell”. One, multiple, or no cells may be sampled or deposited, yet the signals obtained are regarded as equivalent to single-cell data.<sup>102</sup> Some approaches also fall short in terms of capability for live-cell sampling, time-lapse measurements, adequate sample volume, and repeated spot or cell sampling,<sup>105,113,120</sup> resulting in difficulty determining repeatability and measurement certainty. Automated systems that incorporate such functions enable comparable metabolite coverage,<sup>105,115,116,121,122</sup> supporting complex experimental designs and scalable analysis. These are capabilities which manual methods cannot reliably or practically achieve. However, despite these advancements—including the recent developments mentioned below and the microfluidic systems described earlier—such platforms still offer limited flexibility in the culture formats that can be sampled.

The following recent developments represent a critical technological leap for single-cell MS and IMS analyses, enabling



true single-cell sampling and precise, high-throughput, and physiologically relevant investigations of cellular heterogeneity. Recent years have seen significant advancements in automated, nanoliter volume, and scalable sample handling and delivery platforms specifically designed for single-cell MS and IMS. One such system is the robotic capillary (RoboCap) employed for automated nanoflow capillary electrophoresis electrospray ionization mass spectrometry (nanoCE-ESI-MS) (Fig. 2).<sup>109</sup> RoboCap represents a pivotal development in single-cell analysis by automating CE-MS, particularly for very small sample volumes.<sup>109</sup> This robotic platform eliminates manual handling bottlenecks that once limited throughput, enabling consistent and reproducible analysis with minimal human intervention.<sup>109</sup> Additionally, automation enhances sample use efficiency compared to manual conventional  $\mu$ CE.<sup>109</sup> Therefore, RoboCap paves the way for high-throughput single-cell analysis, addressing major challenges related to throughput, scalability, sample utilization, and robustness.<sup>109</sup> To remotely control the system, RoboCap uses a custom-written software virtual instrument.<sup>109</sup> In a recent improvement of MALDI-MSI, a Python program called microMS was used to automate coordinate transformation and laser targeting during fluorescence-guided

sequential single-cell MS for cell-type-specific lipid classification and true single-cell analysis.<sup>112</sup> In this automated workflow, microMS converts fluorescence microscopy pixel coordinates to physical stage coordinates of the MALDI system and—in the same action—removes cell clusters.<sup>112</sup> This multimodal strategy, integrating lipidomics and proteomics on the same cells, together with precise automated targeting, significantly advances both throughput and resolution in single-cell MS.

Commercial systems have also been introduced such as the Single Cellome System 2000, which includes incubation controls that maintain optimal conditions during extraction,<sup>123</sup> time-lapse analysis,<sup>124</sup> and single-cell cloning, ensuring cell and culture integrity.<sup>125</sup> Another commercial platform is the modular single-cell microfluidics sampling platform from iotaSciences<sup>126,127</sup> which can sort and verify single cells,<sup>126</sup> and automates the formation of liquid chambers, single-cell dispensing and visualization, and transferring selected cells into vials for LC-MS analysis.<sup>127</sup>

### Automated chemical mapping of non-flat surfaces

Chemical mapping of real specimens with non-flat surfaces requires the use of adaptable sampling systems that can control the vertical position of the sampling probe establishing contact with the specimen surface. Therefore, the automation of surface sampling has focused on sensing height differences, especially for sampling uneven surfaces, to derive temporal information and spatial information for topographic molecular mapping, without causing sample damage or loss of microjunction. An earlier attempt made use of image-guided feedback control to automate the formation of a microjunction in surface sampling.<sup>128</sup> However, this method was not capable of spot sampling, thereby limiting its application. The use of a robotic arm integrated with a distance sensor was one improved approach, it included a camera and a height calibrated laser pointer, then coupled to a water-assisted laser desorption ionization technology for MSI.<sup>129</sup> More recently, an electrical conductance feedback system was integrated with a modified 3D printer, whereby the sampling probe was mounted on the printer head and its movements were controlled by a custom Python code.<sup>130</sup> Repurposing a 3D printer is a cost-effective approach, and integrating it with a feedback loop is a significant step toward creating accessible, automated, and versatile analytical workflows.

### Automation hardware and software ecosystem

**Electronic modules for automated prototypes.** For the past few decades, chemists have been taking initiative to build customized apparatuses that meet specific research requirements. Some of these apparatuses are unique in their functions, while others resemble costly commercial instruments. As of late, the prototyping of chemical instrumentation has become easier due to the availability of inexpensive tools such as universal electronic modules. There is strong emphasis on the use of open-source electronics and programming skills to construct automated systems.<sup>131–138</sup> For example, this approach was implemented on prototyped systems requiring minimal

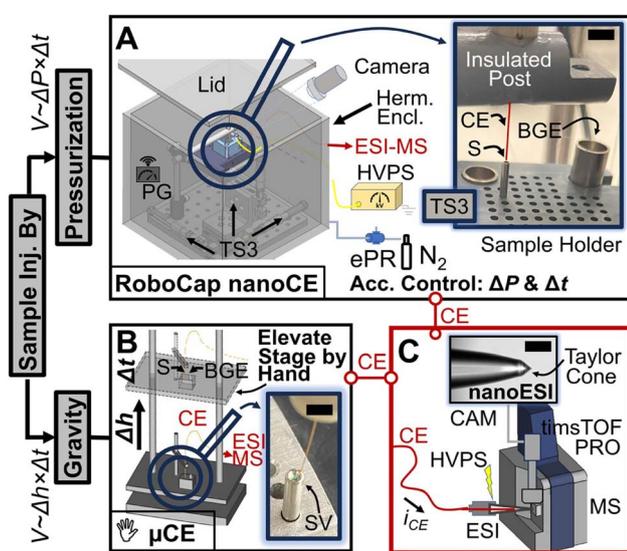
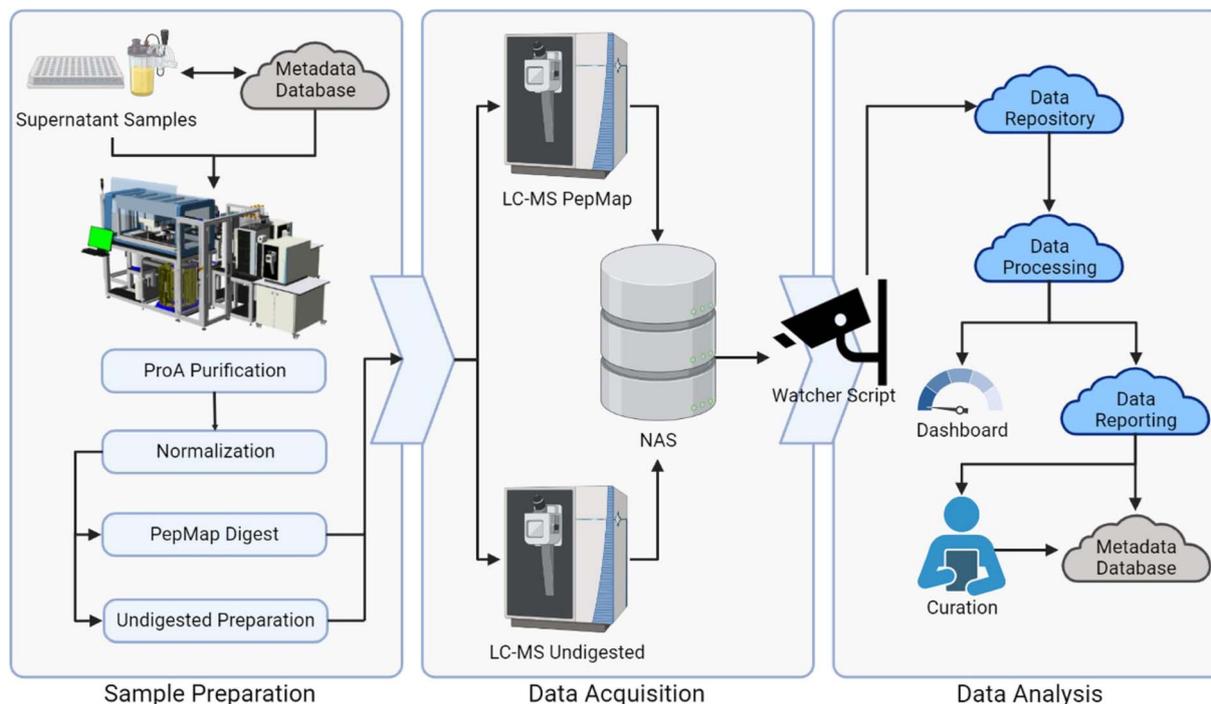


Fig. 2 Comparison of (A) a robotic capillary platform (RoboCap) for automated nano-capillary electrophoresis (nanoCE) with (B) a manual  $\mu$ CE for (C) trace-level (single-cell) CE-ESI-MS proteomics. RoboCap uses (A) an XYZ translation stage (TS3) to inject 10–250 nL from a 100–250 nL sample via an electropneumatic system (ePR), housed in a hermetically sealed environment. Essential components include a high-voltage power supply (HVPS), current monitor (iCE), and wireless pressure gauge (PG). The manual  $\mu$ CE (B) requires manual lifting of the sample to siphon  $\sim$ 20 nL over 120 s. Both platforms connect to the same electrokinetic CE-nanoESI trapped ion mobility time-of-flight (TimsTOF PRO, Bruker) mass spectrometer. Scale bars, 5 mm (A), 3 mm (B), and 50  $\mu$ m (C). Reprinted with permission from D. Jia and P. Nemes, Development and validation of RoboCap, a robotic capillary platform to automate capillary electrophoresis mass spectrometry *en route* to high-throughput single-cell proteomics, *Anal. Chem.*, 2024, **96**, 16985–16993. Copyright (2024) American Chemical Society.





**Fig. 3** End-to-end overview of the automated system. Physical sample preparation is performed on the Hamilton Vantage liquid handler robotic system, and acquired raw LC-MS data are stored on a local NAS, which is then analyzed in the Bysphere Cloud. Reprinted with permission from H. E. Waldenmaier, E. Gorre, M. L. Poltash, H. P. Gunawardena, X. A. Zhai, J. Li, B. Zhai, E. J. Beil, J. C. Terzo, R. Lawler, A. M. English, M. Bern, A. D. Mahan, E. Carlson and H. Nanda, "Lab of the future"-Today: Fully automated system for high-throughput mass spectrometry analysis of bi-therapeutics, *J. Am. Soc. Mass Spectrom.*, 2023, **34**, 1073–1085. Copyright (2023) American Chemical Society.

user interaction. A single-button operation initiates the workflow, automating sequential steps from sample preparation to real-time fluorescence monitoring and direct MS analysis.<sup>139</sup> Other examples are a smartphone-controlled fizzy extraction-MS,<sup>140</sup> an automated dual-chamber sampling MS,<sup>141</sup> automated liquid-liquid extraction-MS,<sup>142</sup> an Open SprayBot robotic platform for paper-spray MS,<sup>143</sup> and an automated small dose continuous sampling GC-MS system.<sup>144</sup> Our research group also prototyped a portable analytical platform for the automated analysis of volatile organic compounds (VOCs) in liquid samples. In this system, fizzy extraction was coupled with IMS.<sup>145</sup> The only user involvement was sample loading into the extraction cell. All subsequent steps such as extraction, detection, and data processing were fully automated. Owing to the portability and fast IMS detection, the automated platform enabled on-site analysis within  $\sim 2$  min.<sup>145</sup> The prototyped systems described were automated by either using Arduino, Netduino, Rumba, or Raspberry Pi electronic circuits, and programs written in C++ or other high-level languages.<sup>140–144</sup>

The Opentrons Python protocol API—an open-source framework—enables users to create or customize protocols for the Opentrons robots, automating liquid handling and precise coordination of steps.<sup>146</sup> In a recent study, an automated sample preparation platform for analyzing proteins and protein modifications, called "AUTO-SP", was written in Python and used to automate the key sample preparation procedures in the 2018 Clinical Proteomic Tumor Analysis Consortium protocol.<sup>147</sup>

AUTO-SP was used with the Opentrons OT-2 and Opentrons Flex robots for automation of liquid handling prior to MS analysis.<sup>147</sup> Additional examples of the use of electronic modules are discussed in other sections, such as those covering digital microfluidics, while further examples related to robotics are provided in the subsequent Robotics section. Adoption of some of these approaches may not be immediate as they require varying levels of programming and hardware integration skills.

**Software ecosystem.** Open-source software has also been used to extend the capabilities of vendor-specific software, particularly when multiple automation systems are integrated into a single workflow. For example, Waldenmaier *et al.* utilized HighRes Biosolutions Cellario,<sup>148</sup> a commercial workflow automation platform, to integrate system devices in their high-throughput MS analysis of bi-therapeutics (Fig. 3).<sup>149</sup> In their setup, the liquid-handling and LC-MS systems were each controlled by proprietary software. In this framework, custom Python scripts were utilized alongside HighRes Biosolutions Cellario and the liquid-handling software for extended flexibility in method configuration (Fig. 3).<sup>149</sup> In another study, Wu *et al.* designed a water sample dispensing module in addition to the existing sample pretreatment modules already integrated into a commercially available robotic platform.<sup>150</sup> Custom scripts were developed to enable the coordination and automation of sequential robotic sample preparations and chromatographic analyses which were controlled by vendor-specific software.<sup>150</sup>





sampling probe,<sup>162</sup> laser ablation/liquid phase collection surface sampling,<sup>163</sup> and sample delivery platforms such as TriVersa NanoMate,<sup>164–166</sup> PAL 3,<sup>167</sup> and SampleStream.<sup>168–170</sup> Several ambient ionization sources, including direct analysis in real time,<sup>171–173</sup> DESI,<sup>174</sup> and paper spray,<sup>175</sup> are now commercially available. These systems enable rapid and direct MS analysis of samples under ambient conditions with minimal or no sample preparation. Many commercial configurations are integrated with autosamplers or robotic stages, allowing automated, sequential analysis of multiple samples. Their software-controlled operation—managing parameters such as voltage, gas flow, and probe positioning—further enhances analytical reproducibility and throughput.<sup>172,176</sup> Automation of paper spray ionization, which was first introduced in 2010 by Cooks, Ouyang and team,<sup>177–179</sup> included the ProSolia paper spray disposable cartridges and autosampler,<sup>180–183</sup> and then VeriSpray PaperSpray which can be coupled to Thermo Fisher Scientific triple quadrupole MS systems.<sup>184–189</sup> The VeriSpray PaperSpray, like most other commercial autosamplers discussed in the Robotics section, uses vendor-specific software which may limit its extendability and customizability.

## Robotics

The increasing demand for sensitive, precise, reproducible, and high-throughput sample analysis has driven significant advancements in MS<sup>190–192</sup> and IM-MS.<sup>193–195</sup> MS has become a widely adopted analytical tool for both routine analysis and advanced scientific research.<sup>190</sup> Similarly, recent advancements have transformed IMS from a tool for detecting chemical warfare agents and explosives to a versatile instrument for analytical and bioanalytical applications.<sup>196</sup> To keep pace with the evolving analytical requirements, robotic systems are increasingly integrated in online analytical workflows. Robotics improves both operational efficiency and reliability of analytical methods by minimizing manual intervention, reducing variability, and enabling continuous operation.

### Robotic sample preparation systems

Robotics was first introduced into the analytical laboratory settings in the 1980s, where it substantially contributed to the advancement of analytical chemistry.<sup>197–199</sup> Its primary application at the time was the automation of sample preparation processes to improve throughput and overall analytical performance.<sup>197</sup> Even today, the majority of robotic applications in analytical laboratories remain focused on sample preparation, as it continues to be a critical step in the analytical workflow. The sample preparation process involves procedures conducted on samples before detection by an analytical instrument.<sup>200,201</sup> Generally, these laboratory procedures are repetitive and routine in nature, which make them particularly well-suited for automating analytical workflows across various analytical instruments. For instance, solid-phase extraction (SPE) is a widely-used technique for isolating target analytes from complex sample matrices. The steps involved in SPE are typically performed manually and are well-established in many

laboratories, making the automation of these routine processes both practical and desirable. For example, Fleischer *et al.* demonstrated the automation of the entire SPE-GC-MS analysis of benzoic acids in water using a dual-arm robotic system.<sup>202</sup> The transition from manual to automated SPE was made possible by the robotic system's ability to perform complex movements. In their work, each arm of the dual-arm robot featured seven servo-controlled joints, facilitating human-like motions to perform extraction, sample handling, and sample delivery to the GC-MS instrument.<sup>202</sup>

### Liquid-handling platforms for sample preparation

Cartesian robots are commonly integrated with liquid-handling platforms and are also extensively used to automate extraction techniques.<sup>150,203–207</sup> Cartesian robotic arms operate along linear *X*, *Y*, and *Z* axes. This robotic arm configuration makes them ideal for automating repetitive procedures such as pipetting, liquid transfers, reagent addition, and cleanup.<sup>208</sup> Given that chromatographic and spectroscopic techniques are readily interfaced with MS, Cartesian robotic systems—which are commonly used to automate online analysis for these techniques—are consequently widely employed in MS and IM-MS workflows.<sup>209–214</sup>

The RapidFire is an SPE-based sample preparation robotic system,<sup>166,215</sup> equipped with multiple pumps synchronized in time and function.<sup>216</sup> It samples from a well-plate,<sup>166,215</sup> and is directly coupled with MS and IM-MS.<sup>209,215</sup> Although the RapidFire system has drawbacks such as fluidic line clogging and sample carryover from complex matrices, it remains a reliable platform widely used for high-throughput screening applications.<sup>166</sup> More recently, a software platform called AutonoMS was developed for automated end-to-end IM-MS metabolomic fingerprinting.<sup>217</sup> Although currently only integrated with RapidFire IM-MS, AutonoMS integrates software control layers of multiple specialized instruments, coordinating entire workflows from sample injection to data transfer and analysis with an automated trigger. Another SPE-based system—called Prospekt 2—integrates various modules, such as an automated cartridge exchange, for automated, online SPE coupled to other analytical instruments such as LC-MS.<sup>218</sup> In addition to SPE, SPME is a well-established sample preparation technique known for its simplicity, solvent-free operation, and ability to preconcentrate analytes from various matrices.<sup>219,220</sup> Since its development in the early 1990s,<sup>221,222</sup> commercial autosamplers for SPME have become available.<sup>167,223,224</sup> Although automation improves reproducibility, SPME is not inherently a high-throughput technique. Recent studies by Pawliszyn's research group have addressed this limitation by implementing automated multiextractions using different SPME geometries, such as fibers and blades, enabling high-throughput analysis in a 96-well plate format.<sup>225–229</sup>

Evosep Eno is a technology that streamlines LC workflows by integrating sample handling steps.<sup>230,231</sup> Its key feature, the Evotip, simplifies sample preparation by integrating desalting with LC-MS sample introduction. Evotip also functions as a temporary storage device by immobilizing analytes, such as



peptides, which can be stored and recovered later without loss.<sup>232</sup> Sample loading on Evtotips can be automated using platforms such as the cellenONE instrument,<sup>233,234</sup> Agilent Assaymap Bravo,<sup>234</sup> Opentrons OT-2,<sup>234,235</sup> or Biomek I-series.<sup>234</sup> The cell processing, peptide digestion, and other sample preparation steps are performed on a chip of the cellenONE,<sup>233,236</sup> equipped with environmental controls.<sup>236</sup> Samples are then either transferred to Evtotips for cleanup<sup>233,236,237</sup> or pooled by directly connecting the chip with the LC autosampler<sup>238–240</sup> followed by MS analysis.<sup>233,236,237,239</sup> Liquid extraction surface analysis (LESA)—developed by van Berkel and group<sup>241</sup>—conventionally uses the commercially available TriVersa Nano-Mate robotic system<sup>242–244</sup> that is capable of X, Y, and Z positional movements. LESA has been directly coupled to IMS,<sup>245,246</sup> MS,<sup>241,247–249</sup> and IM-MS.<sup>250</sup>

### Prototype sample preparation robotic systems

In addition to existing commercial robotic systems, prototyped robotic systems for sample preparation are emerging.<sup>198,251–254</sup> Santos-Neto's research group, for instance, created an open-source, multipurpose Cartesian robotic platform designed for automated sample preparation and online coupling with LC or LC-MS.<sup>251,252</sup> This prototype was developed to perform diverse liquid- and solid-phase microextraction techniques such as single-drop microextraction (SDME),<sup>252</sup> hollow-fiber liquid phase microextraction,<sup>251</sup> and microextraction by packed sorbent.<sup>253</sup> A significant feature of their developed open-source robotic prototype is the integration of SDME with LC or LC-MS. This broadened the range of target compounds to include thermally labile analytes that are better suited for LC-MS. Unlike typical automated SDME setups that rely on expensive commercial robotic autosamplers designed primarily for GC or GC-MS, this prototype employed a lab-made Cartesian robot controlled by open-source electronics (*e.g.*, Arduino). All steps of the SDME process—including syringe rinsing, filling, droplet exposure and withdrawal, and injection into the LC system—were fully automated by the lab-made robot.<sup>252</sup> This system was subsequently improved with a multisyringe configuration for microextraction by packed sorbent.<sup>253</sup> The setup utilized an Arduino microcontroller board to automate six parallel microextractions.<sup>253</sup>

In robotic configurations where multiple samples are processed simultaneously, sample preparation throughput is significantly increased. However, although extractions or multistep sample preparations are performed simultaneously for multiple samples, MS detection is still performed sequentially, resulting in a bottleneck. This stage of the analytical workflow continues to present limitations, emphasizing the need for technical improvements to bridge the gap between high-throughput sample preparation with downstream MS analytical detection. To fully realize the benefits of simultaneous multi-sample processing—whether using commercial or prototype robotic systems—improvements in both extraction and detection are necessary. Integrating multiplexed injection or ionization systems, utilizing fast MS acquisition modes or automating MS acquisition are some approaches that may

further reduce the impact of simultaneous sample preparation with sequential instrument detection.

### Robotic sample delivery systems

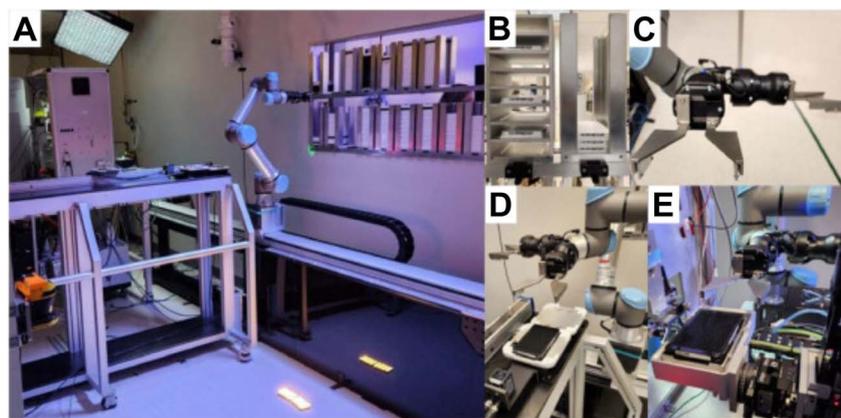
Robotic systems provide precision and flexibility that are challenging to achieve manually. By minimizing operator-dependent variability, these platforms ensure consistent performance across various applications and facilitate the extension of analytical workflows beyond the laboratory. Although robotic arms are less commonly used for routine sample preparation due to their complexity and cost, they are particularly valuable in sample delivery applications where precise positioning, transfer, and reproducibility are crucial.<sup>198</sup> Industrial robotic arms are more complex than automated liquid handlers, pipetting robots, or syringe-based systems, and they also require programming expertise.<sup>255</sup> Laboratories often prefer straightforward, dedicated devices such as Cartesian robotic systems for high-throughput routine sample preparation.<sup>198,206,256</sup> However, robotic arms excel in sample delivery when precise positioning, sample transfer, or integration with multiple instruments is necessary. Their articulated joints and enhanced freedom of motion enable them to handle various sample types, including solids and irregularly shaped materials, with high accuracy.<sup>256,257</sup> Robotic arms can integrate seamlessly with analytical instruments such as mass spectrometers, facilitating consistent and automated sample transfer. This versatility enables specialized robotic approaches for liquid handling, solid materials, volatile compounds, and portable, in-field applications, as will be discussed further in this section.

### Robotic liquid handling workstations

Currently, the most common robotic systems found in analytical laboratories are liquid handling workstations. Examples of commercially available robotic platforms include Eppendorf epMotion,<sup>258</sup> Opentrons OT-2 robot,<sup>259</sup> CTC Analytics HTS PAL Autosampler,<sup>260</sup> Hamilton Microlab Vantage robot,<sup>261</sup> Waters Andrew+ pipetting robot,<sup>262</sup> and Beckman Biomek workstations,<sup>263</sup> among others. These systems are primarily employed to automate routine liquid-handling tasks such as pipetting, serial dilutions, reagent addition, and plate filling. Although setting up these systems requires a considerable investment, they provide significant value in high-throughput analyses, particularly in fields such as pharmaceutical development, clinical diagnostics, and large-scale biochemical studies, where precision, reproducibility, and efficiency are essential.<sup>210,264–268</sup> Beyond routine liquid handling, these platforms can be integrated with other automated modules to enable fully automated analytical workflows. For example, liquid handling platforms can be combined with high-throughput analytical technologies such as acoustic droplet ejection (ADE). ADE uses focused acoustic energy to transfer nanoliter-scale droplets from a source plate without physical contact, providing precise, reproducible sample delivery while minimizing cross-contamination.<sup>269–271</sup>

First demonstrated in the early 2000s by Ellson and coworkers for “moving liquids with sound” and then later





**Fig. 5** Collaborative Robotic Plate Transfer System. (A) A six degree of freedom collaborative robot arm is mounted on a raised linear rail. (B) Cubby-style plate carriers. (C) Dual grippers with custom fingers minimize IR-MALDESI-MS instrument down time by allowing the robot to swap plates without returning to the window. (D) A regrip station justifies plate positioning in the gripper and serves as a barcode scanning station, which in turn allows software to store scan data to files containing plate metadata. (E) The IR-MALDESI-MS nest is the interaction point between it and the CRPTS. Adapted with permission from J. Shanley, F. Pu, J. D. Williams, N. L. Elsen, S. M. Gopalakrishnan, J. Y. Pan, A. J. Radosevich, Collaborative robotics to enable ultra-high-throughput IR-MALDESI-MS, *SLAS Technol.* 2024, 29, 100163. Copyright (2024) Elsevier.

commercialized, ADE established the foundation for automated, contactless liquid handling.<sup>269,270,272,273</sup> Coupled with an open port interface (OPI), which continuously directs droplets into a mass spectrometer, this technology forms the Echo MS system, a commercially available platform for ADE-OPI-MS.<sup>267,274–276</sup> Winter *et al.* demonstrated its first application for high-throughput drug discovery, screening over one million compounds.<sup>274</sup> They highlighted that a critical factor to consider in fully automated ADE-OPI-MS workflows is the risk of clogging in the transfer capillary connecting the OPI to the mass spectrometer, which can occur due to salt deposition after thousands of analyses.<sup>274,277</sup> To mitigate this, hardware modifications were implemented, including in-line capillary cleaning, which allows seamless switching between standard carrier liquid and washing liquid within the automated ADE-OPI-MS workflow.<sup>274,277</sup>

Although ADE-OPI-MS dramatically increases throughput for rapid, label-free analysis of complex biological samples, sample preparation remains a bottleneck, as manual pipetting, reagent addition, and enrichment are slow and variable. Given the high sampling rate of ADE-OPI-MS, an equally high-throughput sample preparation and liquid handling platform is required. Van Puyvelde *et al.* addressed this bottleneck by integrating a robotic liquid handling platform with ADE-OPI-MS for protein biomarker quantification.<sup>267</sup> Because ADE-OPI-MS does not include sample cleanup or separation, the authors evaluated the feasibility of an automated immunocapture protocol. Using a Biomek i7 robotic liquid handler, they automated the immunocapture protocol to improve selectivity even without LC separation, achieving a 15-fold speed improvement over LC-MS across 10 000 peptide measurements.<sup>267</sup>

### Multi-jointed robotic arms

In addition to robotic liquid handling workstations that operate along three linear axes, multi-jointed robotic arms with higher

degrees of freedom are increasingly integrated into analytical MS workflows. Cartesian, or gantry-style, robotic systems provide highly specialized precision liquid handling within a defined, rectilinear area.<sup>208</sup> In contrast, articulated robotic arms offer more flexibility and a broader range of motion.<sup>208,278</sup> Hence, the articulated robotic arms are integrated into the analytical workflow to perform more human-like repetitive tasks such as moving plates, transferring bulk liquids, or loading and unloading instruments—effectively complementing existing liquid handling platforms.<sup>208,278–280</sup> Achieving full automation of an analytical workflow typically requires the coordinated integration of multiple robotic systems. Collaborative robots, or ‘cobots’, are industrial robotic arms designed to safely perform automated tasks with human operators in the same workspace.<sup>281</sup>

Similar to ADE-OPI-MS, another technique that enables rapid MS analysis is infrared matrix-assisted laser desorption electrospray ionization mass spectrometry (IR-MALDESI-MS).<sup>279,282</sup> Ultrahigh-speed IR-MALDESI-MS measurements with sampling frequencies of up to  $\sim 22$  Hz have been previously demonstrated.<sup>282</sup> As discussed earlier, with high-throughput techniques such as ADE-OPI-MS and IR-MALDESI-MS, advancing sample handling capabilities is essential to optimize overall throughput and avoid bottlenecks in the analytical workflow. To address this challenge, Shanley *et al.* developed a plate transfer system using UR5e cobots from Universal Robots to support high-throughput IR-MALDESI-MS analysis.<sup>279</sup> This system was estimated to have the capacity to screen approximately one million compounds in 6–7 working days.<sup>279</sup>

The plate transfer system (Fig. 5) featured a cobot arm mounted on a three-meter seventh-axis linear rail and equipped with a dual-actuator gripper fitted with custom fingers.<sup>279</sup> Additional components included a high-capacity assay plate loading window, a regrip and barcode scanning station, the loading nest of the IR-MALDESI-MS, and a plate conveyor



integrated with a plate management system. With this setup, the only human intervention required is the initial loading of assay plates into a carrier and entering plate and assay information into the software. All subsequent steps—including plate handling, motion scripting, and MS control—are carried out automatically by the system. Because plate retrieval is faster than plate scanning, the IR-MALDESI-MS spends nearly all of its operating time on data acquisition rather than waiting for plates, with the only downtime being the brief interval required for plate exchange. For a system of this scale, it is essential to characterize the accuracy and precision of movement, handling, and positioning—not only of the robotic arm but of all integrated modules—to ensure reliable sample transfer and minimize the risk of errors or misalignment.<sup>279</sup>

Fleischer's group also employed a cobot to handle and transport samples, demonstrating how cobots can be incorporated into high-throughput workflows.<sup>280</sup> In their work, the UR5 cobot from Universal Robots was used to continuously load samples to the autosampler of an inductively coupled mass spectrometry (ICP-MS) instrument. Fleischer's group had earlier shown that sample preparation steps, including microwave digestion, could be automated for elemental analysis with ICP-MS.<sup>283,284</sup> To bridge the gap between automated sample preparation and ICP-MS analysis, the authors have integrated an automated sample transportation and handling cobot to achieve full automation of the entire ICP-MS analytical workflow. Specifically, the cobot was programmed to transport screw-cap vessels to the capping station, open the sample vessel, and load it into the ICP-MS autosampler in a predefined sequence.<sup>280</sup> Analyzing trace metals *via* a fully automated workflow using hardware constructed from metals could be a potential source of contamination. The authors performed a contamination test of their automated system and reported a minor contamination of iron, copper, and zinc in the low ppb-range.<sup>280</sup>

In addition to high-throughput screening, robotic arms have been directly integrated with ionization sources and mass spectrometers to facilitate the analysis of complex, non-planar, or *in vivo* surfaces.<sup>129,285–287</sup> Some approaches employ fully automated operation of a sampling probe (*i.e.*, needle<sup>285,286</sup> or laser probe<sup>129</sup>) mounted on a robotic arm. The robotic system automatically maneuvers the probe to perform surface sampling and subsequent delivery to the MS inlet for ionization. These systems are applied in MSI and are beginning to find potential use in clinical settings. By contrast, in one application, robotic arms rely on partial automation combined with surgical or operator control. For example, the da Vinci Xi surgical system, a minimally invasive robotic surgery platform, has been integrated with the MasSpec Pen for *in vivo* molecular analysis of porcine tissues.<sup>287</sup> The MasSpec Pen operates by dispensing a small, controlled droplet of solvent (commonly water) onto the tissue surface to extract biomolecules through solid–liquid extraction.<sup>288</sup> After a few seconds of contact, the droplet containing extracted biomolecules is aspirated and transported *via* a transfer tube to the inlet of a mass spectrometer.<sup>287,288</sup> To accommodate integration with the da Vinci Xi system, the design and dimensions of the original handheld MasSpec Pen

were modified to function as a laparoscopic device attached to one of the robotic arms. The surgeon controlled the MasSpec Pen remotely through the robotic system's interface, allowing precise positioning and operation during *in vivo* tissue analysis and enabling seamless, real-time chemical profiling in a robotic-assisted porcine surgery model.

### Robotic arms in prototype sample delivery systems

Prototype robotic systems offer flexible and adaptable alternatives for automating MS analytical workflows at a lower cost than industrial robotic systems. Our research group has prototyped robotic analytical systems for MS using low-cost robotic arms and open-source electronic modules. For instance, we have demonstrated a reaction-based MS assay without human intervention.<sup>289,290</sup> The entire workflow—including sample recognition, aliquoting, incubation, ion source delivery, and initiation of data acquisition—was fully automated. The robotic-assisted MS analysis was initially developed using a single robotic arm and later improved with a second robotic arm to enable simultaneous processing of multiple samples.<sup>289,290</sup> We have also recently developed robotized systems for sampling VOCs emanating from solid surfaces.<sup>291,292</sup> A pen-shaped probe was attached to the robotic arm for contactless VOC sampling at multiple defined positions on a solid surface.<sup>291</sup> The robotic sampling system was prototyped using inexpensive electronic modules to enable automated VOC sampling and subsequent delivery to the MS ion source. Specifically, the Arduino Uno R3 controlled the relays for switching the pump on and off, controlling the solenoid valve for nitrogen gas outflow, and triggering the mass spectrometer. This prototyped robotic sampling system—which uses a pen probe to aspirate VOCs—offers versatility that enables adaptation to various detection techniques. For instance, building on this robotic pen-probe sampling, our group has developed a computer vision-assisted variant.<sup>292</sup> In this robotic VOC sampling system, we have incorporated modifications and improvements to automatically sample VOCs from a solid surface and subsequently transfer them to a tritium-based ion source of a DT-IMS.<sup>292</sup> While the precision and accuracy of low-cost robotic arms are limited compared to industrial-grade robotic systems, their use provides a practical and accessible approach to automating MS workflows—particularly when the aim is not high throughput but streamlining the workflow through automation. Moreover, these systems serve as valuable platforms for training researchers, fostering the development of practical automation skills.

### Robotic systems for on-site sampling and analysis

Another important application of robotic systems is sampling and analysis in environments that are hazardous for human operators. Robots play a crucial role by enabling sample collection under conditions that pose significant risks, such as radioactive sites or environments with potentially dangerous and toxic VOC emissions that are inaccessible to humans. In such cases, deploying robotic systems for on-site sampling and analysis is particularly advantageous. For example, Hu's



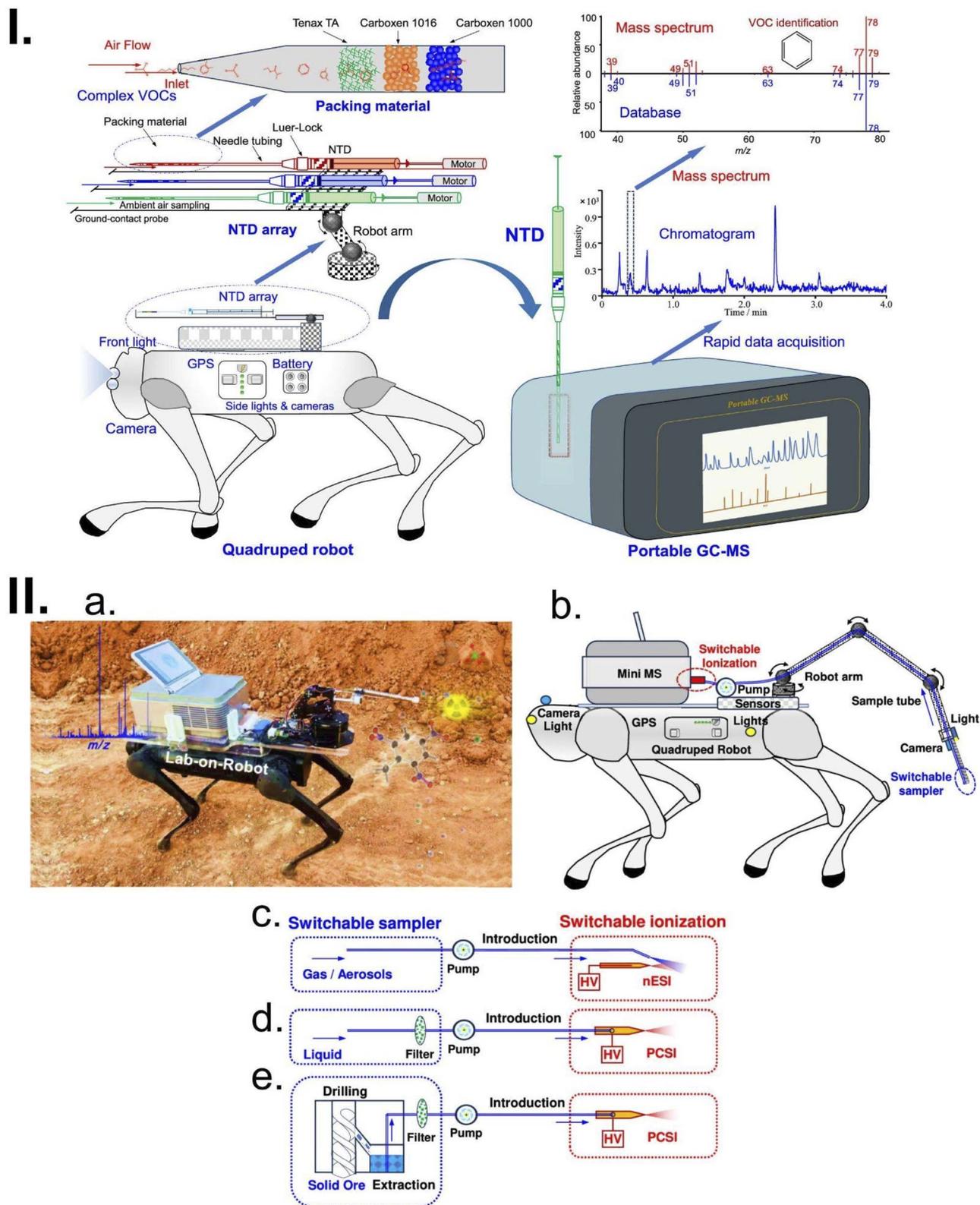


Fig. 6 On-site robotic sampling. (I) Robot-MS system for the on-site detection of hazardous VOCs. Reprinted with permission from X. Liu, Q. Huang, J. Deng, X. Liu and B. Hu, Portable mass spectrometry for on-site detection of hazardous volatile organic compounds via robotic extractive sampling, *Anal. Chem.*, 2024, **96**, 9325–9331. Copyright (2024) American Chemical Society. (II) Lab-on-robot. (a) Graphic depiction of smart MS robot; (b) design of MS robot; (c) sampler of gases and aerosols using a sampling tube; (d) sampler of liquid samples using the sampling tube; and (e) sampler of bulk solid with a drilling device, extraction devices, and sampling tube. Adapted with permission from X. Liu, X. Liu, B. Li, X. Zhang and B. Hu, Lab-on-robot: unmanned mass spectrometry robot for direct sample analysis in hazardous and radioactive environments, *Anal. Chem.*, 2025, **97**, 9126–9130. Copyright (2025) American Chemical Society.



research group developed a 'lab-on-robot' portable MS system to facilitate on-site MS analysis of hazardous and toxic compounds.<sup>293,294</sup> Their on-site MS system incorporated a switchable in-house developed robotic arm sampler, a quadruped robot, and a miniature mass spectrometer (Fig. 6). An earlier design primarily focused on VOC sampling using a needle trap device mounted on a robotic arm, with subsequent analysis using a portable GC-MS instrument (Fig. 6I). Their on-site robotic system was later improved with the addition of a switchable robotic arm sampler and a dual, switchable ionization source (Fig. 6II). This enhanced versatility enabled the analysis of diverse sample types—gases and aerosols delivered to the nESI ionization region, liquids pumped to the paper-capillary spray ionization emitter, and bulk ores processed into powders and introduced for paper-capillary spray ionization—all conducted unmanned and on-site. These advances demonstrate how integrating robotics with MS further extends the analytical capabilities of MS, highlighting the importance of combining creativity and automation with analytical skills.

### Artificial intelligence and its integration to automated and robotic systems

**Artificial intelligence in automation and robotics.** Automation has been integrated into analytical workflows for many years. While the incorporation of robotic systems into routine laboratory practices remains challenging, their adoption is gradually increasing as resources become more accessible through affordable, open-source modules. Similar to early technologies once met with skepticism—such as personal computers, the internet, and smartphones—fearing or dismissing AI may prevent the realization of its full potential in analytical workflows. AI involves the development of computational systems that emulate human cognitive processes, including perception, reasoning, learning, and decision-making.<sup>295,296</sup> AI is increasingly applied in scientific research to enhance automation and autonomy. For example, several AI-driven extraction processes utilize AI to analyze data and optimize solid and liquid phase extractions.<sup>297</sup> Moreover, AI has been integrated into microfluidic systems to enhance sample handling and analytical performance,<sup>298–301</sup> with applications such as droplet size prediction,<sup>298</sup> system stability control,<sup>302</sup> and image-based sample classification.<sup>300</sup> Within IMS and MS, increasing attention has been given to the application of AI, machine learning, and deep learning for intelligent analyses, including experimental design,<sup>303</sup> data analysis and classification,<sup>300,304–306</sup> predictive modelling,<sup>307–309</sup> and maintenance of spectral libraries. The details and examples can be found in recent reviews.<sup>303,310–314</sup>

Automation may require extensive programming, and AI can assist by generating coding scripts. In some cases, the corresponding source code files are freely accessible. Moreover, a free and open-source set of software libraries and tools such as the Robot Operating System is available for developing a control system software.<sup>315,316</sup> Automated intelligent robotic sample treatment platforms are also available, and AI has been used to customize functions and improve instrument performance.

Recent advances in deep learning-based computer vision models, particularly the You Only Look Once (YOLO) series of real-time object detection models, have enabled vision-guided automation in laboratory systems. For instance, YOLOv8 was integrated with the Opentrons OT-2 for real-time feedback on errors and precise recognition of pipette tips and liquid volumes without manual intervention.<sup>317</sup> Moreover, Zheng *et al.* developed an automated, intelligent microfluidic platform for microalgae species detection.<sup>300</sup> YOLOv5 was used for data analysis, while a Raspberry Pi microcomputer controlled the user interface, integrating a low-cost portable USB microscope and a mini-motorized stage.<sup>300</sup> While YOLOv5 is renowned for its speed and ease of use, YOLOv8 offers improved accuracy, multi-task capabilities, and broader flexibility, making it ideal for applications demanding high precision and advanced vision tasks.<sup>318</sup>

**Self-driving laboratories.** Integrating autonomy into automation utilizes AI, particularly machine learning and deep learning. As algorithms process larger volumes of data, their accuracy improves, allowing them to detect patterns and establish relationships between data points and relevant features.<sup>319</sup> Consequently, the system can operate with increasing independence, ultimately achieving the intended level of autonomy.<sup>299,319</sup> When AI is combined with automation and robotics, it results in autonomous or self-driving laboratories.<sup>320–333</sup> Space missions have employed robotic systems capable of performing *in situ* MS, enabling autonomous chemical analysis in space. For example, the National Aeronautics and Space Administration deployed the Curiosity rover on Mars as part of the Mars Science Laboratory mission, which is still ongoing.<sup>334</sup> The Curiosity rover features Sample Analysis at Mars instrument suite, which includes a gas chromatograph, a quadrupole mass spectrometer, and a tunable laser spectrometer.<sup>335</sup> These instruments detect carbon-containing compounds associated with life and examine their formation and degradation on Mars, all performed autonomously by the rover.<sup>190,335,336</sup> Cooper's research group has demonstrated autonomy in a laboratory setting, showing how AI-driven mobile robots can establish a fully autonomous laboratory workflow.<sup>324</sup> The mobile robots—equipped with automated synthesis platforms, LC-MS, and benchtop nuclear magnetic resonance instruments—performed experiments, made data-driven decisions, and planned subsequent reactions without direct human intervention, freeing scientists from routine tasks.<sup>324</sup> Custom Python scripts were used for coordinated sample delivery and data collection, while AI algorithms guided experimental design and optimization.<sup>324</sup>

While augmented reality (AR) and virtual reality (VR) have been widely adopted in other disciplines, they are still considered emerging technologies in laboratory automation and analytical sciences. AR and VR are expected to further enhance laboratory automation and robotics by expanding their accessibility and functionality. These technologies are already being applied in laboratory education and training, where immersive simulations allow users to learn and interact with instruments in a virtual-assisted environment.<sup>337–340</sup> For instance, the Hilton research group developed a VR digital twin of an HPLC



system<sup>339</sup> and, subsequently, a full digital twin laboratory,<sup>340</sup> offering realistic and interactive experiences for both educational training and research. Beyond virtual environments, AR has been successfully applied in robotic-assisted surgery, improving precision and spatial awareness during complex procedures.<sup>341,342</sup> Building on such advances, it is conceivable that AR and VR will soon play a greater role in analytical laboratories, enabling remote operation, immersive interaction, and improved safety. In the longer term, collaborative robots and humanoid systems are increasingly becoming integral to self-driving laboratories, guided by scientists from remote locations—a development that is gradually advancing toward practical realization and, although not yet realized, has the potential to become a routine part of scientific research.

## Concluding remarks

Automation of analytical systems involving MS and IMS is not just trendy; it is a must, especially in applications that require high throughput and handling small samples, such as single-cell analysis. Simple “automation” can be achieved by taking advantage of the FIA system. This can be done by adapting a commercial HPLC system with an autosampler. Sample plugs can be introduced to the flow line—following a preset program—without further intervention of the analyst. Miniaturization has been instrumental in automating MS workflows. However, implementing microfluidic systems for sample handling is generally more cumbersome than conventional FIA, as it requires access to microfabrication infrastructure. Although some commercial microchips and fabrication services are available, these are generally expensive, thus beyond the reach of most analytical labs. Coupling multi-axis robotic systems with MS and IMS provides the highest degree of flexibility enabling direct interfacing of raw sample collection with sample preparation stages. However, such systems are highly sophisticated, and require much expertise during their setup and operation. The proliferation of AI platforms, as well as 3D printing, may likely lower the entry barrier for the prospective users of such systems. Drone technology has also skyrocketed in recent years, partly due to its extensive military uses.<sup>343</sup> Attempts have already been made to implement IMS systems on lightweight drones.<sup>344,345</sup> It is imaginable that unmanned vehicles—whether aerial, aquatic, or terrestrial—will soon carry miniaturized IMS or MS instruments to fulfill chemical surveillance tasks. AI tools will likely be used for data treatment in automated MS and IMS analyses as well as for the design and operation of the newly established automated systems.

## Author contributions

All the authors participated in the writing and editing process.

## Conflicts of interest

P. L. U. is co-inventor of the patented MAMS technology.

## Data availability

No primary research results, software, or code have been included, and no new data were generated or analyzed as part of this perspective article.

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