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Extending the mass range of a miniature ion trap mass spectrometer using the inverse Mathieu q scan

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ABSTRACT

The mass/charge range of a mass spectrometer operated in either the boundary or resonance ejection mode is usually limited by the highest radiofrequency (rf) voltage that can be attained, although lowering the resonance ejection Mathieu q value (q_{eject}) can increase this range at the expense of resolution and unintended boundary ejection can result in spectral complexity. High voltage requirements are particularly troublesome for miniature instruments, which have tight electronic constraints and closely-spaced electrodes prone to discharging. Here we demonstrate an alternative approach to mass range extension based on a method of scanning the resonance ejection frequency nonlinearly in the form of an inverse Mathieu q scan. The results show an increase in mass range of up to 3.5 times on both a benchtop LTQ linear ion trap and the Mini 12 miniature linear ion trap mass spectrometer without instrumental modifications, and unit resolution is observed on the benchtop instrument by controlling the scan rate and minimizing space charge effects.

1. Introduction

Miniaturization of mass spectrometers has been the subject of extensive investigation over the past two decades, resulting in the development of more than thirty complete systems from both academic and commercial laboratories [1–3]. These devices can be designed for targeted or general applications ranging from environmental [4,5] and drug [6,7] screening to bacterial discrimination [8] and hazardous [9] or explosive [10] compound detection. For such applications, usually only modest performance is required – unit resolution over a mass range from 50 Da to <1000 Da and detection limits in the ppm range.

Ionization of complex samples for miniature mass spectrometers commonly is performed using either a spray- or plasma-based ambient ionization method due to the experimental simplicity; moreover, little to no sample workup is required. Common ambient spray sources are desorption electrospray ionization [11,12], paper spray ionization [13–16], leaf spray ionization [4,17,18], and relay electrospray [19], along with their closely related variants [20,21]. Plasma sources, though generally limited to volatile analytes [22,23], include low-temperature plasma [24–26], dielectric barrier discharge ionization [27], and desorption atmospheric pressure chemical ionization [28]. In the experiments using pure samples or simple mixtures described here, nanoelectrospray ionization (nESI) sufficed.

The vacuum system is perhaps the most troublesome component for miniaturization because (i) it is the most power-hungry subsystem and (ii) small pumps inherently have small pumping capacities. Point (ii) is particularly cumbersome because mass analyzers require good vacuum in order to obtain high sensitivity and resolution. The standard configuration for miniature mass spectrometers is to use either a continuous membrane introduction interface [29,30], an analytically limited option, or to use a discontinuous interface (i.e. DAPI or PP-API) [31,32] with a 5 L/min diaphragm pump and a 10 L/s turbo pump [33]. This latter choice provides analytical versatility and good performance at some cost in terms of analysis time. Continuous atmospheric pressure interfaces enabled by differential pumping do exist [23,34], but they trade performance for continuity. Demonstrations of ion trap mass analysis at relatively high pressures, from 15 mtorr [35] up to ~1 Torr [36], signal possible reduction in the need for high performance pumps.

Ion traps are preferable to other mass analyzers in miniature instruments because they operate at higher pressure, their resolution does not *inherently* depend on device size, and they have capabilities for single analyzer tandem mass spectrometry [2]. Geometry is usually simplified in smaller traps for ease of fabrication [37,38], as in cylindrical [39–43] (simplified from 3D

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quadrupole ion trap [44]), rectilinear [16,26,45] (linear 2D [46,47]), and halo [48–50] (toroidal [51–54]) ion traps.

The performance requirements of ion traps in miniature mass spectrometers usually include unit mass resolution with ppm or lower detection limits and a mass/charge range approaching m/z 1000. Higher performance may be achieved without sacrificing simplicity and ease of operation. Resolution scales inversely with operating pressure and directly with rf frequency [36,55–57]. In addition, space charge effects will tend to increase with smaller traps [58], and sensitivity also tends to degrade with pressure.

The subject of this paper is mass range, which in miniature ion traps is primarily determined by the maximum rf voltage ($V_{0\text{-}p,max}$) obtainable during the resonance ejection scan. The highest mass-to-charge value accessible for a linear ion trap is

$$m/z_{max} = 8\,V_{0\text{-}p,max}/q_{eject}\,\Omega^2(x_0{}^2 + y_0{}^2) \quad (1)$$

where q_{eject} is the Mathieu parameter at which the resonance ejection signal is set, Ω is the angular rf frequency, and x_0 and y_0 are the internal radii of the quadrupole field. Mass range in a quadrupole ion trap is additionally dependent upon (i) the pressure in the device and in the ion optics and (ii) the Dehmelt pseudo-potential well depth ($D_{x,y} = qV_{RF}/4$) of analyte ions [59]. In general, in order to trap high m/z ions, a higher pressure must be used in order to collisionally cool the ions, which will tend to have high kinetic energies and low pseudo-potential well depths.

Experimentally, mass range can be extended by (i) decreasing or scanning the main rf drive frequency [60,61], (ii) decreasing the size of the trap, or (iii) decreasing the Mathieu resonance q_{eject} value (i.e. using a lower resonance frequency) [62,63]. Both (i) and (ii) require instrumental modification, whereas (iii), resonance ejection, is the more common method due to its simplicity. However, resolution inevitably suffers at lower resonance q_{eject} values and spectral complexity from associated boundary ejection can be problematic. A fourth alternative, which is adopted in this study, is to scan the resonance ejection frequency at constant rf amplitude, viz. to perform a secular frequency scan.

In secular frequency scanning a linear ramp of the resonance ejection frequency is applied at constant rf amplitude and frequency [64]. Our original aim in exploring this scan was motivated by the possibility of performing very simple single analyzer precursor scans in a miniature mass spectrometer [65]. Although this type of precursor scan can be done, its performance is limited by the range of q values over which ions are fragmented. Nonetheless, we investigated the secular frequency scan (or ac scan) further as a simple alternative to resonance or boundary ejection. Even though resolution was shown to be inferior in these frequency scans, we will show here that it can be improved and unit resolution can be achieved on a benchtop instrument in instances where space charge effects are controlled and scan rate is lowered.

Two of the principal concerns with ac scanning are (i) the effects of nonlinear resonance points and (ii) the nonlinear relationship between m/z and secular frequency (and hence time). We previously showed that nonlinear resonance points resulted in either blank intensity profiles or broadened mass peaks, depending on scan direction [64]. However, in hyperbolic traps, these effects will tend to be minimal. We also demonstrated the complex nonlinear calibration procedure needed for secular frequency scanning [66]. In this method, applied resonance frequencies are correlated to m/z through the Mathieu parameters q and β, and a final linear fit using calibration standards gives the correct calibration. Because calibration will change with rf amplitude, rf frequency, ac amplitude, and start and end ac frequencies, it is preferable to have a linear calibration procedure, which we have recently demonstrated [67]. In that work we showed that by scanning the frequency of the resonance ejection signal so that an inverse relationship between the Mathieu q parameter of the ejected ion and time is obtained, a linear relationship then exists between m/z and time, a feature which has been sought for years.

2. Materials and methods

2.1. Chemicals

Renin substrate tetradecapeptide (angiotensinogen 1–14), neurotensin, insulin-like growth factor fragment 3–40, bovine serum albumin, cesium hydrogencarbonate, and perfluoroheptanoic acid were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Human Ghrelin was purchased from Phoenix Pharmaceuticals, Inc. (Belmont, CA, USA). Trimethylamine hydrochloride and polyethylene glycol (PEG) 4,400 and 14,000 were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI, USA). Concentrations for salts were ~2 mM in methanol/water. Bovine serum albumin was dissolved in water at 20 μg/mL. Polymers were dissolved in methanol/water at ~1 mM with 5,000 ppm triethylamine added as charge reducing agent. Peptides were dissolved in water to concentrations of ~200 μM.

2.2. Ionization

In all experiments ions were produced by nESI at ~1500 V using 5 μm nanospray tips pulled from borosilicate glass capillaries (1.5 mm O.D., 0.86 I.D., Sutter Instrument Co.) by a Flaming/Brown micropipette puller (Sutter Instrument Co. model P-97, Novato, CA, USA).

2.3. Instrumentation

Experiments were performed using both a benchtop Thermo LTQ [46] linear ion trap mass spectrometer (San Jose, CA, USA) as well as the Mini 12 [16] miniature mass spectrometer developed in-house at Purdue University.

For conventional resonance ejection scans on the LTQ, the rf frequency was tuned to 1.175 MHz and built-in scan functions were used with automatic gain control (AGC) turned on. The "normal" scan rate is 16,666 Da/s at an ejection frequency of 490 kHz, whereas the "high mass" (i.e. low q resonance ejection) scan uses a lower scan rate of 2500 Da/s at 200 kHz (q = 0.46) which increases the upper mass/charge limit from 2000 Th to 4000 Th (Th = Thomson = mass-to-charge).

The inverse Mathieu q scan was performed using the LTQ by substituting a swept frequency resonance ejection signal for the LTQ's built-in fixed resonance signal during an Ultrazoom scan with a given lower mass cutoff (LMCO) (proportional to the rf amplitude). As we have described previously, the Ultrazoom scan is a very slow scanning method that allows the rf amplitude to remain nearly constant. We chose this scan method because, of all the built-in scans on the LTQ, the Ultrazoom scan most closely approximates constant rf amplitude conditions.

The resonance ejection signal was constructed in Matlab using the algorithm previously described [67]. Briefly, the resonance frequency is scanned to maintain an inverse relationship between Mathieu q and time, thereby giving a linear mass scan. The waveform was imported to an arbitrary waveform generator (Keysight 36612A, Newark, SC, USA) with sampling rate set to 10 MSa/s. The ac waveform was triggered at the beginning of the mass scan using the triggers in the LTQ Tune diagnostics menu. In general, the scan time was 0.3 s and the highest and lowest Mathieu q values interrogated were 0.908 and 0.05. The amplitude of this resonance signal was generally 2–10 V_{pp}. Automatic gain control (AGC) was turned off during the inverse Mathieu q scan to prevent triggering the ac waveform on the AGC scan. Data were collected using either the