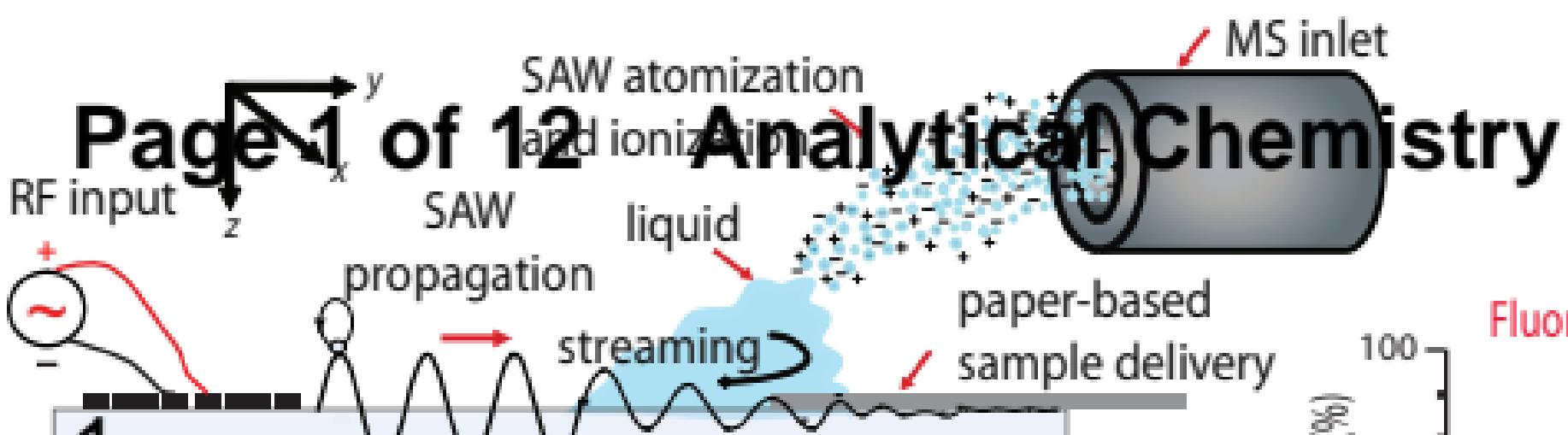


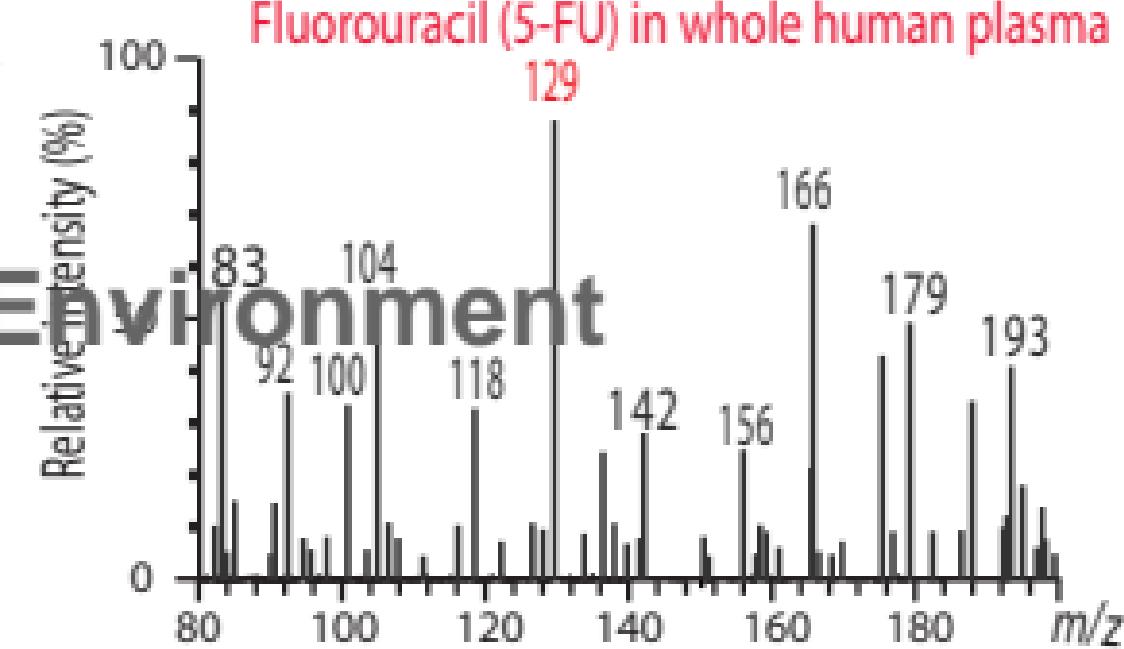
A Paper-Based Microfluidic Surface Acoustic Wave Sample Delivery and Ionization Source for Rapid and Sensitive Ambient Mass Spectrometry

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A Paper-Based Microfluidic Surface Acoustic Wave Sample Delivery and Ionization Source for Rapid and Sensitive Ambient Mass Spectrometry

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Abstract

A surface acoustic wave-based (SAW) sample delivery and ionization method that requires minimal to no sample pretreatment and that can operate under ambient conditions is described. This miniaturized technology enables real-time, rapid, and high-throughput analysis of trace compounds in complex mixtures, especially high ionic strength and viscous samples that can be challenging for conventional ionization techniques such as electrospray ionization. This technique takes advantage of high order surface acoustic wave (SAW) vibrations that both manipulate small volumes of liquid mixtures containing trace analyte compounds and seamlessly transfers analytes from the liquid sample into gas phase ions for mass spectrometry (MS) analysis. Drugs in human whole blood and

plasma and heavy metals in tap water have been successfully detected at nanomolar concentrations by coupling a SAW atomization and ionization device with an inexpensive, paper-based sample delivery system and mass spectrometer. The miniaturized SAW ionization unit requires only a modest operating power of 3–4 W, and therefore provides a viable and efficient ionization platform for the real-time analysis of a wide range of compounds.

Introduction

Mass spectrometry (MS) is a widely used analytical tool for molecular weight determination and structure identification, given its speed, sensitivity, and specificity. One of the longstanding challenges in MS, nevertheless, has been the efficient conversion of neutral molecules into low-internal energy gas phase ions that can be analyzed under medium or high vacuum ($< 10^{-5}$ torr). Over the past two decades there has been a shift toward both atmospheric pressure and ambient ionization techniques, and these have been accompanied by the development of chip-based ion sources.¹ Electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) are popular at-

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mospheric pressure methods for converting non-volatile compounds into gas phase ions, and, along with matrix-assisted laser desorption ionization (MALDI), have enabled many developments in the analysis of large biomolecules. Nevertheless, both ESI and MALDI suffer from analytical shortcomings such as analyte perturbation and signal suppression due to matrix ions.¹ There also remain considerable challenges in extending these techniques for high-throughput or real-time analysis, mostly due to cumbersome and lengthy sample preparation procedures. In addition, whilst a large family of ambient methods which allow the ionization of untreated samples in the open environment has been developed, mainly desorption electrospray ionization (DESI), which uses electrically charged droplets to ionize the surface of interest, and direct analysis in real time (DART),² which uses plasma-based desorption to create gas phase ions, the number of compounds that can be analyzed by these methods are limited. For example, DESI-related techniques are restricted to moderately to highly polar compounds with large molecular masses while DART-related methods are best for less polar or non-polar compounds with low molecular masses.³ A nanoelectrospray ion source has also been developed employing a micromachined ultrasonic array.⁴

Recently, surface acoustic wave (SAW) atomization^{5,6} has been proposed as an alternative method for transferring solution phase analytes from a planar chip into a MS, and Heron et al. have demonstrated this for peptide detection.⁷ In their work, Heron et al. used a SAW device to atomize the sample and a separate, pulsed high voltage (4.5 kV) source was applied between the SAW substrate and the MS inlet. However, since the high voltage pulses were not in contact with the liquid sample, it was unclear what role the high voltage source played during ionization or on the ionization mechanism. In a different study on SAW-induced ionization, a high voltage source (5 kV DC) was applied in contact with a liquid sample on a SAW substrate for a electrostatic deposition (SAW-ED) device developed for the fabrication of protein chips.⁸ Here, we demonstrate a SAW chip-MS interface for the reliable and effective transfer of analytes from solution phase to the gas phase that does not require a separate ex-

ternal high voltage ionization source. Instead, we choose to rely on the inherent charging mechanism of the SAWs themselves, given their electroelastic nature. The elimination of an external high voltage source has practical implications, as not only is a high voltage DC supply unattractive in terms of safety and cost for a portable consumer device, it also limits the ability to miniaturize the device for true chip-scale functionality.

The SAWs used in this study are nanometer amplitude Rayleigh waves that propagate on the surface of a piezoelectric substrate. Though the amplitude of the SAW may only be a few nanometers, the acceleration is very large at 10^6 to 10^9 m/s² due to the high frequency, and, because of the power input, these accelerations can be maintained even after introducing a uid or an entire microuidics structure onto the SAW substrate. In the current context, the large accelerations generated by a SAW can be exploited to rapidly destabilize a drop to produce a jet⁹ or aerosol droplets,¹⁰ it is the latter atomization process that has been exploited in past studies^{7,11,12} and in the present work. Whilst ultrasonic atomization has been used to produce a large volume of nebulized mist into MS systems, in inductively coupled plasma mass spectrometry (ICP-MS) coupled with ultrasonic nebulization and membrane desolvation^{13,14} for example, the piezoelectric transducers typically operate at tens to hundreds of kHz-order frequencies to generate bulk waves. Additionally, cavitation-induced ionization¹⁵ potentially present during operation of these devices can be prone to fragment biomolecules, limiting their usefulness for genomics and proteomics applications. In contrast, SAW atomization utilizes much higher frequencies, typically 10–100 MHz, and the time scales are typically much smaller than the characteristic time scale for molecular relaxation—too short to generate shear gradients that can cause biomolecular degradation.¹⁶ In addition, the small powers required in SAW atomization are too low to induce cavitation,¹⁷ which is another major cause of molecular damage.

A substrate-free MALDI involving the use of acoustically levitated droplets as a sample handling technique has also been proposed to eliminate the artifact of sample supports while enhancing the ionization strength at the droplet surface.¹⁸

The majority of these ionization sources are not ideal for portable field use due to the requirement of large electric fields, nebulizing gas flows, and lasers, therefore hampering the ability to miniaturize the device.¹⁹ Conversely, a significant attraction of the chip-scale MS interface developed in the present work is the ability of the SAW to be coupled with a paper-based sample delivery method that is cheap and disposable, consonant with burgeoning interest in paper-based microfluidic diagnostic devices.^{20,21} This removes the need for bulky and cumbersome peripheral equipment such as pressure-driven pumps, fluid interconnections, and nebulizing gas, typical in most chip-MS interfaces,²² therefore providing further capabilities for miniaturization and complete chip integration, and thus making the technology highly compatible with portable miniaturized mass spectrometers for field-use. Indeed, the basis for the present work arises from our recent demonstration of the use of SAW atomization for extracting fluid or biomolecules from paper-based assays for subsequent detection with little biomolecular degradation.¹⁶ Another key advantage of using paper for sample delivery is that it acts as a filter to separate out contaminants from the sample, therefore facilitating the direct analysis of complex raw samples or with minimal or even no sample pretreatment—this is critical in accelerating therapeutic drug screening and development as well as drug monitoring in clinical disease treatment and forensic applications.

In this work, the role of the SAW is threefold, accelerating the capillary imbibition effect of the liquid through the paper for sample delivery to the SAW substrate, transferring the analytes from solution phase to the gas phase via atomization, and at the same time, charging the atomised droplets for detection via the MS. In the rest of the paper, we report on a miniature SAW atomization platform incorporating a paper-based sample delivery system for sample ionization and MS interfacing under ambient conditions. This could form the underlying technology for an MS-based biosensor for rapid and sensitive detection of drugs, pathogens, and heavy metals, among other chemicals.

Methods and Materials

Figure 1 shows a schematic illustration of the SAW atomization setup for ionization and MS sample delivery. Briefly, a 30 MHz SAW device patterned with pairs of gold-chromium single-phase unidirectional transducers (SPUDTs) was fabricated using sputter deposition, standard UV photolithography, and wet etching onto a 127.86° Y-axis rotated, X-axis propagating single-crystal lithium niobate (LiNbO_3) substrate (Roditi Ltd., London, UK). Due to the inverse piezoelectric property of the substrate, a SAW in the form of a *Rayleigh* wave is generated when an alternating sinusoidal electrical signal is applied to the SPUDTs. Internally placed free electrodes reflect acoustic energy flowing in the “reverse” direction, thus nearly doubling the acoustic energy propagating in the forward direction.²³ Less energy is lost and the risk of interfering reflection is reduced. The concentric elliptical design employed allows the lateral concentration of the SAW energy to a size commensurate with the fluid drop atop the substrate, helping to improve the efficiency of atomization by avoiding energy loss due to acoustic energy passing to either side of the fluid. Polyester-cellulose clean room paper (Lym-Tech, Chicopee, MA, USA) was used as a wick in siphoning liquid from a supply reservoir to provide a continuous supply of the fluid sample through capillary pressure developed in the paper. This provides fluid as needed to the SAW substrate without the need for external pumps, a marked advantage over other continuous-flow microfluidics devices.¹⁶ Before each test, a standard cleaning process—rinse with acetone, isopropyl (IPA), deionized water and dry with nitrogen gas—was required to remove residues/contaminants on the substrate surface.

For this study, we used two model compounds: caffeine (positive mode, molecular weight = 194.19 Da) and the cancer drug fluorouracil (negative mode, molecular weight = 130.10 Da). Caffeine, 5-fluorouracil (5-FU), and other associated reagent grade chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. Single donor human whole blood and plasma (with sodium citrate as anticoagulant) were acquired from Innovative Re-

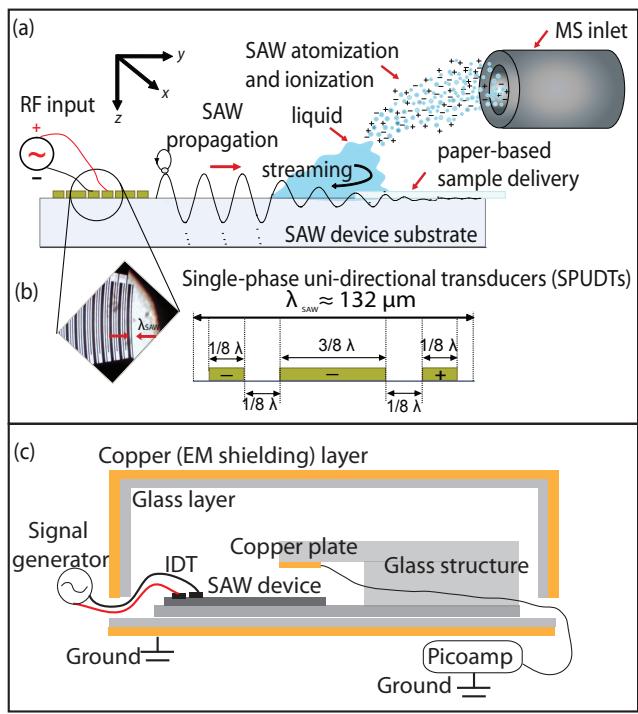


Figure 1: (a) Schematic depicting the SAW chip-MS interface from which samples of complex mixtures are wicked through the paper onto the SAW substrate and subsequently atomised and ionized. The SAW is generated upon application of an alternating sinusoidal electrical signal to (b) a pair of gold-chromium single-phase uni-directional transducers (SPUDTs), and propagates along the substrate until it encounters the liquid, at which point the acoustic energy causes the destabilization and break-up of the liquid interface to produce micron-sized aerosol droplets. In addition, the leakage of the acoustic energy into the drop also drives strong liquid recirculation. (c) Experimental setup for measuring the current of the charged aerosols generated via SAW atomization.

search (Novi, MI, USA). Methanol/deionized (DI) water solution (1:1, vol/vol) was used as the solvent unless otherwise stated.

Mass spectra were acquired on an ion trap mass spectrometer (Esquire 3000+, Bruker Daltonics, Billerica, MA, USA). The end plate at the MS inlet was removed, and the capillary was maintained at 500 V to assist declustering and ion transmission. Counter-flowing dry gas was typically set at 250°C and 2 ml/h unless otherwise stated. Detection of ions was either across the full m/z range or via selected ion monitoring of the expected precursor ion m/z values. A maximum ion trap time of 200 ms was used, and 5 individual scans were averaged to give a spectrum while the SAW-MS data acquisitions were continuously run for 2 mins.

Additionally, electric current measurements using the setup shown in Figure 1(c) were conducted to verify whether the electric fields ($\sim 10^4$ V/m) generated as a consequence of the SAW propagation on the piezoelectric substrate were sufficient to adequately ionize the liquid solution atop the substrate. In order to minimize the ambient background electromagnetic (EM) wave interference, a small glass enclosure layered with copper foil was constructed around the device. The current associated with the aerosols collected on the copper plate placed above the device directly where the aerosols are generated was measured using a picoammeter (Model 6487, Keithley, Cleveland, Ohio, USA). Fluids of high viscosity (such as mixtures of water and glycerol), low surface tension (such as ethanol), and higher conductivity (such as tap water) were selected to study the relationships between the aerosol size/conductivity and the current. Glycerol and ethanol were purchased from Sigma-Aldrich (St. Louis, MO, USA). The properties of the fluids are shown in Table 1.

SAW Aerosol Charging Mechanism

We turn to the use of a numerical model order to provide an estimate of the electric field in the fluid. Details of the model, which involves the use of a finite difference time domain method to solve the equations governing the motion of the piezoelectric substrate and the fluid film, Maxwell's

Table 1: Fluid properties and current measurement

	Density (kg/m ³)	Viscosity (10 ⁻⁴ Pa.s)	Surface tension (N/m)	Conductivity (μS/cm)	Q (nA.s)
DI water	~ 1000	~ 9	0.078	~ 3	~ 118 ± 51
DI water + 12% glycerol	~ 1031	~ 15	–	~ 280	~ 117 ± 40
DI water + 50% glycerol	~ 1130	~ 85	–	~ 112	~ 205 ± 50
Tap water	~ 1000	~ 9	0.078	~ 750	~ 267 ± 138
Ethanol	~ 789	~ 11	0.02275	~ 14	~ 155 ± 96

equations for the electromagnetic field, and the constitutive equation describing the relationship between stress and strain together with perfectly matched boundary layer conditions to minimize wave reflection at the substrate edges and the application of a sinusoidal electric potential input, are provided elsewhere.^{5,24} Given that the velocity of the elastic wave is several orders of magnitude smaller than that of the electromagnetic wave, the dynamics of the piezoelectric effect in generating a mechanical wave occurs on a much longer time scale than the electromagnetic field; consequently, it is common to assume that the electric field is *quasi-static*: there is no magnetic field formation. The propagation of acoustic waves in the fluid is described by linearised (first-order) continuity, momentum and equation of state. At the solid-fluid interface, continuity of velocity and force balance are applied, whereas at the fluid-air interface, a normal and tangential stress balance, together with a kinematic boundary condition, are applied. To compute the electric field in the fluid, we further invoke Laplace's equation ($\nabla^2 \varphi_f = 0$), and the boundary conditions at the solid-fluid interface ($\varphi_{LN} = \varphi_f$, $\epsilon_{33} \partial \varphi_{LN} / \partial n = \epsilon_f \partial \varphi_f / \partial n$) and at the fluid-air interface ($\varphi_f = \varphi_a$, $\epsilon_f \partial \varphi_f / \partial n = \epsilon_a \partial \varphi_a / \partial n$), where φ_{LN} , φ_f and φ_a are the potential in the piezoelectric substrate, the fluid, and the air, respectively; ϵ_{33} , ϵ_f , and ϵ_a are the permittivity of the substrate (in the directional normal to the free surface), the fluid, and the air, respectively. For this model, we have omitted the presence of surface charge at the solid-fluid interface (see **Supplemental Information** for details).

Brief results of the computation are shown in Figure 2. Figure 2(a) shows a contour plot of the instantaneous velocity amplitude in the lithium niobate substrate, and the inset shows the ampli-

tude of the electric potential in the fluid parcel (φ_f), which is only ~1 V. Figure 2(b) shows the amplitude of the vertical displacement ξ_3 of the substrate induced by the SAW, which propagates along the surface of the substrate at a phase velocity $c_{SAW} \sim 3980$ m/s, as well as the motion of the free surface of the fluid h_1 . Note that the displacement of the fluid h_1 is in phase with the vertical displacement x_3 , since the height of the liquid film is on the order of the length scale of the acoustic wavelength in the fluid, i.e., $H \sim \lambda_f$.²⁴ Figure 2(c) and (d) show the computed electric field in the directions parallel (E_x) and perpendicular (E_z) to the substrate surface at the solid-fluid interface (Figure 2(c)) and at the fluid-air interface (Figure 2(d)). For displacement amplitudes $\xi_3 \sim 1.5$ nm, the results show that the induced electric field at the solid-fluid interface is ~10⁵ V/m as a result of the small scale and permittivity differences between the substrate and liquid, whereas the electric field at the fluid-air interface is ~10⁻⁷ V/m. Figure 2(a) also shows that the induced electric potential only penetrates a short length into the fluid (< λ_f) and becomes negligible at the fluid-air interface as a consequence of the permittivity difference at the solid-fluid interface ($\epsilon_{33}/\epsilon_f \sim 0.4$). This large electric field difference polarizes the liquid at the substrate surface and at its free interface, forming ions that are then ejected in droplets. These droplets undergo evaporation and potentially further *Rayleigh* fission or ion evaporation events to produce molecular ions detected by the MS. Additionally, the electric field will be enhanced at the contact line of the fluid-surface-air interface, resulting in greater ionization, though this wasn't modeled explicitly.

In order to confirm that the SAW device generates charged droplets, current measurements us-

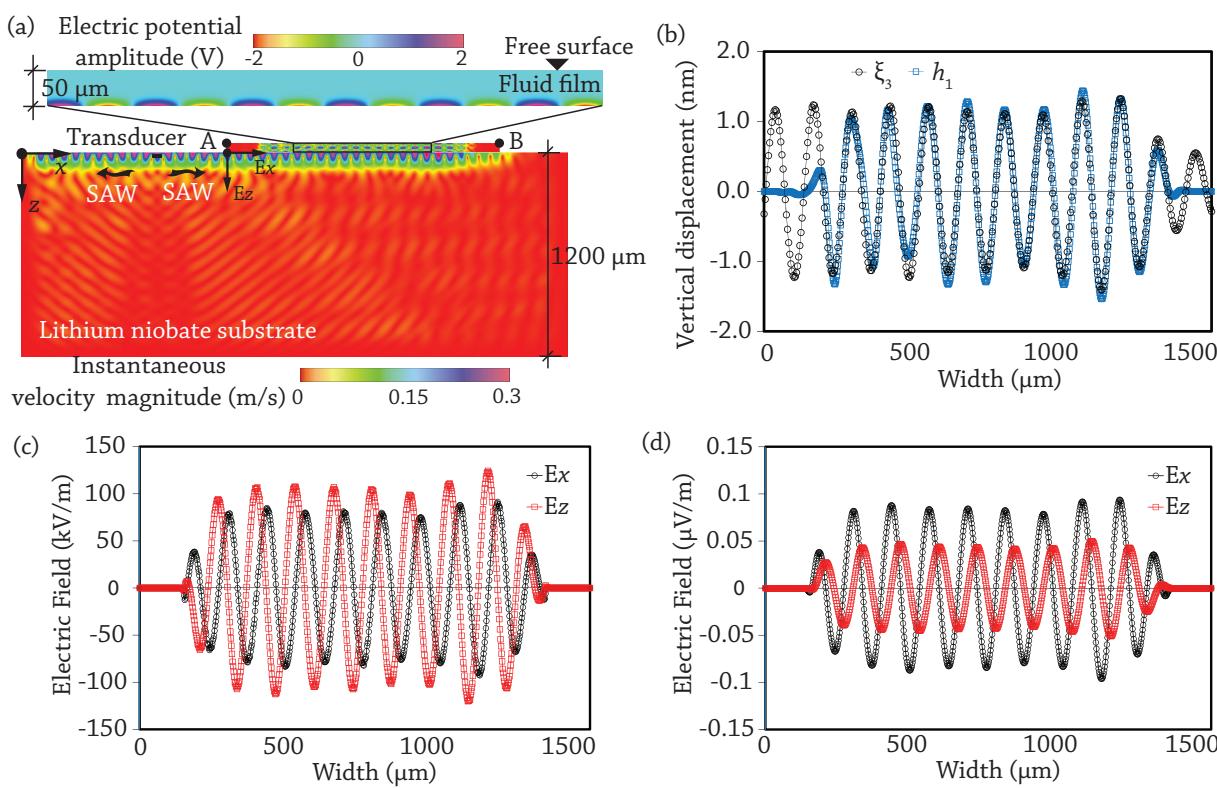


Figure 2: (a) Contours of the instantaneous velocity magnitude for the propagation of a 30 MHz SAW on the surface of a 127.86° $y-x$ LiNbO₃ substrate over 15 sinusoidal cycles ($t \sim 15f^{-1}$). The motion of the substrate is confined to within about a SAW wavelength ($\lambda_{\text{SAW}} \approx 133 \mu\text{m}$) from the substrate surface. The inset shows the induced potential in the fluid film. (b) The instantaneous displacement amplitude of the substrate ξ_3 and the fluid free surface h_1 , along the line A–B shown in (a). Typically, to induce strong acoustic streaming using 30 MHz SAW, the displacement amplitude ξ_3 must be greater than $\sim 1 \text{ nm}$. (c) The induced electric field at the solid-fluid interface, and (d) the induced electric field at the fluid-air interface due to the elastic motion of the piezoelectric substrate. Note here that the results are obtained through numerical simulation.

ing the apparatus in Figure 1(c) were conducted over 80 seconds for DI water alone, DI water + 12% glycerol, DI water + 50% glycerol, tap water alone, and pure ethanol (physical properties are given in Table 1). By integrating the current, i.e., $Q = \int I dt$ from $t = 0$ to $t = 80 \text{ s}$, we obtain the total charge measured over 80 seconds as shown in Table 1. The results clearly demonstrate that the electric field in the liquid generated by a SAW is able to ionize aerosols, i.e., an appreciable current was detected in each measurement. Since the SAW is generating charged aerosols, consequently, for integration with MS, no external high voltage source is required (see **Supplemental Information** for more discussion on these measurements).

SAW-MS Interface: Detection of Drugs and Heavy/Toxic Metals in Complex Mixtures

The ability to accurately and precisely detect trace target analytes in physiological fluids and tissue with parts per billion (ppb) sensitivity is vital to the development of new drug therapies with improved efficacies. Nevertheless, complex mixtures such as these first require separation using chromatographic methods to preconcentrate the analytes and to minimize suppression effects during ionization before sensitive MS analysis can be carried out. The similarities of target analytes to endogenous matrix components and their susceptibility to degradation at elevated temperatures also

1 impose further limitations on the detection—this is
2 especially true for physiological samples containing
3 blood cells and plasma.²⁵ As a consequence,
4 the rate at which drugs can be analyzed in these
5 physiological fluid samples is too slow. The ability
6 to rapidly detect trace analytes in physiological
7 fluids without requiring sample pretreatment or separation
8 is therefore an attractive alternative. Although ESI remains the most widely used sample
9 delivery and ionization technique for MS detection,
10 it is particularly ineffective for aqueous solutions or buffers with ionic strengths above
11 0.01 M,²⁶ therefore limiting its applicability for in-line, rapid, real-time analysis for applications
12 such as drug development, forensics and homeland
13 security, and environmental monitoring.

14 The paper-based SAW-MS interface was first
15 characterized for complex biological mixtures—in this case, both human whole blood and plasma.
16 Specifically, 1 μl of whole blood or plasma was
17 spiked with a model therapeutic "drug" (caffeine
18 or 5-FU), added into 100 μl of methanol/water
19 (1:1, vol/vol), and delivered to the substrate via
20 the paper wick. Tests were conducted using ionization
21 and operational parameters—solvent composition,
22 applied voltage, capillary voltage, distance between
23 the SAW device and the MS inlet, and drying gas temperature—that were optimised
24 to achieve the best MS signal intensity of the target analyte using the SAW-MS configuration (see
25 **Supplemental Information** for details). As observed in Figure 3(b), a signal-to-noise (S/N) ratio
26 of around 15 was achieved for protonated caffeine
27 in whole blood at concentrations as low as 9 nM (corresponding to 176 pg of analyte), while
28 a much better S/N ratio (> 30) could be achieved
29 at higher concentrations (Figure 3(c)). After SAW
30 atomization, most of the blood cell debris were ob-
31 served to be retained at the edge of the paper strip,
32 while the drug and other molecules presumably re-
33 mained dissolved in the solvent and were partly
34 retained and partly aerosolized.

35 The mass spectra collected for human plasma
36 containing caffeine displayed a similar pattern to
37 that in human whole blood (Figure 4), thus reaffirming
38 our observation that the blood cells are not taken up in the molecule-laden aerosols but re-
39 tained within the paper. The paper delivery system
40 therefore also serves as a filter to retain blood cells

41 and other coarse contaminants, thus facilitating the
42 direct analysis of raw and complex samples. Ad-
43 ditionally, a non-planar sample delivery mecha-
44 nism in the form of a fabric thread can also be
45 used in place of the paper strip that has a specific
46 pore size. Fabricating such a cheap, disposable
47 and flexible three-dimensional thread-based fluid
48 delivery system is simple and straightforward by
49 interweaving a hydrophobic thread around a hy-
50 drophilic one. There is also a possibility of using
51 glass fibers for reactive fluids, paper sandwiched
52 between polymer thin films to prevent evaporation,
53 or surface-treated paper for enhanced and thor-
54ough in-line analysis. Another major advantage
55 we have demonstrated in our study is the absence
56 of clogging problems for highly viscous samples
57 such as whole blood which is routinely encum-
58 bered by costly maintenance in chromatographic
59 methods.

60 For a more realistic demonstration of SAW-MS,
61 we considered 5-FU as our model compound. 5-
62 FU is a widely used cytostatic agent with a promi-
63 nent role in the treatment of various malignancies
64 especially solid tumours, and the development of
65 detection and quantification methods for 5-FU is
66 important to support clinical studies. Therapeutic
67 drug monitoring of 5-FU, for example, is essential
68 to improve its use in clinical practice—especially
69 to improve personalized therapeutic regimens and
70 to reduce the potential for toxicity. Chromato-
71 graphic methods such as high-performance liquid
72 chromatography (HPLC) as a separating modal-
73 ity, and fluorescence, ultraviolet, or MS as de-
74 tection techniques are frequently reported for the
75 measurement of 5-FU in specific biological matri-
76 ces; however, none of these has been validated us-
77 ing FDA guidelines.²⁷ The major disadvantage of
78 these techniques is the poor retention of 5-FU: due
79 to its high polarity, it is typically eluted close to the
80 solvent front.²⁸ These assays are further hindered
81 by the fact that 5-FU is difficult to separate from
82 structurally-related compounds such as uracil, thus
83 rendering its detection a time-consuming process.
84 Here, we demonstrate that the paper-based SAW-
85 MS interface developed here can circumvent these
86 problems since no elution is involved. The same
87 procedure used for caffeine was applied for the
88 analysis of 5-FU in negative ion mode. The mass
89 spectra recorded for 5-FU as pure analyte and in

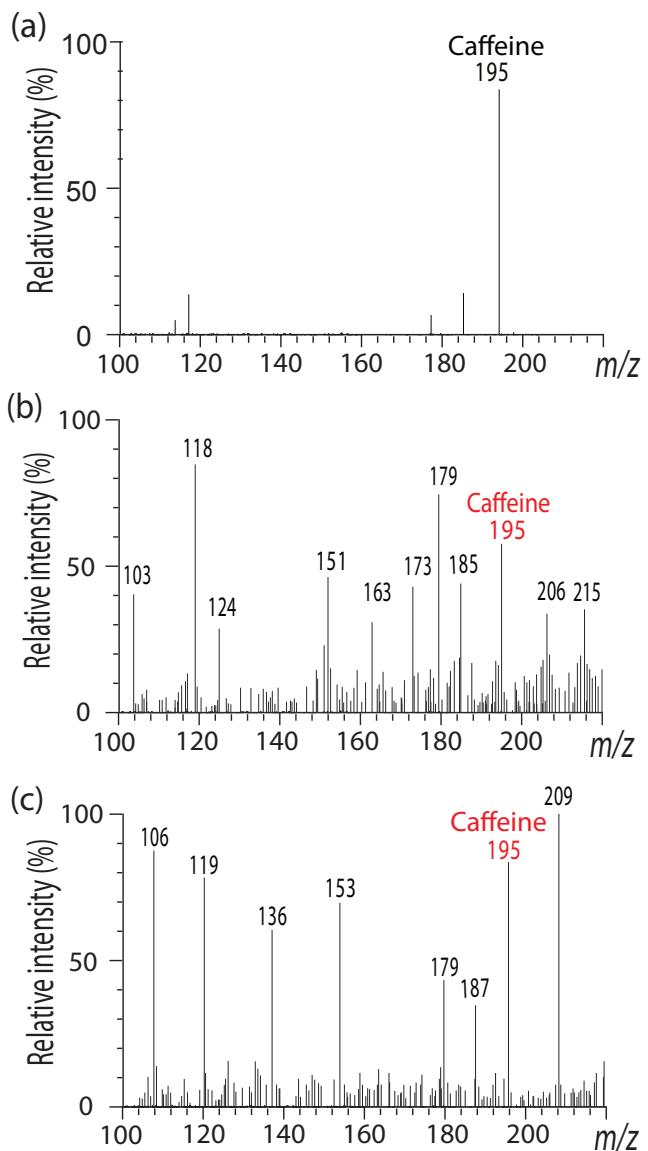


Figure 3: Positive ion mass spectra of (a) 100 nM caffeine in methanol/water, (b) 9 nM caffeine in human whole blood, and (c) 100 nM caffeine in human whole blood.

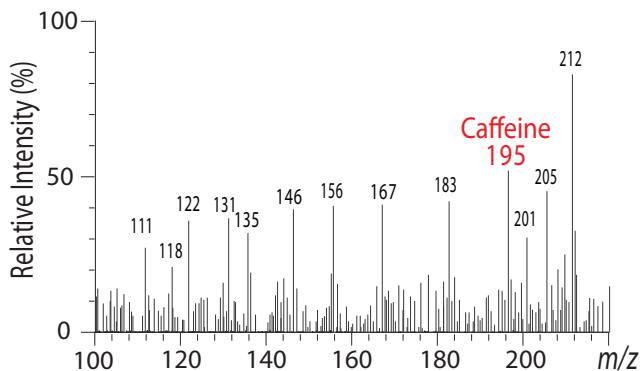


Figure 4: Positive ion mass spectrum of 9 nM caffeine in human plasma.

human whole blood are shown in Figure 5(a) and Figure 5(b), respectively. The detection limit is slightly higher for 5-FU when suspended in whole blood (20 nM, corresponding to 258 pg of analyte), which can primarily be attributed to its unstable nature in whole blood as a result of dihydropyrimidine dehydrogenase activity (the steady loss of 5-FU is as high as 94% in concentration over 24 hr in whole blood at room temperature, although its stability does improve at lower temperatures).²⁸ As such, it is recommended that blood samples should be placed on ice immediately after patient collection and the plasma is required to be separated from the blood cells within 1 hr after collection to minimize haemolysis. However, such limitations are not a concern with the real-time analysis ability of the current SAW-MS interface—considerably less interference was observed for 5-FU detection in human plasma at the same detection limit, as seen in Figure 5(c). Interestingly, Figure 4 and Figure 5 revealed that the mass spectra associated with both whole human blood and plasma in the positive and negative modes displayed several identical peaks which could represent other significant molecules present in the biological matrices. In any case, SAW ionization can be considered a soft ionization technique that results in little to no ion fragmentation. The times scales of the SAW oscillation are far shorter than the oscillatory time scales of inertially-significant parts of biomolecules, and furthermore the wavelength of the acoustic wave is long—even at these frequencies—in comparison to the dimensions of the molecules, reducing

the possibility of a shear gradient appearing across a given molecule (and therefore an internal force sufficient to break the molecule up).

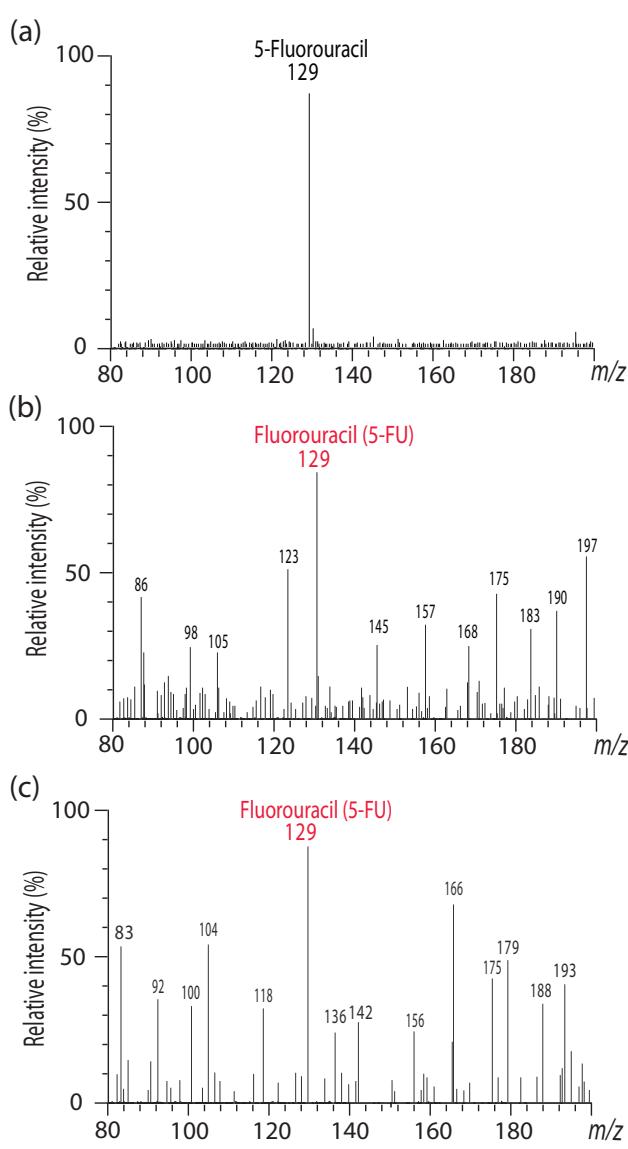


Figure 5: Negative ion mass spectra of (a) 200 nM 5-FU in methanol/water, (b) 20 nM 5-FU in human whole blood, and (c) 20 nM 5-FU in human plasma.

We also explored using SAW-MS for the detection of toxic "heavy" metals in water, a potentially useful application for on-site environmental remediation. Heavy metals are categorized as environmental toxins, harmful at even very low concentrations because of their inherent toxicity and low decomposition rates. The high ionic strength in water samples due to high concentrations of dissolved inorganic salts often suppresses the signal

intensity when using ESI-MS, producing a large negative peak relative to the background signal of the solvent.²⁹ Encouragingly, the limits of detection obtained using SAW-MS for the analysis of untreated tap water was approximately in the order of 10^{-9} M and 13 heavy metals were identified (**Supplemental Information**). Drinking water standards of the United States Environmental Protection Agency³⁰ require mercury (Hg), cadmium (Cd) and antimony (Sb) at concentrations less than 10 nM, 40 nM and 50 nM, respectively, suggesting that the SAW-MS at least approached these limits. While not as low as the detection limit achievable with ICP-MS, typically regarded as the gold standard for heavy and toxic metal detection, the SAW-MS interface has the added benefit of portability for *in situ* monitoring of high ionic strength samples; ICP-MS is not easily miniaturized for portable field-use and typically requires prior sample processing such as solid phase extraction. Although biosensors utilizing functional nucleic acids including aptazymes have been developed for heavy metal detection with similar limits of detection, the number of metals that can be detected are still limited.³¹ Further, we note that the use of a paper-based SAW ionization source with a miniature MS system achieves a trade-off between the dilution and the detection limit for heavy metals and inorganic compounds analysis in water samples. The possibility of using labeled internal standards to allow more accurate systematic quantification in a variety of sample matrices is still being investigated.

Conclusions

We have developed a chip-based SAW interface that combines a paper-based sample delivery technique with an efficient mechanism for simultaneously transferring and ionizing analytes from a solution phase into the gas phase for subsequent MS detection under ambient conditions. The SAW draws the sample from a reservoir through a paper wick onto the substrate, from which the sample is atomized to form a monodisperse distribution of micron diameter aerosol droplets. Due to the induced surface electric field that is associated with the SAW on the piezoelectric substrate,

polarization of the liquid at the substrate surface and at its free interface occurs, particularly at the contact line where the atomization is strongest. As such, the droplets that pinch-off the substrate during atomization possess a native charge, from which gas-phase ions are produced upon evaporation and potentially in-flight *Rayleigh* fission/ion evaporation. Optimal MS detection sensitivity can be achieved by manipulating the solvent composition, working distance between the device and the MS inlet, drying temperature, input power and capillary voltage. We demonstrate the use of this SAW-MS interface for the direct analysis of raw complex mixtures and even those with high ionic strengths and large viscosities without the need for either sample pretreatment or nebulizing gas streams. Further, we show that drugs or heavy metals present in trace quantities as low as nM concentrations can be detected in both positive and negative ion modes from untreated physiological fluids or tap water samples. The chip-based format of this simple, rapid and high-sensitivity technique is already compatible for interfacing with portable mass spectrometry for field use and is a powerful tool for facilitating high-throughput compound characterization that could play a major role in advanced diagnostics, drug screening and environmental monitoring.

Associated Content

Supplemental Information. Additional information as noted in text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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