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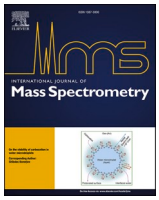

Triboelectric nanogenerators: Low-cost power supplies for improved electrospray ionization

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A B S T R A C T

Electrospray ionization (ESI) is one of the most popular methods to generate ions for mass spectrometry (MS). When compared with other ionization techniques, it can generate ions from liquid-phase samples without additives, retaining covalent and non-covalent interactions of the molecules of interest. When hyphenated to liquid chromatography, it greatly expands the versatility of MS analysis of complex mixtures. However, despite the extensive growth in the application of ESI, the technique still suffers from some drawbacks when powered by direct current (DC) power supplies. Triboelectric nanogenerators promise to be a new power source for the generation of ions by ESI, improving on the analytical capabilities of traditional DC ESI. In this review we highlight the fundamentals of ESI driven by DC power supplies, its contrasting qualities to triboelectric nanogenerator power supplies, and its applications to three distinct fields of research: forensics, metabolomics, and protein structure analysis.

1. Introduction

Since its initial implementation in 1968 by Malcolm Dole [1] and the subsequent parallel studies by John Fenn [2] and Lidia Gall in 1984 [3], electrospray ionization has cemented itself as a keystone technique in the field of mass spectrometry (MS), proteomics, metabolomics, and structural analysis of biological macromolecules, leading to the Nobel Prize being awarded to John Fenn in 2002 [4]. Unlike electron impact (EI) and atmospheric pressure chemical ionization (APCI), electrospray ionization (ESI) is a "soft" technique that retains molecular identity for analytes ranging from small molecule drugs to supramolecular protein complexes and viruses [5,6]. A key aspect to ESI's continued success is the versatility and breadth of experimental conditions that can be modified, such as: emitter size and material, flow rate, solvent additives, emitter geometry, the development of electrospray under nano-flow conditions (nESI), and online hyphenation to front-end liquid chromatography (LC) to name a few variables within researchers' control. Because of this adaptability, ESI has paved the way for a myriad of different MS-based approaches with applications as diverse as human health [7–9], environmental [10–12] and chemistry in space [13].

However, and despite its widespread application, ESI technology is far from perfect, with several outstanding limitations. ESI is concentration dependent, and decreased flow rate leads to improved sensitivity. However, low flow rate systems are difficult to operate robustly while maintaining reproducibility. Another ESI limitation results from the differing ionization efficiencies of different compounds. Since ESI operates as a controlled current electrochemical cell, there is competition between molecules for the available electrical charge, leaving certain compounds overrepresented in the mass spectrum, with others being partially or totally suppressed. Additionally, the fundamental mechanisms of the late stages of the ESI ion formation process are still not fully understood [14]. While several theories that correlate to molecular class have been proposed, these generalizations are not always applicable, and the mechanism becomes increasingly complicated when additives such as charge manipulation reagents are used [15–17]. Accurate molecular dynamic simulations of the ESI processes under the variety of conditions employed in practice are challenging, time consuming, and require numerous constraints to accurately reproduce all the involved processes [18,19].

Most ESI sources operate under direct current (DC) conditions. With the stable application of μA currents and kV potentials, ions are generated continuously. This continuous ionization process generates a stream of ions well matched to ion filters such as quadrupoles. Continuous ionization, however, is not well matched to relatively slower mass analyzers (i.e., Orbitraps, FT-ICR) or intrinsically discontinuous systems (time-of-flight, ion mobility) due to their mismatched duty cycles. While analysis conditions can be optimized with these platforms to improve duty cycle, it is not always possible to do so for a wide range of mass-to-

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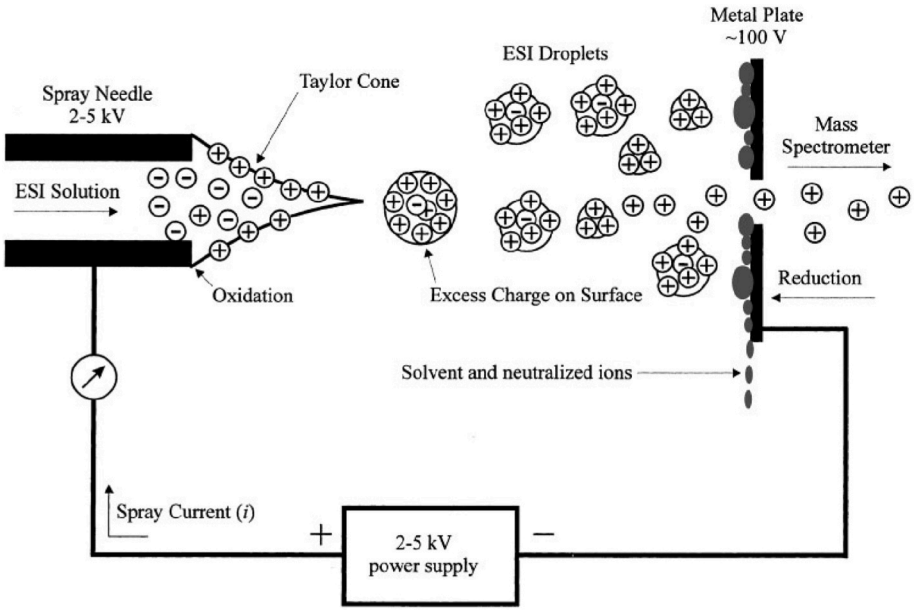

Fig. 1. Schematic of the ESI process. The analyte solution is pumped through a needle to which a high voltage is applied. A Taylor cone with an excess of positive charge on its surface forms as a result of the electric field gradient between the ESI needle and the counter electrode. Charged droplets are formed from the tip of the Taylor cone, and these droplets evaporate as they move towards the entrance to the mass spectrometer to produce free, charged analyte molecules that can be analyzed for their mass-to-charge ratio. Reprinted from Mass Spectrometry Reviews, 20, 362, Cech et al., "Practical implications of some recent studies in electrospray ionization fundamentals", 2001, with permission from John Wiley and Sons.

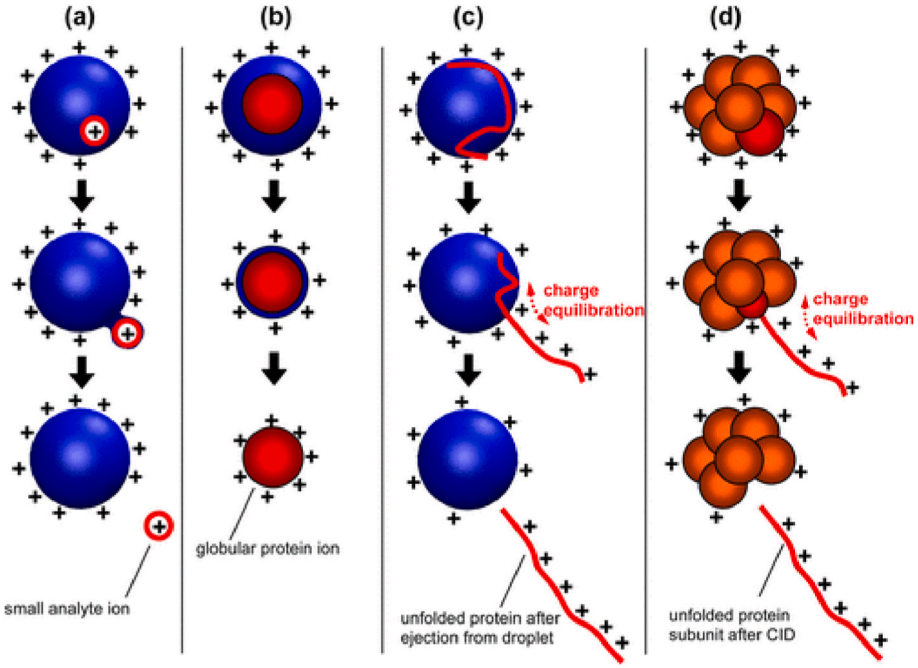

Fig. 2. Summary of ESI mechanisms. (a) IEM: Small ion ejection from a charged nanodroplet. (b) CRM: Release of a globular protein into the gas phase. (c) CEM: Ejection of an unfolded protein. (d) Collision-induced dissociation of a gaseous multiprotein complex. Charge equilibration in panels c and d is indicated by red arrows. Reprinted with permission from {14}. Copyright 2013 American Chemical Society.

charge (m/z) ratios.

Triboelectric nanogenerator (TENG) technology promises to be an invaluable tool towards addressing the challenges outlined above by replacing, or working in tandem with, traditional DC ESI sources. In this short review, we describe the developments of TENG ESI technology, its recent applications in several distinct areas, and its outlook for the broader MS community.

2. Fundamentals

2.1. Electrospray ionization

ESI is a technique used to transfer solution-phase analytes into the gas-phase as ions. This can be accomplished in several ways, but typically a solution with the analyte(s) of interest is injected into a conductive emitter (i.e., working electrode) that is either at ground or at

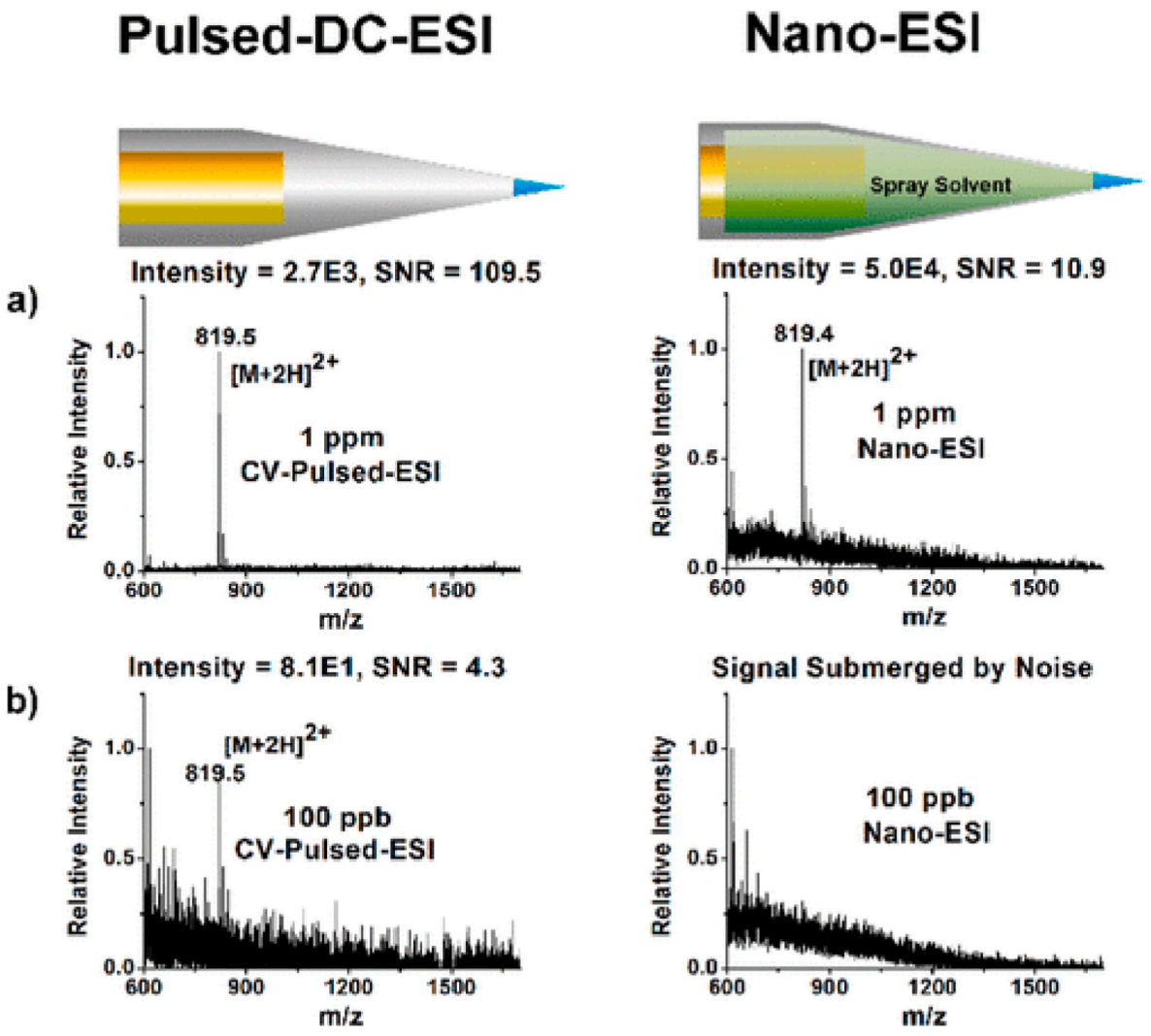

Fig. 3. LOD of nano-ESI and pulsed-DC-ESI. All the spectra showed here were from one scan event during MS analysis. For the nano-ESI, the sample (370 ± 30 pL) was only enough for one scan event (~0.5 s). Since pulsed-DC-ESI could achieve better SNR, the LOD of pulsed-DC-ESI for somatostatin was 100 ppb compared to 1 ppm achieved by nano-ESI. Considering the average flow rate of pulsed-dc-ESI was about 380 pL/min and the spectrum of 100 ppb somatostatin analyzed by pulsed-DC-ESI was 0.51 s, we could estimate the absolute detection amount of pulsed-DC-ESI was about 200 zmol, compared to 240 amol achieved by nano-ESI. Reprinted with permission from {25}. Copyright 2015 American Chemical Society.

a floating potential relative to the inlet or sampling cone (i.e., the counter electrode). These conditions create an electric potential gradient that guides the charged droplet stream toward the mass spectrometer inlet [5]. The resulting electro-osmotic flow induced by the potential on the emitter results in charged analyte moving towards the counter electrode and, when correctly implemented, results in a stable Taylor cone that dissipates excess charge as a fine aerosol of charged liquid droplets (Fig. 1).

As droplets move towards the counter electrode, solvent evaporates until reaching the Rayleigh limit [20]. At this point, charge repulsion forces overcome the surface tension of the droplets, and smaller droplets are created from a so called “Coulombic explosion” due to electrostatic repulsion. This process of droplet repulsion combined with solvent evaporation repeats until charged analytes in the gas phase are created, which can then be manipulated by the electric/magnetic fields within the mass spectrometer. The exact mechanisms of the last stages of the ESI process are not fully established, however three distinct models are typically used to describe the ion generation process itself: the ion evaporation model, the charge residue model, and the chain-ejection model (Fig. 2). The current consensus is that a combination of all three models is needed to fully describe the range of ESI processes, each model describing the likely ionization pathway followed by different molecule types. Further discussion of the relative value of each ESI mechanism is beyond the scope of this work; readers are directed to the excellent research article from Konermann et al. for additional literature on the subject [14].

Of all experimental variables affecting the ESI process, the inner diameter (i.d.) of the ESI emitter has one of the most pronounced effects on ion yields. In general, a reduced i.d. allows lower flow rates and more efficient solvent evaporation, lowering the rate of sample consumption and raising the overall ionization efficiency. Smaller average droplet sizes are generated from emitters with a smaller i.d. compared to larger diameter emitters, leading to higher charge density and better overall signal without sacrificing specificity [21,22]. Additionally, the lower flow rate of smaller emitters does not sacrifice sensitivity due to the concentration dependency of ESI [23]. Efforts have been made to overcome the poor sample economy of continuous ESI by implementing pulsed DC ion sources [24]. These have been shown to significantly boost sample economy, with up to a 52-fold improvement compared to traditional ESI. Some studies have also observed signal-to-noise ratio (SNR) improvements, up to 30-fold, depending on the analyte [25]. As an example, improvements in somatostatin SNR with pulsed ESI are

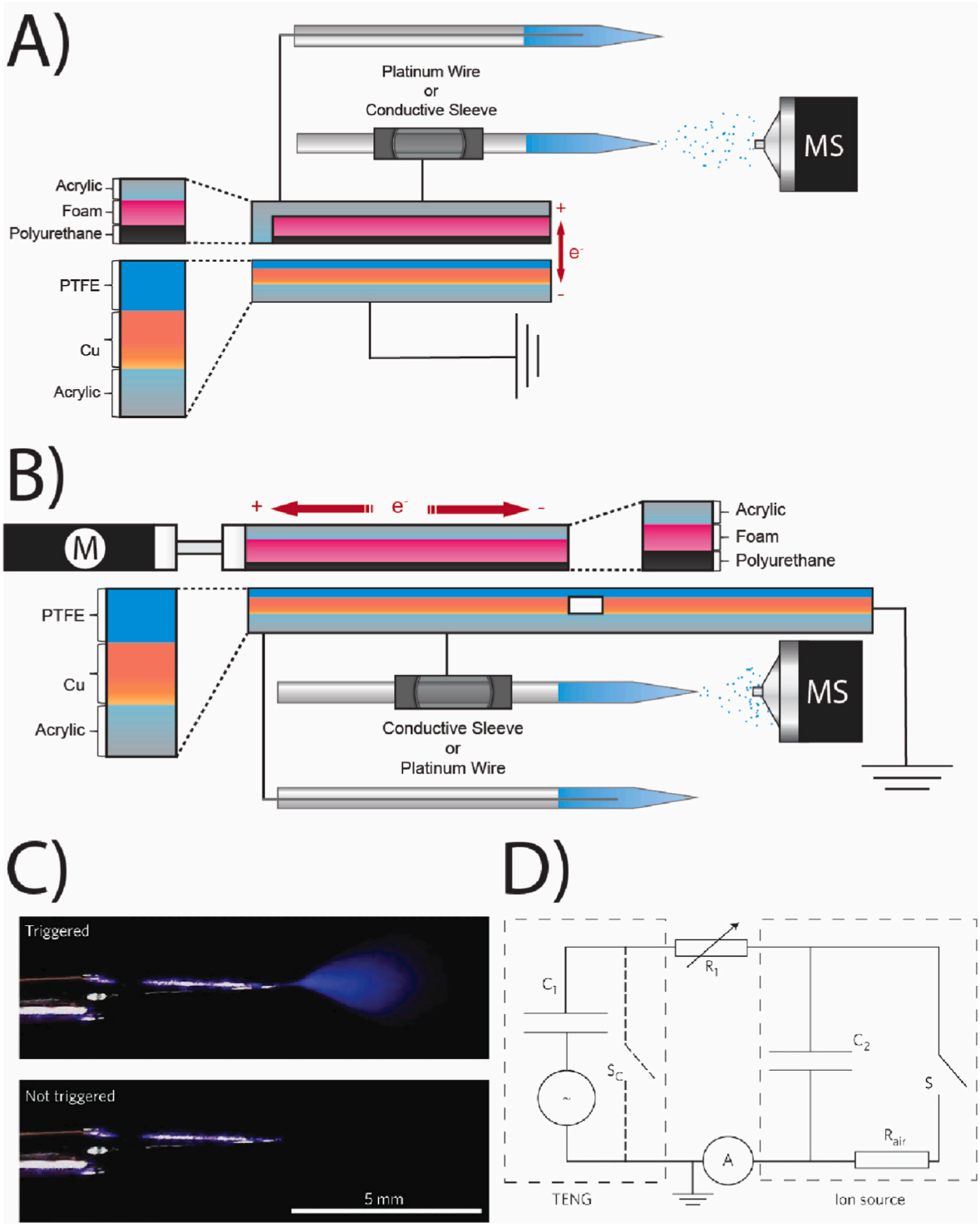

Fig. 4. (A,B), Schemes showing the mechanism of contact-separation (CS; a) and sliding freestanding (SF; b) mode TENGs. Yellow, copper electrode layers; blue, fluorinated ethylene propylene layers. The red arrows and pulses denote moving directions of the TENG electrodes and the corresponding charge flow (e−, I) to the ion source, such as the nanoelectrospray emitter represented by the needle shape. The vertical rectangle represents a steel plate collecting the ion current, which is measured by a picoamperemeter (represented by the A symbol). c, Dark-field images of a nanoelectrospray emitter showing an electrospray plume triggered by the TENG charge flow. d, In an equivalent electronic circuit, the TENG is symbolized by a capacitor (C1) together with the components in the dashed rectangle on the left; the nanoESI emitter is equivalent to a capacitor (C2) that would leak (S) after reaching an onset charge value, represented by the components within the dashed rectangle on the right. The leaked charges (that is, generated ions) fly through the air gap (R_{air}) between the emitter and the mass spectrometer or picoamperemeter (A). Note that the CS-TENG electrodes (a) are extended on the side to reset the electrostatic status at the contact position, represented as switch SC in d. Adapted from Nature Nanotech, 12, 481–487, Li, A et al., "Triboelectric nanogenerators for sensitive nano-coulomb molecular mass spectrometry",2017, with permission from Springer Nature.

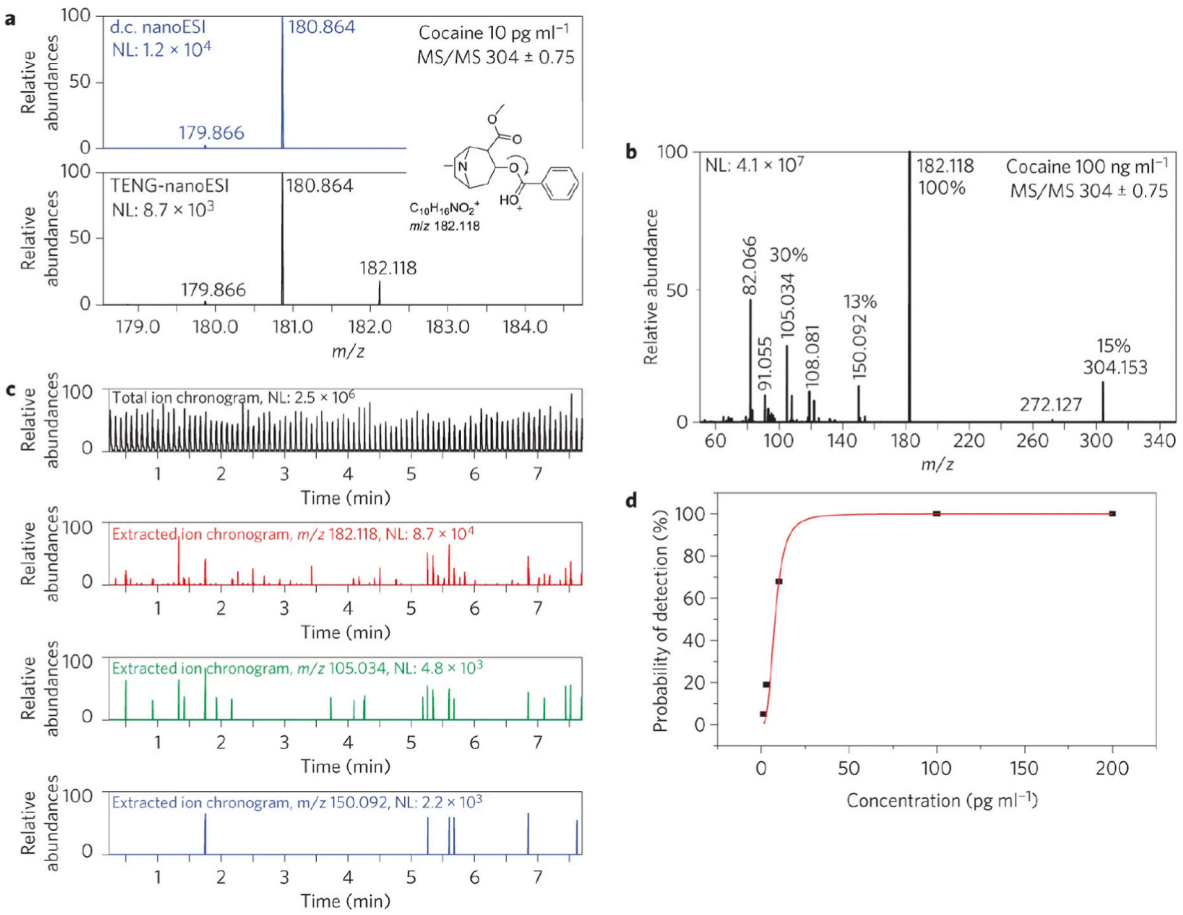

Fig. 5. **a,** Signature fragment ion (*m/z* 182.118) can only be observed by the SF-TENG when analyzing a cocaine solution (10 pg ml^{-1}) in positive-mode nanoESI MS/MS. b, In the fragmentation pattern, protonated cocaine cation observed under a higher (100 ng ml^{-1}) concentration. The relative abundances of four signature fragment ions are labelled. c, Mass analyzing consecutive SF-TENG nanoESI pulses for a 10 pg ml^{-1} cocaine solution under MS/MS mode. The extracted ion chronograms of the fragment ions with lower relative abundances (b), show a decreasing probability of detection (POD). All the peaks in (a–c) were normalized according to the base peaks, whose absolute intensities were labelled as the normalized levels (NL). d, The POD values (symbols) fitted to a logistic function (red line) so that detection limits can be calculated. Reprinted from Nature Nanotech, 12, 481–487, Li, A et al., "Triboelectric nanogenerators for sensitive nano-coulomb molecular mass spectrometry", 2017, with permission from Springer Nature.

displayed in Fig. 3 at both 1 ppm and 100 ppb concentrations compared to continuous nano-ESI. A clear boost in SNR with pulsed DC ESI was observed, in addition to reduced sample consumption. Traditional nESI consumed 400 pL of sample in approximately half a second, while pulsed DC nESI was able to ionize the sample for about 1 min [25]. Similar improvements in SNR, sensitivity, and reduced sample consumption rates are all achievable with the TENG ionization technology described here, with the additional advantage of extended analyte polarity coverage and the ability to perform in-source ion molecule reactions for lipids.

2.2. *Triboelectric nanogenerators*

TENG-based power sources operate on the principle of triboelectricity. Triboelectricity, or the triboelectric effect, generates electric charge through friction of at least two compatible materials [26]. The amount of charge generated is dependent on the material used [27,28], as well as the mechanical/physical variables (e.g., pressure of friction, speed, surface area, temperature, etc.) used in the engineered device or experimental environment [29,30]. The induced charge can then be routed either to a capacitor for energy storage or through a circuit to power electronics. Li et al. showed for the first time that induced triboelectric charge from a TENG device can be routed to an ESI emitter to drive MS ion generation processes [31].

There are several practical designs that can be implemented for TENG-based ion generation. The two most common designs are contact-separation (CS) and sliding freestanding (SF) TENG (Fig. 4). In CS mode, the two electrodes are physically separated by an air gap and mechanically pressed together with a specific pressure. When the two electrodes are separated, the built-up charge is released through the external circuit into the emitter. In SF mode, charge is generated from mechanically actuating (i.e., linear motors, physically sliding, etc.) the "sliding" electrode across two electrodes separated by an air gap. When the sliding electrode clears the air gap, the charge is built up and released through the external circuit simultaneously; charge is no longer generated when the electrode stops at the end of the actuation cycle. A notable difference between CS and SF modes is that in SF both positive and negative currents can be generated, or the desired polarity can be locked with a diode rectifier [31].

There are several analytical advantages to TENG-based ESI over traditional DC power ESI ion sources. However, the main five are: 1) low material cost, 2) flexible design space, 3) intrinsic pulsed nature, 4) low flow rates leading to minimal volume consumption, and 5) increased sensitivity. The simplest design for a TENG power supply requires a conductive material (e.g., copper, tin, gold, etc.) nested between two triboelectric materials (e.g., polyurethane and polytetrafluorethylene (PTFE)), and an insulating, mechanically robust substrate (e.g. acrylic). This simple layered design and the affordability of these materials in bulk enable a flexible design space for rapid prototyping of different experimental variables such as materials employed, electrode surface

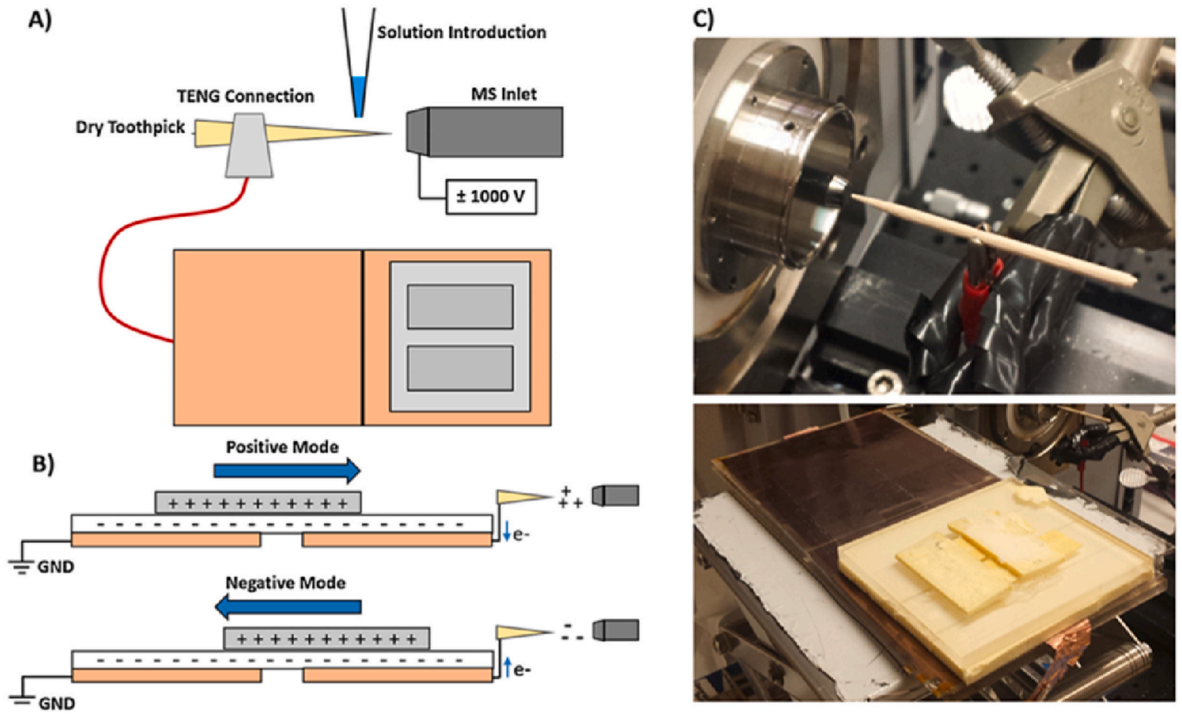

Fig. 6. (A) Schematic of the sliding freestanding TENG wooden-tip setup used in these experiments. (B) The two TENG copper electrodes on the bottom layer are shown in light orange, while the sliding piece with lower charge density is shown in gray and the insulating middle layer is shown in white. Charge is produced by the SF TENG in discrete pulses stemming from the flow of charge created when the top electrode is moved from one end to the other end of the stationary electrode. This charge is directed to the wooden tip facing the inlet. (V) Close-up image of the dry toothpick and mass spectrometer inlet setup as well as the SF TENG source used. Reprinted from Rapid Communications in Mass Spectrometry, 32, 1585–1590, Li, A et al., "Triboelectric nanogenerator (TENG) mass spectrometry of falsified antimalarials", 2018, with permissions from John Wiley and Sons.

areas, and electrode geometry.

The pulsed nature of TENG-powered ion sources enables synchronization with trapping or time dispersive instrumentation such as high-resolution FT-ICR and Orbitrap, or even ion mobility platforms. Ion source/mass analyzer synchronization boosts sample economy by limiting the number of ions lost in between analysis cycles, and proactively improves the duty cycle of the overall analysis method. TENG ion sources inherently alternate between positive and negative modes during operation. This dual-polarity nature can be leveraged by coupling with instrument polarity switching to acquire two spectra, one in each polarity, in a single TENG actuation cycle. This more advanced synchronization mode increases the analytical information generated in each individual TENG pulse.

Lastly, it has been shown that TENG can provide increased sensitivity compared to traditional DC-powered ESI sources [32]. Previous work by Bouza et al. has demonstrated that TENG ESI initially produces a Taylor cone that rapidly evolves into the transient jet or dual-jet mode, quickly diminishing back into the standard Taylor cone regime before ionization stops at the end of the TENG actuation [33]. This multimodal ESI dynamic produces substantially more droplets, and therefore more ions relative to traditional DC-based ESI with a static mode Taylor cone. The improvements in sensitivity yielded by operating the ESI in a multimodal electrospray regime were identified in initial benchmarking work conducted by Li et al. where zeptomole (10^{-21}) analyte quantities were readily detected (Fig. 5).

TENG provides all the same benefits as other pulsed DC ESI ion sources, with several additional benefits in terms of construction and analytical capabilities. Traditional DC power supplies for ESI applications are not only expensive (ranging generally between $1000–10,000 for dedicated power supplies, and exceeding $10,000 for commercial instrument sources), but also may have limited capabilities in relationship to their price point. The bulk materials for TENG provide not only a cheaper device for ESI applications, but also a modular design space for researchers to fabricate TENG sources to fit their needs. The current design produces a pulsed spray, as well as a polarity switching mechanism between each pulse (i.e., alternating between a positive spray, negative spray, positive spray, *etc.*). These features improve sample economy and sensitivity for each individual TENG cycle [33]. These advantages have been leveraged over the last few years for several applications involving MS workflows, as discussed below.

3. Applications

3.1. Forensic analysis

From drug screening to crime scene analysis, MS plays a pivotal role in forensics [34]. MS is considered a category A, or highly discriminating, analytical technology by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) [35], which provides guidelines and best practices for standard operating procedures (SOPs) for forensic analysis of such drugs [36]. As a result of its categorical classification, MS is often considered a "confirmatory" rather than a "presumptive" technique and is used to positively identify drugs from earlier screening assays. While positive identification by MS may still require further analysis by complementary analytical technologies, its sensitivity and reproducible nature, and vast spectral libraries make it a cornerstone of the forensic analysis pipeline.

Currently, separation methods such as GC-MS and LC-MS remain the gold standard in forensics [37,38]. However, while well validated, these methods often require minute-to-hour timescales, reducing sample throughput. As an alternative, ambient MS methods that require minimal sample preparation and yield throughputs in the second-to-minute timescales by releasing analytes from their substrates through direct liquid extraction, plasma desorption, vibrational/acoustic nebulization, or laser ablation have been proposed for forensic analysis [39–46].

Of all ambient MS techniques, paper spray ionization (PSI) has

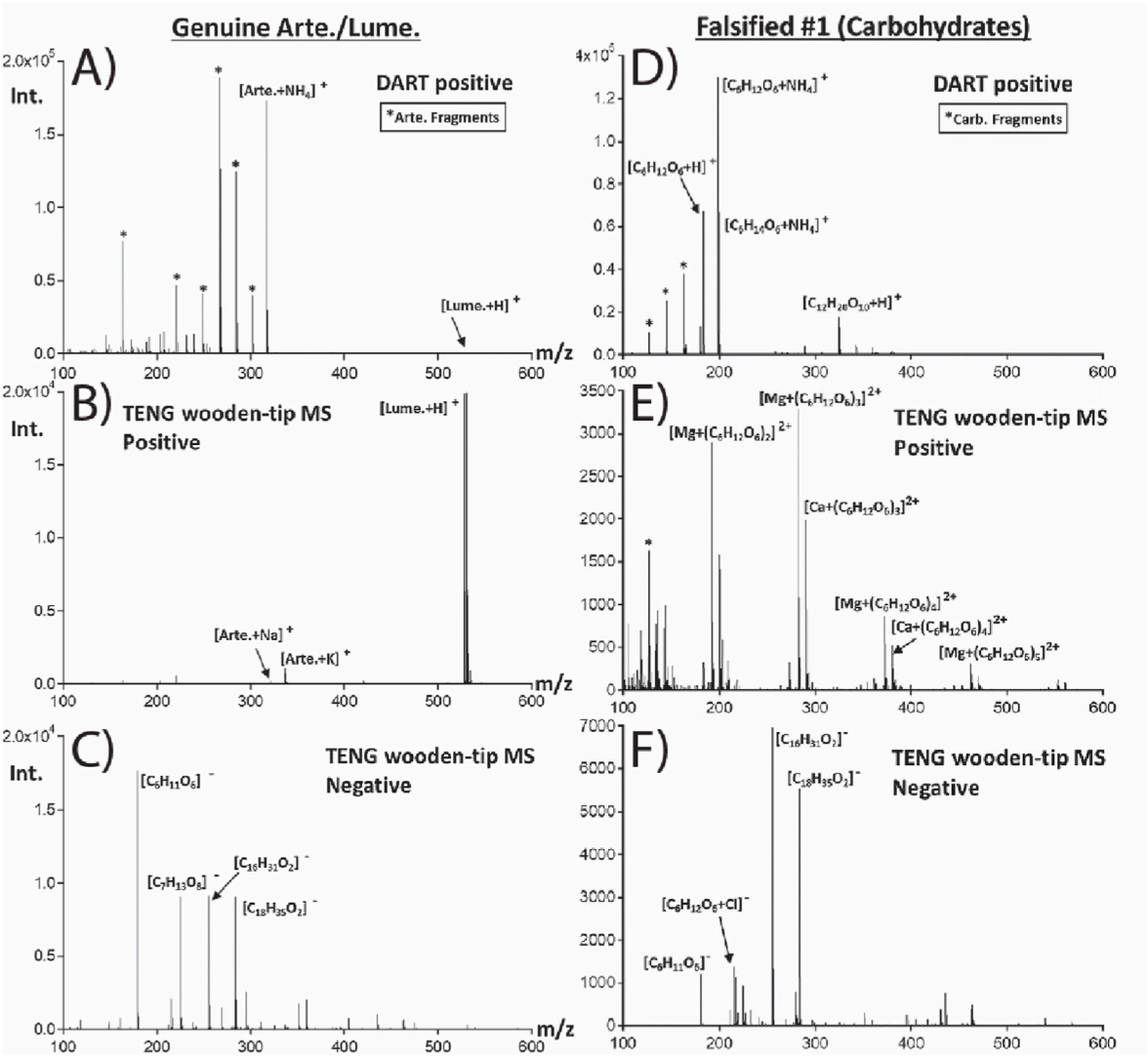

Fig. 7. Comparison of SF TENG wooden-tip MS and DART-MS results for the analysis of genuine artemether-lumefantrine antimalarial tablets. For TENG wooden-tip MS, powdered samples were extracted in methanol and the extract was deposited on the wooden tip. (A) DART positive mode MS analysis. (B) and (C) show TENG wooden-tip MS results in positive and negative ion mode, respectively. Comparison of TENG wooden-tip MS and DART-MS results for the analysis of three different classes of falsified artemether-lumefantrine antimalarial tablets: (D) DART positive mode; (E) SF TENG positive mode; and (F) negative mode TENG wooden-tip MS. Reprinted and adapted from Rapid Communications in Mass Spectrometry, 32, 1585–1590, Li, A et al., "Triboelectric nanogenerator (TENG) mass spectrometry of falsified antimalarials", 2018, with permissions from John Wiley and Sons.

shown significant promise for forensics. This technique uses a triangular-shaped paper substrate, sometimes functionalized, where the liquid sample is deposited. Following sample deposition, a potential is applied to the paper to generate ions via ESI. PSI has been shown to reduce the limits of detection (LOD) for several drug compounds detectable in dried blood spots [47], quantitate nicotine from cell cultures [48], and chemical warfare agents in blood and urine samples [49], among other forensic applications. Somewhat analogous to PSI is probe electrospray ionization (PESI), which uses a solid needle with the sample deposited at the tip to generate ions [50,51]. Wooden tip (i.e., toothpick) ESI falls between PESI and PSI, taking advantage of both techniques' attributes such as the absorption qualities of PSI and the stability of PESI, with the added advantage of very affordable consumables.

TENG power sources can be easily combined with ambient MS techniques that leverage ESI, such as desorption electrospray ionization (DESI), laser ablation electrospray ionization (LAESI) and nanoDESI. As the first demonstration in the field of ambient MS, TENG was used to power a wooden tip ESI ion source to screen for falsified antimalarial drugs (Figs. 6 and 7), demonstrating its capabilities for desorbing and ionizing the target compounds of interest without sample preparation. Results of this work showed that TENG wooden tip ESI provided comparable data quality and detection limits as direct analysis in real time (DART), but without the need for pressurized gases or high-power voltage supplies [52]. This study highlighted the analytical capabilities ambient TENG MS can offer towards forensic analyses where sensitive, sample conscious methods, and fieldable applications may be desirable.

3.2. *Metabolomics*

Metabolites are the myriad of small molecular weight compounds that are consumed or created by cells during enzymatic processes. These compounds are used to maintain homeostasis, support cellular growth and proliferation, and involve the removal of cellular waste [53]. Included in this definition are lipids, carbohydrates, amino acids, short chain peptides, and other small molecules involved in cellular pathways. Metabolomics is the comprehensive measurement of large subsets of

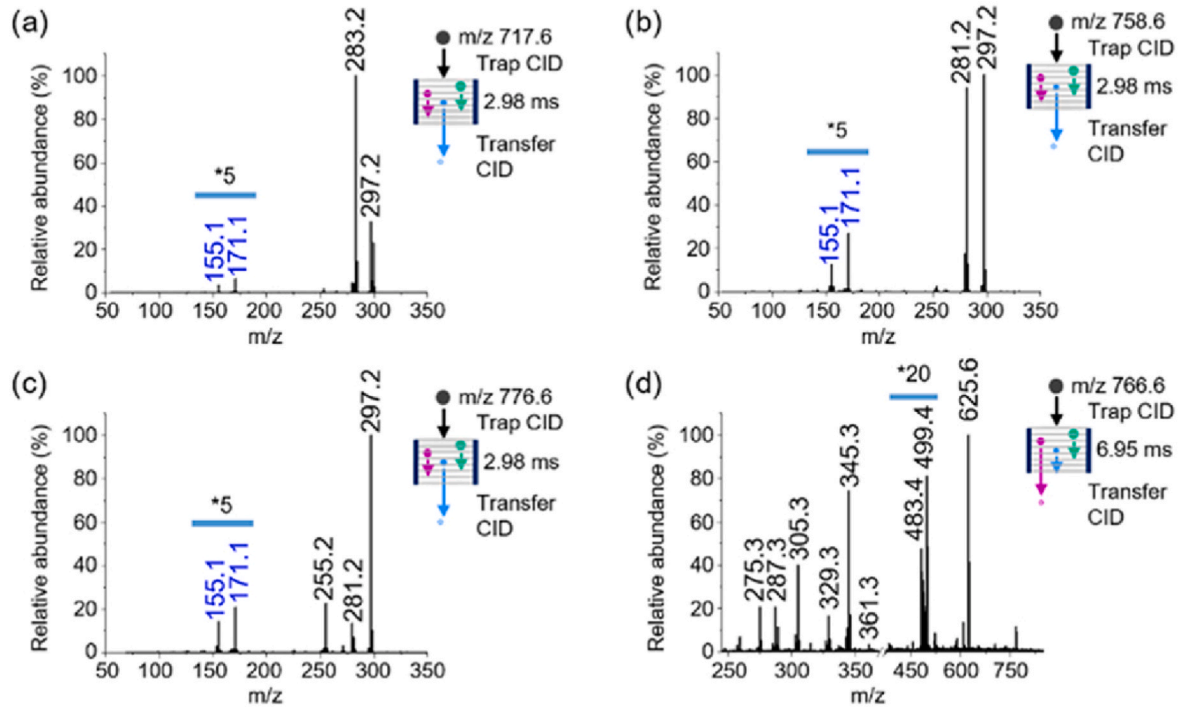

Fig. 8. TENG TAP IM-MS analysis of different GP. (a) PA(18:0/18:1(9Z)) in negative-ion mode, (b) PE(18:1(9E)/18:1(9E)) in negative-ion mode, (c) PS(16:0/18:1(9Z)) in negative-ion mode, and (d) PE(18:1(9E)/18:1(9E)) in positive-ion mode. Negative-ion mode experiments used 25 mM NH4OAc as an additive. Positive-ion mode experiments used 5 mM LiOAc as an additive. Reprinted with permission from {55}. Copyright {2021} American Chemical Society.

these low molecular weight compounds, with typical non-targeted assays detecting thousands of distinct species [54]. Metabolomics experiments reflect cellular activity at a given time, yielding a biological phenotype on the status of the system. Measuring metabolite concentration changes at differing points of the cellular life cycle or under differing environmental conditions provides a more sensitive snapshot than any of the other 'omics techniques, explaining the growing interest in the field.

Despite the unquestionable power of metabolomics, many challenges remain in this field. Since metabolites do not contain a single underlying chemical structure, like nucleotides in nucleic acids or amino acids in proteins, determining metabolite structure is a time consuming and multi-tiered endeavor. TENG ion sources have been shown to alleviate this challenge, specifically pertaining to lipid structure elucidation. To determine lipid structure, TENG ESI has been shown to enable the location of unsaturated lipid double bond positions and *sn*-chain position via ion mobility-MS/MS experiments. This is possible by increasing the surface area of TENG electrodes, which leads to a transient corona discharge during each actuation cycle [55]. Reactive oxidized species are formed from the corona discharge that generate epoxides at the lipid fatty acid double bonds. This epoxidation creates intermediate species that enable *sn*-position assignment and chemically activates the carbon-carbon double bond, producing a more favorable fragmentation site that can be targeted during MS^n experiments. The resulting diagnostic fragments that result from cleavage at the double bonds contain the chain length information and allow pinpointing of double bond positions on the chains. An example of this workflow is presented in Fig. 8. This process, in tandem with database matching, allows more thorough annotations of lipids.

Another challenge in metabolomics is that amplification of metabolites is not possible as it is with nucleic acids, raising the importance of increasing the sensitivity of metabolomics assays. Currently, comprehensive metabolomics studies of extremely low volume samples remain difficult due to the rapid sample consumption in traditional nano-ESI. TENG ion sources are excellent at performing low volume metabolomics assays, mainly due to their pulsed nature and high sensitivity. When coupled to inductive charging of the liquid solution, each TENG pulse has been estimated to consume ~50 pL. Moreover, the transient corona discharge created in TENG ion sources with larger (12 × 9.75 cm) electrodes enables their operation in a dual mode that encompasses both ESI and atmospheric pressure chemical ionization (APCI), enabling the ionization of low polarity compounds not readily ionized by ESI [55]. A unique property of this transient discharge is that it does not damage the emitter, as demonstrated by electron microscopy experiments [55]. Fig. 9 highlights the low sample consumption capability and multimode ionization by showcasing analytes that were detected with TENG, but not with a DC-ESI source. High quality spectra were obtainable from sub-nanoliter volumes of sample. This opens the interesting possibility of applying TENG ionization to monitor a wider array of compounds, or even the most sensitivity-challenged applications, such as single cell metabolomics. Along these lines, TENG has been applied to a few sample-limited test beds, such as mesenchymal stromal cells (MSC) and exhaled breath condensate. Typical MSC LC-MS metabolomic experiments require 1e6 cells, which is impractical as it requires a large number of passages to reach these target cell numbers. Li et al. were the first to demonstrate sub-nanoliter metabolomics applications using TENG, yielding reliable data when LC-MS could not easily be performed [56].

Finally, the diversity of metabolites makes it challenging to obtain full coverage from a single metabolomics assay. Over 3000 chemical classes comprise the metabolome and upwards of 100,000 compounds have been identified in humans alone [57]. The overwhelming number of compounds makes it nearly impossible to capture the entire metabolome in a single study, but studies that can observe a wider breadth of compounds offer a more robust insight to the biochemical processes in the system under study and may lead to the identification of newer altered pathways. However, some metabolites only readily ionize in positive ion mode (e.g., phosphatidylcholines), while others ionize more efficiently in negative mode (e.g. phosphatidylinositols) meaning experiments that obtain both MS polarities provide a more comprehensive

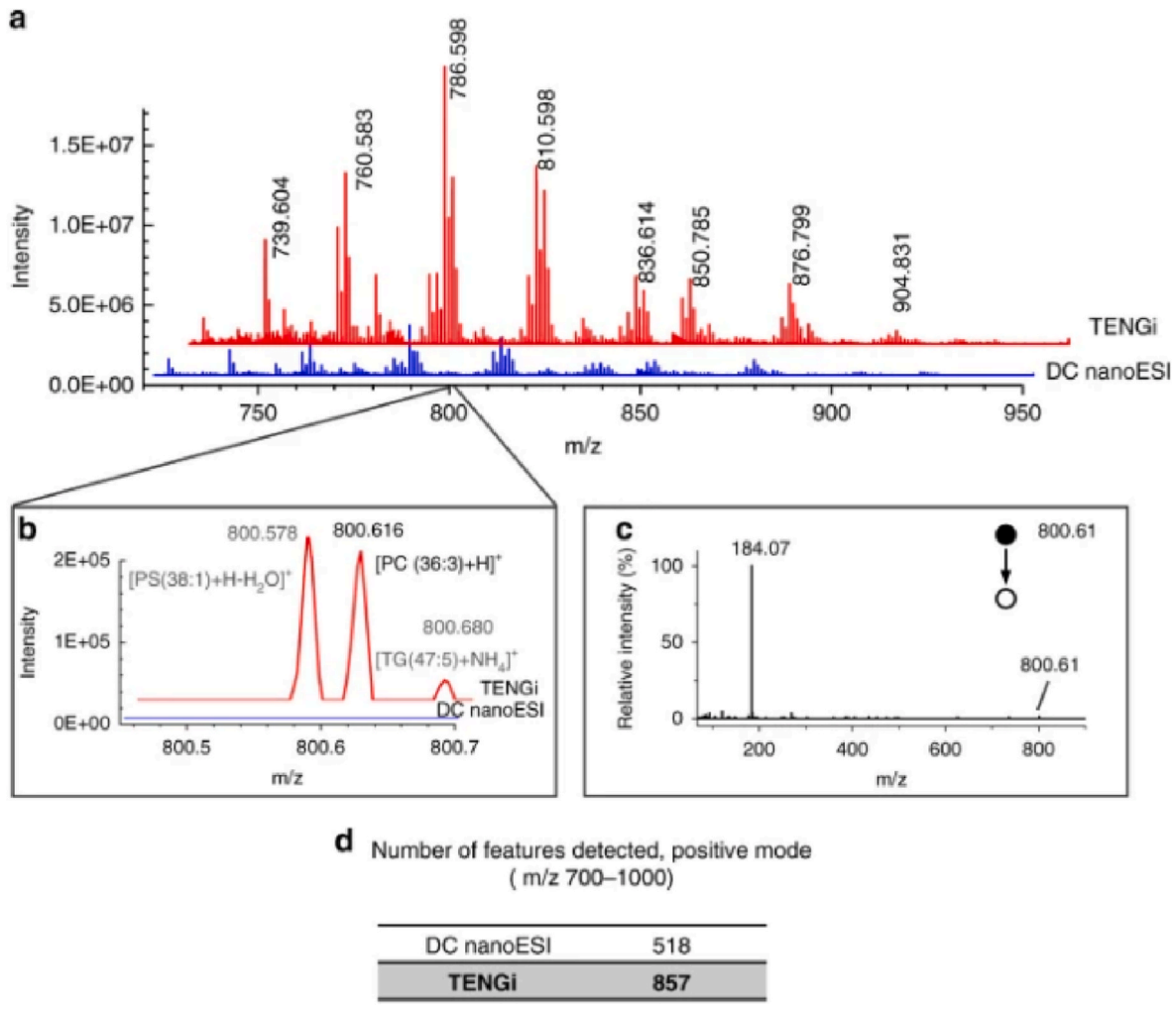

Fig. 9. a–d Positive-ion mode MS comparison: a full MS, b enlarged view of *m/z* 800.616 that was detected by TENGi but not by DC nanoESI, c TENGi MS/MS identification of the species with *m/z* 800.616; d number of features detected in positive-ion mode in the 700–1000 *m/z* range. Reprinted and adapted from Nature Communications, 11, 5625, Li, Y et al., "Sub-nanoliter metabolomics via mass spectrometry to characterize volume-limited samples", 2020, with permission from Springer Nature.

coverage of metabolites [58,59]. The inherent capability of SF TENG to alternate polarity in every cycle with sub nanoliter sample consumption makes it a valuable tool to further improve coverage in shotgun metabolomics experiments in combination with high resolution MS.

3.3. Proteins

Proteins are formed by polypeptide chains composed of amino acids that lead to the formation of three-dimensional structures with biological activity. As with metabolites, understanding a protein's structure and function, or changes in structure and function, is crucial to understand its relationship to disease and human health [60]. There are several structural biology techniques used for protein structural analysis including X-ray crystallography [61–63], cryo-electron microscopy (Cryo EM) [64,65], nuclear magnetic resonance (NMR) [66,67], and MS [68–70]. Of these, MS is one of the most versatile methods, mostly when combined with the separation capabilities of chromatography or ion mobility [68,71,72].

With MS-based methods, proteins can be analyzed at the primary (1), secondary (2), tertiary (3), or even quaternary (4) levels of structural information [73]. Bottom-up methods where the protein is enzymatically digested into relatively short peptide fragments at the amino acid (AA) positions in the AA chain are advantageous for in-depth sequencing as well as cataloguing the various post-translational modifications (PTMs) of the protein of interest [74]. However, since the enzymatic digestion indiscriminately reacts with the protein of interest the resulting peptide fragments may have multiple PTMs that do not necessarily correspond to a single structure and may instead belong to several proteoforms (i.e., different genomic sequence variants) [75].

When correlation between higher-order structure (HOS) and function of proteoforms is desired, middle-down, or top-down methods are preferable. Middle-down methods often leverage enzymatic digestions that are sequence specific for a protein target to generate relatively large peptides or smaller protein domains compared to the whole proteins structure [76]. A particularly poignant example is GingisKHAN™, a proteolytic enzyme used to specifically cleave the specific amino acid (KSCDK/THTCPPCP) located above the hinge region in IgG1 monoclonal antibodies (mAbs) into the F(ab)2 and Fc effector domains. Top-down methods by contrast do not use any enzymatic digestion, and instead aim to study the entire protein sequence in denaturing conditions. By studying proteins with top-down methods individual proteoforms can be analyzed, but complete sequence coverage can be challenging even with state-of-the-art instrumentation and non-covalent interactions are lost through the denaturing conditions [77,78].

Native MS (nMS) enables the measurement of the non-covalent interactions of protein macromolecules and their complexes in the gas-phase and continues to be a transformative tool for structural biology [79]. Notably, it is exceptional at topology and stoichiometric

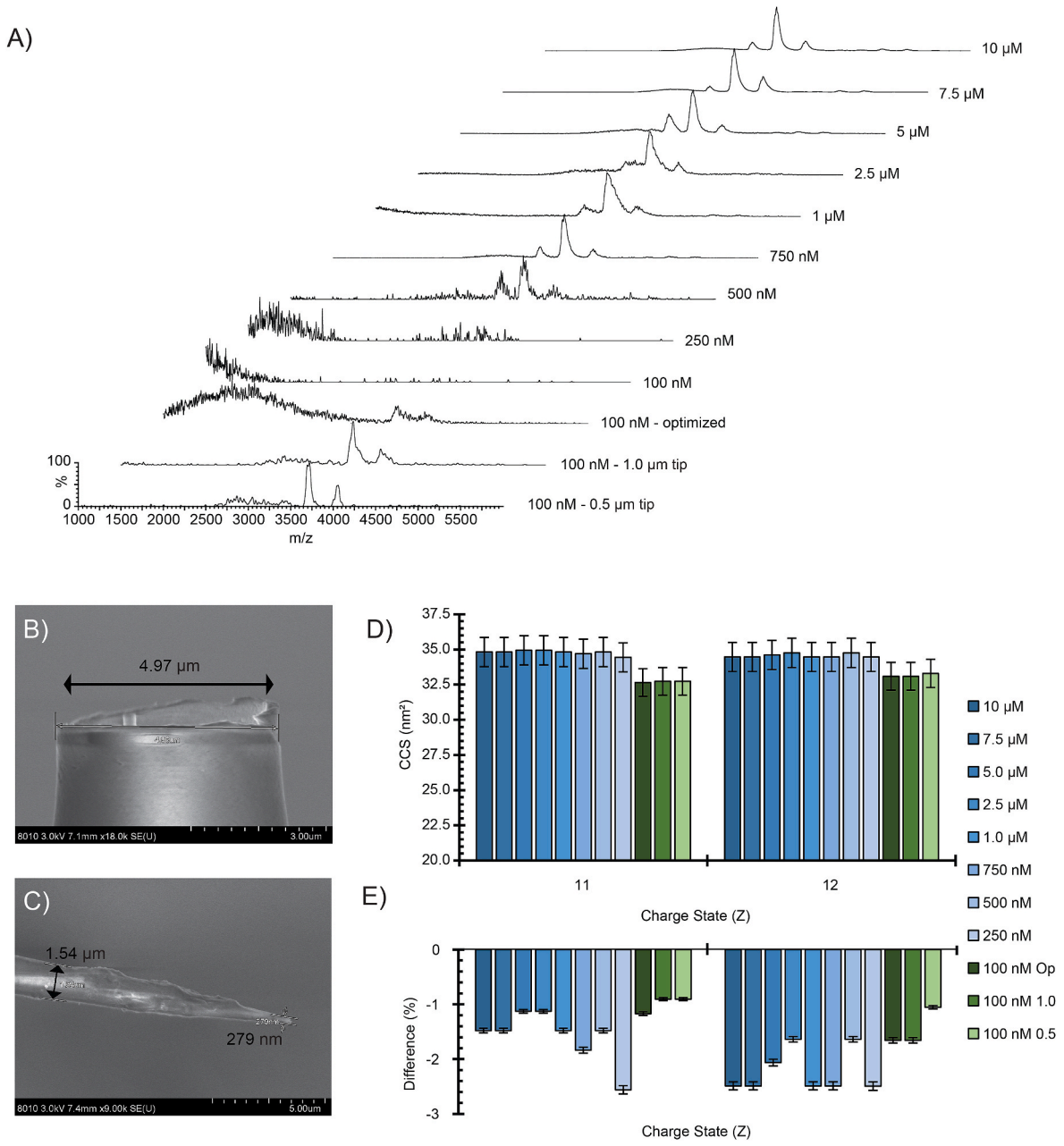

Fig. 10. (A) Mass spectral overlay for ovalbumin across a range of concentrations: 10 µM, 7.5 µM, 5 µM, 2.5 µM, 1 µM, 750 nM, 500 nM, 250 nM, and 100 nM. At 250 and 100 nM S/N sharply decreases primarily due to ion suppression from salt clusters. 100 nM signal can be partly recovered through instrument parameter and quadrupole tuning, but salt clusters remain present. The 100 nM signal can be further improved using submicron emitters. SEM images of (B) 5 µm and (C) 0.28 nm emitters. (D) Calculated CCS values for ovalbumin concentration gradient. (E) Percent difference of experimental vs. theoretical CCS values, which all fell within 3 % for ovalbumin. Reprinted from Analytica Chimica Acta, 1269, 15, Vallejo et al., "Native triboelectric nanogenerator ion mobility-mass spectrometry of egg proteins relevant to objects of cultural heritage at picoliter and nanomolar quantities", 2023, with permission from Elsevier.

determination of unknown protein complexes [80] such as Cascade, a ribonucleoprotein complex for *Escherichia coli* immunity to CRISPR (clustered regularly interspaced short palindromic repeats) [81] and membrane protein (e.g., aquaporin Z) sensitivity to lipids [82]. When combined with ion mobility (IM-MS), additional information about the protein structures size and stabilities can be obtained, and often can be compared with strong correlations to other structural biology techniques [70,80]. However, despite the capabilities of nMS most current assays rely on proteins that can be purchased as pure standards, prepared at sufficient concentrations, and may be acquired through recombinant expression [80,83]. However, for precious sample analysis where additional acquisition is either restrictive or impossible, (e.g., patient biopsies, cultural heritage materials, etc.) more sensitive techniques are required [84].

By leveraging the analytical capabilities of TENG ion sources towards nMS protein MS methods can be brought closer to the ultra-precious sampling regime. Initial studies of the capabilities of TENG by Li et al. demonstrated that characteristic mass spectrum for intact cytochrome C could be acquired at nanomolar concentrations with only a few TENG pulses. This work was followed by Bouza et al. where a new TENG design was implemented to increase the effective peak voltage and currents that could be applied to the ESI emitter. This change in design to a TENG with approximately 1.75-fold larger electrode sizes increased the yield of ions through the ESI process, and greatly improved the SNR of characteristic

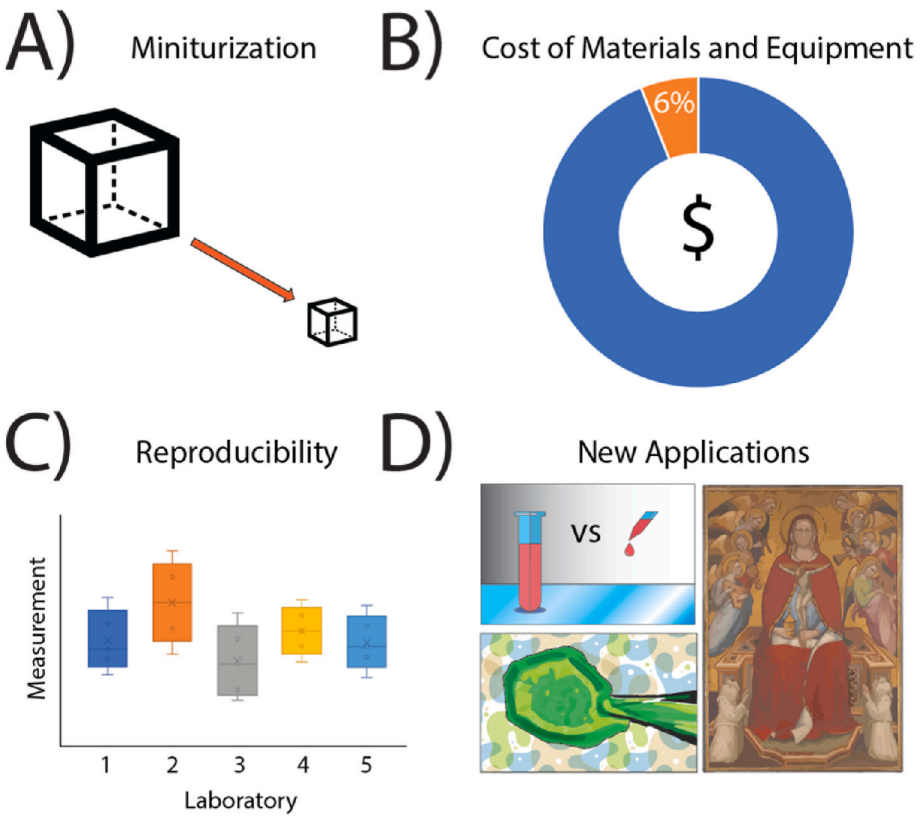

Fig. 11. A cartoon representation of major areas for TENG-based ionization approaches to address. Three immediate areas include (A) miniaturization and (B) reducing materials and equipment costs for fabrication, and (C) evaluating the reproducibility of TENG through intra- and inter-laboratory studies. (D) Lastly, new explorable research areas include interest in ultra-precious materials (e.g., reducing patient sample size, studying single-cells, and cultural heritage research).

protein mass spectra for cytochrome C and albumin at nanomolar concentrations [33]. However, both of these previous reports used 50:50 water:methanol solvent compositions for the proteins and did not include IM-MS, so questions remained on whether TENG could produce "native-like" ions. Recent work has addressed these questions, demonstrating that TENG is not only capable of producing nMS data within good agreement to literature (i.e., within 3 % of protein database measurements), but that comparable information content can be obtained with substantial reduction in sample consumption, with low nL volumes and femtomole sensitivity relative to standard nMS protocols (Fig. 10) [85]. These improvements in sample consumption requirements to obtain high fidelity nMS datasets could ease prohibitive sample requirements for protein systems that are challenging to express or ultra-precious clinical or material samples.

4. Conclusions

Triboelectric nanogenerators show significant promise as alternative power sources for ESI MS. The improvements in sample economy, modularity, and low cost of production make TENG an interesting candidate for a variety of different applications, ranging from single-cell metabolomics to native MS proteomics and beyond. Previous work has showcased the ability of TENG technology to identify lipid double bond positions, testing of counterfeit pharmaceuticals, and boosting sample economy for low-volume metabolomics. Adoption of this technology by the larger analytical chemistry community has great potential to extend its use to a variety of yet untested applications.

5. Future outlook

TENG-based ion sources provide improved sensitivity and sample consumption for precious materials. However, more improvements are still needed to further advance the technology. The most readily apparent is the reduction in unit cost for a single device's fabrication. The current design TENG ion source cost is approximately $10,000 in parts and materials and requires a dedicated computer to communicate with the linear motors used for actuation. However, with the advent of 3D printing and consumer-grade electronics, we estimate this cost can not only be drastically reduced (<10 % or $1000), but that the footprint and geometry of the device can be reduced substantially to enable easier integration with MS instrumentation. With a reduced footprint and cost, TENG could enable inexpensive ESI ion sources for field-operated MS platforms and drive other ambient MS sample introduction methods such as low temperature plasma in sources, paper spray, or coated blade spray. The improvement in sensitivity and reduction of sample consumption makes it an attractive option for other sample limited applications such as single-cell –omics (i.e., metabolomics, proteomics, etc.) or cultural heritage samples, and its flexible design space and controlled charge delivery may provide new avenues for research in accelerated microdroplet organic reactions (Fig. 11).

Author statement

Daniel D. Vallejo: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision; Joseph L. Corstvet: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization; Facundo M. Fernandez: Conceptualization, Writing - Review & Editing, Supervision.

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Facundo Fernandez has patent #US-11476778-B2 issued to Georgia Tech Research Corporation.

Data availability

No data was used for the research described in the article.

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