Resonance Methods in Quadrupole Ion Traps

Dalton T. Snyder¹; Wen-Ping Peng^{1,2}; R. Graham Cooks^{1*}

Keywords: quadrupole ion trap; resonances; quadrupole potential; secular frequency; nonlinear field

Abstract

The quadrupole ion trap is widely used in the chemical physics community for making measurements on dynamical systems, both intramolecular (e.g. ion fragmentation reactions) and intermolecular (e.g. ion/molecule reactions). In this review, we discuss linear and nonlinear resonances in quadrupole ion traps, an understanding of which is critical for operation of these devices and interpretation of the data which they provide. The effect of quadrupole field nonlinearity is addressed, with important implications for promoting fragmentation and achieving unique methods of mass scanning. Methods that depend on ion resonances (i.e. matching an external perturbation with an ion's induced frequency of motion) are discussed, including ion isolation, ion activation, and ion ejection.

1. Introduction

Quadrupole ion traps are widely used devices for chemical analysis. Typically traps are used to study *external* dynamical systems like monitoring chemical reactions in a reactor [1] or the composition of the atmosphere [2, 3]. In contrast,

1
2
3
4 before ion traps were used for mass analysis, physicists used them as storage
5
6 devices for studies of trapped ions [4, 5]. Similarly, the chemical physics community
7
8 has used traps largely for the examination of *internal* dynamic systems, that is,
9
10 reactions or other chemical or physical phenomena that take place within the mass
11
12 spectrometer. For example, ion traps have been used for studying photodissociation
13
14 dynamics [6, 7], ion/molecule reactions [8], ion cluster formation [9-12], and to
15
16 follow induced ion motion using ion tomography [13, 14]. Other increasingly
17
18 popular applications of ion traps in chemical physics are for quantum information
19
20 processing [15-22], production and study of Coulomb crystals [23-26], and
21
22 ultraviolet/visible and infrared spectroscopy of cold ions [27-32].
23
24
25
26
27
28

29 The topic of this review is resonances in quadrupole ion traps, which are key
30
31 aspects of both routine and advanced operation of these devices as mass
32
33 spectrometers. They significantly contribute to the behavior of many of the mass-
34
35 selective operations that can be performed, including ion isolation, ion activation
36
37 and ion ejection, while simultaneously encoding mass-to-charge ratio information.
38
39
40

41 Resonances are a common phenomenon in chemical physics. They determine
42
43 transitions between allowed quantum spin states [15, 33], electronic transitions for
44
45 molecules irradiated by electromagnetic waves [34], nuclear energy transitions (the
46
47 Mossbauer effect) [35], nuclear magnetic resonance transitions [36], electron
48
49 paramagnetic resonance transitions [37, 38], and certainly much more.
50
51
52

53 In a simple macroscopic example, a child on a swing, having a particular
54
55 frequency of motion, can be *resonantly* excited by exerting a force in a time-
56
57 dependent manner that corresponds to the pseudo-pendulum's frequency of motion
58
59
60
61
62
63
64
65

[39], consequently resulting in a greater *amplitude* of motion. This type of resonant phenomenon is known as a parametric resonance because it exhibits an energy transfer which causes an *instability* phenomenon, and the effect is utilized in many fields, e.g. optics [40] and in quadrupole ion traps [41].

Resonance frequencies of ions in quadrupole ion traps can be determined analytically via Mathieu equations, along with the resonance effects using the specific case of the Hill equation when the force on the system takes a sinusoidal time profile. Consequently, the Mathieu equations can be used to predict ion motion and correlate physically-meaningful quantities (e.g. mass) with, for example, instability in ion motion. Unlike the pendulum, an ion's frequency of motion in a quadrupole ion trap is mass-to-charge-dependent. This fortunate relationship between frequency and mass-to-charge allows resonances to be used for mass-selectively interrogating ion populations for various purposes i.e. for performing ion isolation, ion activation, and ion ejection.

2. Quadrupole Ion Trap: Quadrupolar and Higher-order Resonances

2.1 The quadrupole field & Mathieu parameters

A pure “quadrupole field” is produced when four infinitely long electrodes with the appropriate hyperbolic cross sections are arranged at the corners of a square, as in **Figure 1a**. The quadrupolar (quadratic) nature of the *potential* dictates

that the force on a point charge in the electric field varies linearly with the distance from the quadrupole center. Because of this relationship, the *field* is not quadrupolar but rather the *potential* is. Nonetheless, it is common to refer to “quadrupolar fields,” despite the misnomer.

Equations governing ion motion in a quadrupole field are described in *Quadrupole Mass Spectrometry and Its Applications* [42] as well as *Quadrupole Ion Trap Mass Spectrometry* [41] and are taken from Knight [43]. Here we will restrict our discussion to the most important equations in this derivation. In a quadrupole device the potential varies quadratically according to

$$\Phi_{x,y} = \frac{\Phi_0}{2r_0^2}(x^2 - y^2) \quad \text{Eq. 1}$$

where x and y are the dimensions of the quadrupole field, Φ is the potential at a given point within the field, and r_0 is the half distance between opposite rods.

Because the potential varies quadratically from the center of the quadrupole, the derivative of the potential, the electric field strength, varies linearly with respect to distance. The *Mathieu differential equation* [44] can be used to describe the electric field in the ion trap and its solution can be used to determine the ion motion in the electric field as follows,

$$\frac{d^2u}{d\xi^2} + (a_u - 2q_u \cos 2\xi)u = 0 \quad \text{Eq. 2}$$

where u is a displacement, ξ is a parameter related to time t by $\xi = \Omega t/2$, Ω is the angular frequency of the main trapping radiofrequency (rf) signal, and a_u and q_u are dimensionless *Mathieu parameters*. The values of the Mathieu parameters determine the characteristics (especially the stability) of the trajectories of ions

within the quadrupole field. For the case where the spacing in x and y are identical (i.e. $x_0 = y_0 = r_0$) in a 2D linear ion trap, the Mathieu parameters are defined by:

$$a_x = -a_y = \frac{8zU}{mr_0^2\Omega^2} \quad \text{Eq. 3}$$

$$q_x = -q_y = \frac{-4zV}{mr_0^2\Omega^2} \quad \text{Eq. 4}$$

where z is the elementary charge, U is the DC potential applied to the rods in a quadrupolar manner (as in **Figure 1a** where the trapping potential is applied in a quadrupolar manner), and V is the zero-to-peak amplitude of the trapping rf potential, and m is the mass of the ion.

The Mathieu parameters a_u and q_u , where u is a quadrupole dimension (x , y , r , or z), determine regions of ion stability illustrated by a *Mathieu stability diagram* as shown in **Figure 1b**. Any ions with m/z -dependent Mathieu parameters that fall within the enclosed region will have stable trajectories and thus may be trapped successfully; other ions will be ejected or will crash into the electrodes. Usually ion traps are operated without trapping DC potentials on the quadrupole rods, so $a_u = 0$, putting all ions on the q_u axis. Because both a_u and q_u are inversely proportional to m/z , ions will be distributed on the q axis as a reciprocal of their m/z values, with higher m/z ions falling at lower q_u and lower m/z ions residing at higher q_u . This distribution results in higher mass dispersion at low q but lower mass dispersion at high q , which is useful for mass analysis and other ion manipulations.

Each ion also has an m/z -dependent pseudopotential well depth, calculated at low q_u using the Dehmelt approximation [45],

$$D_{x,y} = \frac{q_u V}{4} \quad \text{Eq. 5}$$

where $D_{x,y}$ is the pseudopotential well depth (note that the constant in the denominator will depend on device geometry). This approximation is only valid for $q_u < 0.4$, although it remains a reasonable approximation up to $q_u = 0.7$ [46]. Exact pseudopotential well depth can be calculated numerically for different geometries, as shown in **Figure 1c** [47, 48] for a specialized square sinusoidal ion trap (SIT) configuration. The well depth describes a harmonic oscillator trapped in a potential well. If the ion obtains kinetic energy equaling or exceeding the well depth, the ion can escape from the trap.

2.2 Quadrupole ion trap geometries

There are two standard geometries for producing a quadrupole electric field for trapping and mass analyzing ions. The first, developed by Wolfgang Paul in the 1950s [4], is the 3D quadrupole ion trap (QIT), also known as the quadrupole ion storage device (QUISTOR). As shown in **Figure 2**, the QIT is constructed from a ring electrode and two endcap electrodes. Typically, the trapping rf potential is applied to the ring and the endcaps are used for ion injection, ejection, and frequency-based ion manipulations using low-voltage ac waveforms. Schwartz [49], Hager [50], and Bier [51] developed 2D linear ion traps (LIT), which have four parallel rods with hyperbolic cross sections for radial trapping and endcaps with DC potentials or multiple-section quadrupole rods with DC offsets for axial trapping. The LIT has two principal performance advantages over the QIT: 1) increased ion storage capacity (hence a reduction in space charge effects) and 2) dramatically increased ion injection efficiency.

Many geometrically simplified versions of these devices exist (**Figure 2**), usually developed for ease of fabrication and miniaturization or purposeful introduction of higher-order fields [52]. For example, the cylindrical ion trap, simplified from the 3D ion trap, has electrode surfaces that are planar rather than hyperbolic [53-57]. Similarly, the rectilinear ion trap also has planar surfaces, but is a variant of the 2D linear ion trap [58]. The toroidal ion trap is produced by rotating a 3D trap about an axis parallel to its trapping region [59-62]. The halo trap is a simplified variant of the toroidal trap with planar electrode structures [63]. While these simplified traps benefit from easier fabrication methods, they inherently introduce higher-order fields that can degrade (and occasionally enhance) performance, as discussed later.

2.3 Ion dynamics and nonlinear field contributions

Trapped ions will behave according to their Mathieu parameters a_u and q_u , but these parameters not only determine their *trajectory stability*, they also determine the actual ion motion within the trap. Ion motion is described principally by a *fundamental secular frequency*

$$\omega_{u,0} = \frac{\beta_u \Omega}{2} \quad \text{Eq. 6}$$

where the parameter β_u ($0 \leq \beta_u \leq 1$) is calculated using a continued-fraction expression in terms of a_u and q_u

$$\beta_u^2 = a_u + \frac{q_u^2}{(\beta_u+2)^2 - a_u - \frac{q_u^2}{(\beta_u+4)^2 - a_u - \frac{q_u^2}{(\beta_u+6)^2 - a_u - \dots}}} + \frac{q_u^2}{(\beta_u-2)^2 - a_u - \frac{q_u^2}{(\beta_u-4)^2 - a_u - \frac{q_u^2}{(\beta_u-6)^2 - a_u - \dots}}$$

$$\text{Eq. 7}$$

By using the Dehmelt approximation, we can simplify equation 7 to

$$\beta_u = (a_u + \frac{q_u^2}{2})^{1/2} \quad \text{Eq. 8}$$

so that we can approximate the secular frequency from the experimental parameters giving (with $a_u = 0$)

$$\omega_{u,0} = \frac{\sqrt{2}zV}{\Omega u_0^2 m} \quad \text{Eq. 9}$$

Thus we see that an ion's secular frequency is *approximately* inversely proportional to its m/z value. In this regard, an ion trapped in a quadratic potential is more akin to a mass at the end of a spring than to a mass on a pendulum. In the case of the spring, the frequency of oscillation is inversely proportional to the square root of the mass, whereas the pendulum's frequency has no mass dependence.

Ions also have *parametric* resonances,

$$\omega_{u,n} = |n + \beta_u| \Omega / K \quad -\infty < n < \infty; K = 1, 2, \dots \quad \text{Eq 10}$$

where K is the order of the resonance [64, 65]. The first order parametric resonance is twice the fundamental secular frequency.

More generally an ion will have multiple frequency components of motion in a pure quadrupole field, described by

$$\omega_{u,n} = |2n + \beta_u| \Omega / 2 \quad -\infty < n < \infty \quad \text{Eq 11}$$

where n is an integer, and where the amplitudes of each component varies.

Figure 3a shows a calculated frequency spectrum of an ion oscillating in a pure quadrupole field [66] at a q value of 0.68 ($\omega_z = .27$ MHz, $a_z = 0$). The primary frequency at which the ion oscillates in the trap is the secular frequency $\omega_{u,0}$ but there are smaller contributions from sideband frequencies $\Omega - \omega$, $\Omega + \omega$, and $2\Omega - \omega$.

The sideband frequencies result from interference of the ion's secular frequency and the driving rf frequency. However, note that no driving frequency, Ω , is observed in this Fourier analysis. As the ion approaches the right-hand side boundary of the stability diagram ($q_u = 0.908$, $\beta_u = 1$), the sideband oscillations become much more prominent and dominate ion motion over the secular frequency [67].

In practice, pure quadrupole fields do not exist because of real-world constraints. For example, electrode misalignments exist which can degrade the electric field [68]. Electrodes cannot be manufactured to have perfectly smooth surfaces [69] or ideal hyperbolic cross sections, nor can they be infinitely long. Furthermore, slits and apertures must be integrated into the hyperbolic electrodes for ion introduction, ion injection, and often for ionization [70, 71]. Because of these constraints, *higher-order fields* are introduced.

A higher-order field is described by both its *order* as well as its *multipole coefficient* [72-74]. For example, 0, 1, 2, 3, 4,... stand for monopole, dipole, quadrupole, hexapole, octopole,..., components, respectively. Importantly, the potential in the field varies as r^n , where n is the order of the field. Mathematically, multipole coefficients originate from the spherical distribution of the potential in the 3D trap

$$\Phi(\rho, \theta) = \Phi_0 \sum_{n=0}^{\infty} A_n \frac{\rho^n}{r_0^n} P_n(\cos \theta) \quad \text{Eq. 12}$$

Here ρ and θ are spherical coordinates, A_n is the multipole coefficient of order n and $P_n(\cos \theta)$ is a Legendre polynomial. In a pure quadrupole field $A_2 = 1$ and $A_n = 0$ for all other n , implying that the electric field strength increases linearly and the potential increases quadratically with the distance from the quadrupole center.

1
2
3
4 However, when higher-order fields are added, the potential deviates from ideality.
5
6 For example, the octopole (A_4) potential exhibits an r^4 dependence so that the
7
8 electric field exhibits an r^3 dependence.
9
10

11 Here we are concerned with the effect of higher-order fields on ion
12
13 frequencies of motion, which can be determined either numerically or measured
14
15 experimentally by laser or DC pulse tomography [13, 75, 76]. Both the magnitude
16
17 and direction of the effect are determined by the nature of the higher-order field,
18
19 that is, by whether the higher-order field is mathematically *odd* or *even*. Odd-order
20
21 fields (e.g. hexapole, $n = 3$) cause the potential in the trap to deviate in a
22
23 mathematically *odd* manner, where the potential increases from ideality near one
24
25 electrode but decreases near the opposite electrode. The net result is that ions
26
27 occupy regions of weaker field strength than they would had the field been purely
28
29 quadrupolar [66], thereby lowering their secular frequencies. For even-order fields
30
31 (e.g. octopole, $n = 4$), the opposite is true. The electric field strength will be higher
32
33 than a pure quadrupole field, particularly near the electrodes where higher-order
34
35 fields are more prominent, thereby *raising* the ions' secular frequencies [77-79]. In
36
37 summary, odd-order fields decrease secular frequencies, though only slightly, and
38
39 even-order fields increase or decrease secular frequencies (compared to a pure
40
41 quadrupole), depending on the nonlinear field polarity. The resulting effect on
42
43 resonance methods will be discussed later.
44
45
46
47
48
49
50
51
52

53 Higher-order fields additionally cause the introduction of further frequency
54
55 components to ion motion [66]. As shown in **Figure 3b**, the addition of (for example
56
57 20%) hexapole field introduces even and odd overtone frequencies (e.g. $2\omega_{u,0}$, $3\omega_{u,0}$,
58
59
60
61
62
63
64
65

etc.), with the driving rf frequency Ω , and even and odd sideband frequencies (e.g. $\Omega + 2\omega_{u,0}$, $\Omega + 3\omega_{u,0}$). Introduction of (for example 20%) octopole field induces only odd overtones and their sidebands (**Figure 3c**) [80].

Although these additional frequencies can complicate mass analysis (after all, ions are mass-selectively interrogated using their secular frequencies), the more significant consequence of higher-order fields is ion frequency shifts. But what effect does this have on mass-selective operations?

2.3.1 Effect of higher-order fields on mass analysis

The most basic and significant mass-selective operation is mass analysis, that is, scanning ions out of the trap in order of m/z to determine the ions' m/z values. Typically, this is done using resonance ejection, in which a small supplementary ac field is applied in a dipolar manner to the endcap electrodes (3D trap) or x electrodes (2D trap) [81, 82]. When the ac frequency matches the frequency of motion of ions of a given m/z value, then those ions will gain kinetic energy and increase their radial and/or axial amplitudes in the trap until they are ejected. If the rf amplitude is ramped linearly with time [83], then ions are scanned linearly into the resonance frequency and ejected linearly in order of m/z . This process maintains linearity for a pure quadrupole (linear) field. However, if a non-linear odd-order field such as a hexapole field is introduced, then the ion's secular frequency will decrease as the ions distance from the quadrupole center [79] changes. This variation of frequency as a function of distance from the center is typically much smaller than it is for even-order field distortion [77, 84], however

the result is that ion secular frequencies will either decrease or increase with the radial distance from the trap center depending on the type of field distortion (**Figure 4a**). Note that traps with both axial and radial symmetry generally only contain even-order fields in which ion secular frequencies will increase with the radial distance for a positive field contribution [85, 86]. The corresponding effect on mass spectral performance with resonance ejection is that, for traps with positive even-order fields, resolution is *increased* when scanning the rf amplitude from low to high, but *decreased* when scanning from high to low, as shown in **Figure 4b** [87-89]. This is because as ions are brought to the resonance ejection working point, they increase their amplitudes in the trap. When scanning the rf amplitude forward, the ion secular frequencies, which increase with the rf amplitude, shift *towards* the supplementary ac frequency as the ions are being ejected because of the even-order fields, thereby increasing their rate of ejection. On the other hand, when the rf amplitude is scanned downward, the ion secular frequencies shift *away* from the supplementary ac frequency as they are being ejected, thereby delaying the process. Despite the improvement in resolution, these frequency shifts can also result in a loss in calibration linearity (i.e. m/z vs. time). Not only do the shapes of the electrodes alter the nonlinear field contributions, but the inter-electrode distance and alignment also alter the field, which can then have a negative effect on resolution (**Figure 4c**) [90].

Resolution is not the only mass spectral characteristic altered by nonlinear field contributions. Chemical mass shifts can also be induced (**Figure 4d**) [91, 92].

As an ion's secular frequency changes with its distance from the trap center, it's

1
2
3
4 *apparent m/z* will also change. Each m/z correlates with a particular frequency of
5
6 motion, so any frequency shift induced by higher order fields will have a
7
8 corresponding effect on peak location in the mass spectrum, resulting in mass shifts.
9
10 Space charge, in which Coulombic repulsion affects ion motion, can have a similar
11
12 effect on ion frequencies [93-96], which can degrade both resolution and mass
13
14 accuracy. A third, similar parameter that affects resolution and mass accuracy is the
15
16 momentum of the ions, which is modulated in ion traps with a light bath gas (e.g.
17
18 helium) [97]. For example, additional damping from collisions with gas molecules
19
20 delays the onset of ion ejection (the voltage needed for resonant ejection), and this
21
22 relationship is highly dependent on the ion's q_u parameter.
23
24
25
26
27
28
29
30
31

32 2.3.2 Effect of higher-order fields on ion excitation

33
34 The ion excitation process is also affected by higher-order field components.
35
36 There are many ways to kinetically or internally excite ions in an ion trap [82, 98-
37
38 102]. The most typical method though, is resonance excitation [82]. In this method,
39
40 ions are simply excited at their secular frequencies by applying a low-amplitude (a
41
42 few hundred millivolts) dipolar ac signal matching the ion's secular frequency. The
43
44 resonated ions will then gain kinetic energy and collide with bath gas molecules,
45
46 gaining internal energy until dissociation channels are accessed which generate
47
48 fragments reminiscent of the precursor ion. However, in the presence of higher-
49
50 order fields the ion's secular frequency will shift as a function of the radial
51
52 amplitude in the trap [103], thereby causing the ion to go out of resonance with the
53
54 excitation. This frequency shift can be beneficial, as it allows higher ac amplitudes to
55
56
57
58
59
60
61
62
63
64
65

be used for excitation which may increase fragmentation efficiency. On the other hand, there are methods to compensate for any ion frequency shift, some of which involve exciting the ion with a frequency sweep ('chirp'), a band of frequencies [104], or a high-amplitude off-resonance frequency [105].

2.4 Nonlinear Resonances

Not only do higher-order fields affect ion secular frequencies, but they also induce *nonlinear resonances* [66, 106, 107]. At these points ions pick up energy and their amplitudes of motion increase hyperbolically; that is, their trajectories can become quite unstable. The general resonance condition is

$$n_r \omega_r + n_z \omega_z = \nu \Omega \quad \text{Eq. 13}$$

where n_r , n_z , and ν are integers. Symmetry forces n_r and n_z to be even for symmetric traps and even order fields; however, n_z may be either even or odd for odd-order (nonsymmetrical) fields.

As an example, consider the case where $n_r + n_z = 3$, i.e. the hexapolar resonance. In this case a nonlinear resonance line is observed at, for example, $\beta_z = 2/3$, depending on the values of n_r and n_z . For a second example where $n_r + n_z = 4$, octopolar resonances are observed. When $n_r = 0$ and $n_z = 4$, a resonance is observed at $\beta_z = 1/2$. Many other resonance lines are observed (for example, a weak dodecapole resonance at $\beta_z = 1/3$), but we limit our discussion here to these octopole and hexapole resonances lines, which are the strongest and have the most utility.

Nonlinear resonance lines are important to understand because they can significantly alter mass spectra. For example, artifact peaks, often called 'ghost'

1
2
3
4 peaks, can be observed during a scan of the rf amplitude when obtaining a full scan
5
6 mass spectrum. While most ions will be ejected when their Mathieu q_u values match
7
8 the q_u value of the resonance ejection signal or when they reach the stability
9
10 boundary ($q_u = 0.908$), other ions can be ejected when they pass through nonlinear
11
12 resonance lines, particularly when the ion cloud is large (e.g. when sample
13
14 concentration is high or when ions have previously been resonantly excited).
15
16
17 Typically, 'ghost' peaks are broader than other mass spectral peaks and so can often
18
19 be distinguished from boundary and especially from resonance ejection peaks.
20
21
22 Other methods of distinguishing all of these potential causes of mass spectral peaks
23
24 have been investigated [108].
25
26
27

28
29 So-called 'black holes' or 'canyons' are another consequence of the
30
31 imposition of higher-order fields on the standard quadrupole field [109-112].
32
33
34 Unexpected black holes appear most prominently when ions are accumulated in the
35
36 trap or are formed inside the trap and happen to fall on a non-linear resonance. Any
37
38 activity that places ions close to the electrodes where higher-order fields are more
39
40 prominent can enhance the observation of these effects. In tandem mass
41
42 spectrometry spectra (MS/MS), product ions that are produced and fall on a
43
44 nonlinear resonance line are inefficiently stored, resulting in diminished intensity in
45
46 the normal mass scan (**Figure 4e**). Similar results have been reported in chemical
47
48 ionization (CI) mass spectra, particularly when the chemical ionization reagent is
49
50 introduced in high proportions, where space charge effects push ions into large
51
52 radial displacements. Full scan mass spectra can be affected when long ion storage
53
54 times are used. The intensities of ions stored at the nonlinear resonance points have
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 been observed to decay [113], and the absolute signal attenuation has been
5
6
7 observed to be dependent upon scan direction. Moreover, the ion losses appear –
8
9 reasonably - to be more prominent when the rf is scanned more slowly. Frequency
10
11 scanning methods (e.g. secular frequency scanning) have also reportedly observed
12
13 mass spectral changes from black holes, either observed as blank intensity profiles
14
15 or broadened mass peaks, depending on scan direction [114] (**Figure 4f**).
16
17
18
19
20

21 3. Ion Trap Resonance Methods 22 23

24 We broadly divide ion trap resonance methods into three distinct categories
25
26 based on their consequences: ion isolation, ion excitation, and ion ejection. The first,
27
28 isolation, is usually used to decrease chemical noise in mass spectra, to decrease
29
30 space charge effects, or to select an ion population for ion excitation. In the second,
31
32 ion excitation, selected precursor ions undergo sufficiently energetic collisions with
33
34 background gas molecules, causing the generation of product ions which are
35
36 indicative of the molecular class and/or the structure of the precursor ion. The final
37
38 step, and perhaps the most fundamental to mass spectrometry, is to measure the
39
40 mass-to-charge ratios of the ions in the trap, which is usually accomplished by mass-
41
42 selectively ejecting them in order of increasing m/z into a detector, which
43
44 subsequently converts the ionic particles to a current and voltage that can be
45
46 measured and computerized. Measuring ion mass/charge ratios internally using
47
48 charge detection is also possible.
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

3.1 Isolation

The isolation step in ion trap mass spectrometers is often overlooked but grants a great deal of flexibility as an analytical tool. Without ion isolation there would be ambiguity in identifying a compound of interest using a fragmentation step due to the difficulty in assigning relationships between precursor and product ions. Moreover, ion isolation allows extension of the dynamic range of the ion trap for isolated analytes; dynamic range in ion traps is limited relative to other mass analyzers because of a limited trapping volume and because the relative contribution of space charge effects decreases with ion velocities. For monitoring chemical reactions, ion isolation is particularly effective for allowing detection of trace quantities of starting material, product, or reaction intermediates.

Modern ion isolation methods are surprisingly complex, often requiring complicated electronics and software for custom waveform calculations and implementation. Ion secular frequencies are utilized by resonantly ejecting particular ions while retaining other ions by removing their frequencies from a multi-frequency resonance ejection isolation waveform. Important performance and operating parameters to consider include m/z isolation width, isolation efficiency, the time required for isolation, waveform amplitude, bandwidth, and complexity, and the pseudopotential well depth of the ion to be isolated compared to other ions in the trap. We note that while isolation techniques are usually performed after ion injection and cooling, they are equally useful for preventing certain ions from being trapped during the ion injection stage, a time-saving trick but with poorer performance compared to in-trap isolation if the trap is not perfectly symmetrical.

1
2
3
4 Isolation techniques can be subdivided into methods that 1) modulate the
5 trapping rf waveform (many of which are not strictly resonance methods), 2) use
6 low-voltage resonance ac waveforms with constant rf parameters, or 3) a
7 combination of the two.
8
9

10
11 The first category encompasses rf-only isolation (a nonresonance method,
12 yet still significant enough to include here) in which ions of a particular m/z are
13 isolated by ejecting the ions lower in m/z at the upper stability boundary ($q = 0.908$)
14 and also those of higher m/z near the lower stability boundary ($q \sim 0$) where their
15 kinetic energies outweigh their well depths. This is accomplished by increasing and
16 then decreasing the rf amplitude [83, 115]. The quadrupole ion trap can further be
17 used as a quadrupole ion store (QUISTOR) by operating it in rf/dc mode [116],
18 wherein the rf and dc potentials are fixed so that the ion to be isolated is placed at
19 the apex of the Mathieu stability diagram (approximately $\beta_z = 1$, $\beta_r = 0$ in **Figure 1b**),
20 causing the trajectories of all other species to become unstable. Similarly, the
21 rf/resonance ejection method uses the already-discussed rf ramp for ejection of
22 low-mass ions but adds a supplementary ac signal at a constant Mathieu q_u value
23 just below that of the ion to be isolated, thereby removing the higher m/z ions
24 during the rf ramp [117]. An alternative approach only uses the resonance signal,
25 not the stability boundary, to eject unwanted ions [118]. In this case the rf signal is
26 ramped so that the lower m/z ions are ejected up to the resonance point, at which
27 time the supplemental ac is switched off and the rf is increased to bring the ion to be
28 isolated above the q value of the resonance point, and finally the resonance point is
29 restored and the rf amplitude again ramped (this time from high to low) to eject
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 higher m/z ions. By tuning the frequencies and amplitudes of the resonance signal
5
6 and also by using fast (low resolution) and slow (high resolution) ejection scans,
7
8 high resolution isolation can be accomplished [119].
9

10
11 Besides using the rf amplitude for ion isolation, the m/z dependence of each
12
13 ion's secular frequency in an ion trap can be exploited. Applying a dipolar ac field in
14
15 resonance with a particular ion's secular frequency will, at the very least, excite that
16
17 ion and if the amplitude and time of application are high enough, the ion can be
18
19 mass-selectively ejected. The simplest way to effect frequency-based isolation is to
20
21 perform a frequency sweep, or 'chirp' [115, 120-122], whereby the supplemental ac
22
23 frequency, either chosen to be mono- or polychromatic, is ramped through ion
24
25 secular frequencies. Unit isolation width has not been demonstrated using a
26
27 frequency chirp, and broadband waveforms have largely replaced the chirp as the
28
29 primary method of broadband excitation.
30
31
32
33
34
35

36
37 Broadband waveforms can be synthesized by the stored waveform inverse
38
39 Fourier transform, a sum of sine waves approach, filtered noise filtering, and
40
41 frequency modulation and mixing. The stored waveform inverse Fourier transform
42
43 (SWIFT), adopted from the Fourier transform ion cyclotron instrument [123-126], is
44
45 perhaps the most difficult method because it requires specialized circuitry and
46
47 complex computations to implement. In brief, a band of secular frequencies (**Figure**
48
49 **5a**) are inverse Fourier transformed from the frequency domain to the time domain
50
51 (**Figure 5b**) in order to obtain a complex waveform that can near-simultaneously
52
53 excite a wide swath of ions, hence making this method more time-efficient than a
54
55 frequency sweep. If a 'notch' is incorporated in the frequency domain, those
56
57
58
59
60
61
62
63
64
65

frequencies are not incorporated into the waveform and so the corresponding ions will be retained in the ion trap [127]. Perhaps the simplest example of ion isolation using a multi-frequency waveform is that which uses only *two* frequencies [128], that is, dual frequency isolation. In principle one should be able to eject a wide range of m/z values higher than the target ion by using a high-amplitude, low frequency sinusoid, and also eject ions lower in m/z with a high-amplitude, high frequency sinusoid. In this case, it is the amplitude of the waveform that provides the necessary broadband ejection capabilities, but isolation efficiency is understandably low.

Although the SWIFT technique is more time-efficient than frequency sweeping, experimental results have demonstrated that similarities still exist. For example, not all frequencies are present at all times in a SWIFT waveform. This can lead to problems with using ion injection waveforms because unwanted ions will enter the trap at some time during the application of SWIFT. A sum of sines approach with appropriate phase distribution, currently implemented in Thermo Finnigan mass spectrometers, alleviates this issue because all frequency components are present at all times [129]. Unit isolation width can be accomplished using this method.

Other simpler, but still high-performance, methods of performing broadband excitation of ions do exist. For example, Hilger *et al.* demonstrated a simpler broadband excitation method wherein a broadband waveform produced by frequency modulation was mixed with a sine wave with frequency matching the target ion's secular frequency (**Figure 5c**). The performance was shown to be

1
2
3
4 equivalent to apex and SWIFT isolation, though it required a longer isolation time
5
6 than the apex method [130]. The filtered noise method is another broadband
7
8 technique for ion excitation (**Figure 5d**) [131, 132]. A broadband filtered noise
9
10 waveform can be produced by a function generator, and frequencies can be
11
12 individually removed in a waveform editor, allowing for 'notched' waveforms to be
13
14 used for isolation. Note that, just as in SWIFT isolation and frequency modulation
15
16 and mixing, multiple 'notches' can be used to simultaneously isolate multiple
17
18 nonadjacent m/z ions. In practice, filtered noise is problematic because of the
19
20 randomness of the noise, which can result in holes in the isolation window. As such,
21
22 current implementations of filtered noise are more akin to a sum of sine waves.
23
24
25
26
27
28

29 Another way to effectively isolate and trap ions with a predetermined mass-
30
31 to-charge ratio is to apply the auxiliary voltage to the end cap electrodes, where the
32
33 auxiliary voltage has a frequency spectrum with a first notch at the secular
34
35 frequency of the object ions and a second notch at a beat frequency to expel non-
36
37 object ions still remaining in the ion trap space while the RF voltage is applied to the
38
39 ring electrode to trap the object ions [133].
40
41
42
43

44 Perhaps the best method for ion isolation, achieving unit isolation width, was
45
46 demonstrated by Wells *et al.*, who combined the broadband techniques with rf ramp
47
48 methods [134]. A broadband waveform was first used for coarse ejection of ions
49
50 over a broad mass range during the ionization stage. Subsequently the ions with
51
52 m/z values below the target ion were ejected by moving the ion to the stability
53
54 boundary while simultaneously applying a resonance ejection signal with frequency
55
56 approximately half the driving rf frequency. Ions with m/z higher than the target ion
57
58
59
60
61
62
63
64
65

were then ejected by moving the target ion to $q = 0.84$ and applying a broadband waveform covering the higher m/z ions.

In contrast to sinusoidal traps, the digital ion trap (DIT) uses duty cycle manipulation to effect ion isolation (**Figure 5e,f**) [135, 136]. The digital trap uses square waves generated by high-frequency switching technology to trap ions. The switching for the DIT can be completely controlled by a computer so that mass scanning is comparably quite simple, while complicated LC tank circuits are often required to produce the high trapping rf voltage for conventional sinusoidal waveform-driven ion traps. For ion isolation in the DIT, the duty cycle of the trapping digital waveform is manipulated so that it is not equal to 50%, which introduces a pseudo-dc potential because the average potential of the trapping waveform will then be nonzero (unlike a sine wave centered at zero). Precisely speaking, the nonzero pseudo-dc component does not change the Mathieu a_u parameters of all the ions in the trap but instead changes the boundary conditions so that a small range of m/z values is trapped (**Figure 5f**) [137]. There are many other advantageous features of digital ion traps associated with the precision and speed with which square wave signals can be controlled, but they cannot be discussed here [138, 139].

3.2 Activation

The second general use of resonances that we discuss here is for *ion activation*, the process by which ions' kinetic and/or internal energies are increased, usually resulting in fragmentation. The usual use for activating ions is for generating product (fragment) ions, which can be used for structural characterization or

unambiguous confirmation of the identity of the precursor ion. However, activation can also be used for other purposes. For example, reactions in the trap can be inhibited by activating ions to reduce the overlap between reactant ions, e.g. in a method known as parallel ion parking [140]. Note that this method can also be used to reduce overfragmentation in photodissociation techniques such as infrared multiphoton dissociation (IRMPD) and ultraviolet photodissociation (UVPD). Reactions and molecular fragmentation can also be *induced* by colliding reactant ions with surrounding bath gas molecules (e.g. unimolecular dissociation).

Ion activation in quadrupole ion traps is usually effected by a variant of collision-induced dissociation (CID), in which ions are resonantly excited and absorb power from the driving rf, gain kinetic energy, collide with intentionally-introduced bath gas molecules, and fragment, generating product ions that can then be further fragmented or mass analyzed [141]. The most common method is *resonance excitation* (**Figure 6a**), in which a small supplementary dipolar ac waveform at a particular ion secular frequency is applied across the endcaps (z direction, 3D trap) or across x/y electrode pair (2D linear trap) in order to mass selectively excite a sub-population of ions [81]. Important parameters are the ion's Mathieu q_u parameter, which controls CID efficiency through the Dehmelt potential well depth, product ion mass range, product ion collection efficiency, and excitation frequency, and parameters not dependent upon q_u , including excitation time, bath gas pressure, and excitation ac amplitude. A high Mathieu q_u parameter for a precursor ion will allow more energy input than low q_u CID due to higher potential well depths [45] and higher ion oscillation frequencies (higher velocities) but will

sacrifice product ion mass range ($m/z_{\text{product}} > m/z_{\text{precursor}} * q_{\text{precursor}} / 0.908$, where 0.908 corresponds to q value at the right-hand side boundary of the Mathieu stability diagram). CID at low Mathieu q_u values increases product ion mass range but limits energy deposition because of lower frequencies of ion oscillation (lower velocities) and because the precursor ion can more easily be ejected. As a result, optimum values of Mathieu q_u parameters for excitation are ~ 0.2 - 0.35 , which balances fractional product ion mass range and adequate energy deposition.

There are many other methods for fragmenting ions over a small mass range. As mentioned previously, ions can be resonantly excited by a single frequency ac wave. A variant which increases CID efficiency is dual direction excitation [142] (**Figure 6b**), in which ions are excited in both x and y in a linear ion trap by applying a single dipolar ac to each pair of electrodes. Because ions are excited simultaneously in both directions, the kinetic energy of the ions increases, thereby promoting more and higher-energy collisions.

A key characteristic of CID is the time required to generate the product ion mass spectra. This is particularly important for applications that require methods on the chromatographic time scale (>10 spectra/sec). Another concern with CID in traps is the lower-mass cutoff imposed by the stability boundary associated with the driving rf. The latter problem can be mitigated by using “pulsed Q dissociation” (PQD) [100, 143] (**Figure 6c**). In PQD, the ion to be excited is placed at a high q_u value (0.6 - 0.8) and is resonantly excited with a short ($\sim 100 \mu\text{s}$) pulse with a high amplitude. After a short time delay ($\sim 100 \mu\text{s}$), the rf amplitude is quickly decreased so the ion is at a low q_u value. The short sequence of events preserves low mass

product ions while also leading to higher-energy collisions. Similar methods include high amplitude short time excitation (HASTE) [144] and “fast excitation” CID [145] (**Figure 6d**), both of which use high excitation amplitudes over a short period of time.

Although the intuitive method of ion activation is through use of *on-resonance methods*, *off-resonance methods* can be equally appealing because an ion’s secular frequency (eq. 6) will shift if the strength of trapping field deviates from linearity, that is, if there is any contribution from higher-order fields. Red-shifted off-resonance large-amplitude excitation (RSORLAE) [146], blue-shifted off-resonance CID [105], and dynamic CID (DCID) [147-150] all take advantage of the large distribution of ions that are excited when a high-amplitude ac signal is used. Typically, a red-shifted (i.e. lower than the ion’s secular frequency) ac signal is used instead of a signal with frequency matching the ion’s secular frequency. The utility of the off-resonance signal is that it 1) allows higher energy deposition than on-resonance CID does, and 2) any shift in ion secular frequency caused by introduction of higher-order fields is mitigated because the high-amplitude signal excites ions over a wide m/z range. In the case of DCID, a two-frequency excitation waveform is used. The two frequencies are spaced very closely from one another (~ 1 kHz difference) so that a beat frequency develops (**Figure 6e**). This technique also allows for high energy deposition when compared to conventional on-resonance activation and CID.

Although collisions with background gas molecules are most commonly used, ions can also be forced to collide with a surface in the technique of surface-induced

dissociation (SID) [98]. The energy absorption profile is significantly different than that for CID. In CID, ions slowly convert kinetic energy into internal energy, usually resulting in labile bond fragmentation, often giving less informative product ions [151]. In SID, the large mass of the collision partner results in high-efficiency kinetic to internal energy conversion despite the low translational energies (eV) involved. For analytes like peptides and proteins, SID is particularly useful because of the extensive backbone cleavage observed. Conventionally, SID employs two separate mass analyzers, one to guide ions into a surface while the products are extracted into the second analyzer (e.g. a second quadrupole mass filter). SID can also be performed in a single quadrupole ion trap by resonantly exciting the precursor ions until they collide with the quadrupole electrodes, thereby inducing fragmentation [152]. Unfortunately, trapping of the product ions is inefficient, so SID has not been extensively implemented in QITs.

So far we have discussed single resonance techniques that fragment ions over a small m/z range, but there are also *broadband CID* methods which fragment ions over a wide range of m/z values. For example, dipolar DC collisional activation [153-155], a non-resonance technique, can fragment ions over a wide m/z range by displacing the entire ion cloud from the center of the trap using a dipolar DC potential. Because ion secular frequencies are not interrogated this is not a mass-selective method.

A secular frequency scan [114, 156], in which the rf frequency and amplitude are held constant (i.e. ion Mathieu q values do not change during the scan), can effect broadband fragmentation of ions. This experiment is useful in combination

1
2
3
4 with mass-selective detection of specific fragment ions in single analyzer ion traps.

5
6
7 The result is a precursor ion scan in a single mass analyzer [157, 158].

8
9 Unfortunately, there is a nonlinear relationship between secular frequency and m/z ,
10
11 so if the ac frequency is scanned linearly (the easiest method to implement) then the
12
13 resonance time will vary with m/z . Furthermore, each ion is only on resonance for a
14
15 very short period of time, limiting energy deposition and hence fragmentation.
16
17

18
19 Although the stored waveform inverse Fourier transform is more commonly
20
21 associated with ion isolation, it can also be used for fragmentation [123-126, 159,
22
23 160]. The results from broadband SWIFT excitation are comparable to ac frequency
24
25 scanning excitation; however, the former is more time-efficient. In broadband CID
26
27 techniques, each mass-selected ion is excited for the duration of the excitation
28
29 waveform, whereas for the secular frequency scan each ion is only on-resonance
30
31 when its secular frequency matches the ac frequency. As in isolation, notches can be
32
33 incorporated into the activation waveform in order to prevent activation of some
34
35 ion species. Equivalently, a filtered noise field (FNF) can produce notched
36
37 broadband waveforms [131, 132]. A useful example of broadband excitation using
38
39 SWIFT and FNF is for parallel ion parking in ion traps, a technique for consolidating
40
41 protein charge states [140].
42
43
44
45
46
47

48
49 While broadband waveforms provide an efficient means of broadband CID,
50
51 they are limited in ion traps by the fundamental laws governing ion trap CID as
52
53 mentioned above, related to the balancing of potential well depth, activation
54
55 frequency, and fractional product ion mass range. This train of thought has recently
56
57 been extended to broadband CID in a method termed “multigenerational CID” [161]
58
59
60
61
62
63
64
65

1
2
3
4 **(Figure 6f)**. In this method the excitation Mathieu q_u value is fixed at an optimal
5
6 value (in the range 0.2-0.35) by setting the ac waveform at the corresponding
7
8 frequency. The fixed excitation frequency only fragments ions over a limited range,
9
10 so in order to fragment a wide range of m/z values, the rf amplitude must be
11
12 scanned from high to low, thereby fragmenting ions successively from high to low
13
14 m/z . Because each ion is fragmented at the same q_u , chosen to balance precursor
15
16 well depth, ion secular frequency (velocity), and fractional product ion mass range,
17
18 higher intensities of product ions are observed and a wider distribution of product
19
20 ion m/z values is also observed.
21
22
23
24
25

26
27 The term ‘multigenerational’ refers to the characteristic wherein multiple
28
29 generations of fragment ions are produced from a single scan of the rf amplitude
30
31 [162]. An equivalent, but experimentally limited Wideband Activation method is
32
33 available on Thermo ion trap instruments [163]. While Wideband Activation, as
34
35 commercially implemented, is limited to a 20 Th mass range, multigenerational CID
36
37 is much more versatile because the rf amplitude is scanned over a larger range,
38
39 thereby extending the excitation mass range. Useful applications of
40
41 multigenerational CID and Wideband Activation are included in the practical
42
43 applications of ion trap mass spectrometry, e.g. in discrimination of designer drugs,
44
45 which have similar MS^2 spectra but also often have unique MS^3 fragments. Molecules
46
47 with hydroxyl, carbonyl, and sulfate functional groups, which often give
48
49 uninformative neutral losses of water, carbon dioxide, and sulfite, respectively, are
50
51 fragmented more extensively with either of these newer methods. The spectra that
52
53 are observed with a single sequence of ion injection, CID, and mass scanning contain
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 combinations of ions from the fragment ions which would otherwise be observed in
5
6 discrete MS^2 , MS^3 , etc. spectra.
7

8
9 The multigenerational effect can also be observed by using a frequency
10
11 sweep of the resonance ejection signal while keeping the rf parameters constant
12
13 [121]. The observed fragmentation patterns are nearly identical to the rf ramp case.
14
15 However, because the precursor and many generations of product ions lie on
16
17 different locations of the Mathieu q axis, their fractional product ion mass ranges
18
19 will differ, as will their excitation frequencies.
20
21
22

23
24 The digital ion trap can also be used to perform MS^n , and the implementation
25
26 is similar to that using sinusoidally-powered ion traps. Major differences are the
27
28 naturally deeper potential well in the DIT because of the higher average potential of
29
30 the trapping waveform as well as the reduced mass range (boundary at $q = 0.712$
31
32 compared to $q = 0.908$ for rf trap) although there are DIT methods of broadening
33
34 this range. The first implementation of CID in the DIT used conventional sinusoidal
35
36 dipolar ac waveforms [164], but further investigations yielded a more appropriate
37
38 digital method of CID wherein the digital resonance excitation signal, obtained by
39
40 dividing down the digital trapping waveform, was duty cycle modulated to provide a
41
42 dipolar waveform for CID. For example, the digital trapping waveform can be
43
44 divided by 3 to obtain a nonlinear resonance condition at $\beta_z = 2/3$ (i.e. a double
45
46 resonance, explained in the ejection section), which is used for ion ejection. Dipolar
47
48 DC CID was accomplished by increasing the duty cycle of the supplemental digital
49
50 waveform, introducing a radial DC component so as to displace the ion cloud from
51
52 the center of the trap, thereby inducing rf heating and thus fragmentation. The CID
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 efficiencies approach 100% in some cases, but this technique is not mass-selective
5
6 so that the ions to be activated must first be isolated to preclude spectral
7
8 complexity. Further work showed that the frequency of the dipole activation
9
10 waveform could be modified by varying the trapping waveform frequency because
11
12 the former is simply a constant fraction of the latter and the latter can be varied,
13
14 thereby varying the activation frequency [165]. High efficiencies were again
15
16 observed for reserpine ions (~100%), and a relationship between secular frequency
17
18 in the DIT and m/z was experimentally derived [166].
19
20
21
22
23
24

25 3.3 Ejection

26
27 The most fundamental operation in mass spectrometry is to determine the
28
29 m/z ratios of the ions of interest, that is, to obtain a *mass spectrum* (a plot of ion
30
31 intensity vs. m/z). In order to obtain a mass spectrum, ions must be *mass-selectively*
32
33 *detected*. Detection can be accomplished in quadrupole ion traps in one of two ways:
34
35 1) destructive external detection, or 2) nondestructive image charge detection. We
36
37 begin with the former method, which is by far the most common and certainly much
38
39 more promising as evidenced by having been commercialized for many years.
40
41
42
43
44

45 Ions are typically ejected from an ion trap by resonance or *boundary ejection*
46
47 or a related method and electrostatically focused into a detector, which can be an
48
49 electron multiplier (low pressure) or a Faraday cup (high pressure). In boundary
50
51 ejection, also known as the *mass selective instability scan*, the trapping rf amplitude
52
53 is ramped linearly with respect to time, thereby moving each ion to the stability
54
55 “boundary” of the Mathieu stability diagram ($q = 0.908$), at which point ions of that
56
57 particular m/z are ejected from the trap [83]. Since the rf amplitude and m/z are
58
59
60
61
62
63
64
65

1
2
3
4 directly proportional, ions are ejected *linearly with time* from low to high m/z . The
5
6 signal from the detector is recorded as a function of time, thereby generating an
7
8 intensity vs. time dataset. Mass calibration, in which compounds of known
9
10 monoisotopic mass are analyzed in order to linearly correlate time and m/z , then
11
12 yields ion intensity vs. m/z , viz. a mass spectrum.
13
14
15

16
17 Importantly, the resolution obtained from these mass-selective scan modes is
18
19 dependent upon the initial conditions of the ions, which will enter the trap with
20
21 varying x, y, and z coordinates and will also have a range of kinetic energies,
22
23 velocities, and positions. In order to optimize resolution, these parameters must be
24
25 randomized and the deviation of each reduced. The most common way to
26
27 accomplish this is by using a process known as collisional cooling [83, 167, 168]. In
28
29 this method, a light bath/buffer gas such as helium is present in the trap so that
30
31 collisions between ions and the light neutrals collisionally cool and collapse the ion
32
33 cloud to the center of the trap, reducing the variation in the initial ion parameters.
34
35
36
37
38

39 The more common method of ion ejection is resonance ejection (**Figure 7a**)
40
41 [81, 82], where a small supplementary ac signal is applied across opposite
42
43 electrodes (e.g. endcaps for the QIT, x electrodes for the LIT) 180 degrees out-of-
44
45 phase to generate an approximately dipolar field. This scan mode, called the *mass-*
46
47 *selective instability scan with resonance ejection*, can be illustrated on the Mathieu
48
49 stability diagram as a “hole” (“black hole”) of instability imposed on the q axis (more
50
51 precisely, instability occurs along an entire iso- β line). As in boundary ejection, the
52
53 rf amplitude is ramped linearly, bringing ions’ secular frequencies consecutively
54
55 into resonance with the supplementary dipolar field such that they pick up energy
56
57
58
59
60
61
62
63
64
65

1
2
3
4 from the driving rf voltage, are excited to higher amplitudes in the trap, and, if the
5
6 time and amplitude of the ac signal are high enough, the ions are ejected from the
7
8 trap in order of increasing m/z . Resonance ejection offers better performance than
9
10 mass-selective instability in terms of both resolution and sensitivity due to a more
11
12 efficient ejection process. Both resonance and boundary ejection of ions can be
13
14 observed simultaneously if there is a substantial residual population of ions
15
16 between the resonance point and the boundary (inset, **Figure 7a**) [169]. These
17
18 processes can generally be differentiated by their respective peak widths and
19
20 fundamental substructure.
21
22
23
24
25

26
27 The choice of both scan *rate* and scan *direction* is critical in resonance
28
29 ejection. Decreasing the scan rate generally increases resolution [170, 171], while
30
31 very fast scanning has the advantage of improving signal intensity [172]. The
32
33 damping rate must be optimized for the given scan rate, with the resolution being
34
35 inversely related to the scan rate (ignoring space charge effects) [171]. As stated
36
37 previously, the forward resonance ejection scan (i.e. scanning the rf amplitude from
38
39 low to high) gives much better sensitivity and resolution (**Figure 4b**) due to
40
41 forward ion secular frequency shifts (**Figure 4a**) [66, 77, 85, 87, 173]. The ideal
42
43 choice of scan direction, however, depends on the characteristic fields of the ion
44
45 trap.
46
47
48
49
50

51
52 The scan direction additionally affects mass assignments due to space charge
53
54 effects [94, 173]. In the forward scan, lower mass ions will experience more space
55
56 charge effects than high mass ions, causing shifts in mass that are particularly
57
58 noticeable for isotopic distributions. Mass shifts can be reduced by increasing the
59
60
61
62
63
64
65

ejection q_u value, increasing the excitation amplitude, and increasing the scan speed [95]. The usual method of controlling mass shifts to maintain linear mass calibration is a linear ramp of the amplitude of the supplemental ac waveform [174]. However, an interesting application of mass shifts is resolution of isobars and isomers, by taking advantage of the dependence of mass shifts on chemical structure [175, 176].

Pressure is another variable that has a significant effect on resonance ejection. While ~mTorr pressures of bath gas are desirable to increase injection efficiency and mass resolution by collisional cooling [83], in general the buffer gas will broaden mass peaks during mass analysis. It should be noted that very high scan speeds will tend to decrease the effect of buffer gas pressure [177], whereas at low scan speeds there will be an optimal pressure of bath gas (and pressure-dependent ac amplitude) which gives maximum resolution [178, 179]. In general, the equation governing mass resolution ($\Delta m/m$) in ion traps is

$$\Delta m/m \propto P/\Omega = 4\sqrt{3} / \Omega \tau \quad \text{Eq 14}$$

where P is the buffer gas pressure and τ is the ion motion relaxation time caused by collisions with the bath gas molecules [180, 181]. Resolution is expected to linearly decrease with bath gas pressure, but this can be countered by operating at higher drive frequency (which, in turn, requires either a smaller trap radius or higher operating voltage).

While ions are generally scanned out via apertures in electrodes (endcaps with holes or x electrodes with slits), unidirectional ion ejection can be

1
2
3
4 accomplished by using a resonance ejection waveform that is a linear combination
5
6 of the nominal dipolar excitation frequency as well as the second harmonic [182].
7
8 The direction and efficiency of ejection can be controlled by modifying the ratio of
9
10 the signal amplitudes. Unidirectional ejection is achieved when the harmonic has
11
12 the larger amplitude. In modern commercial instruments, ejection direction can be
13
14 controlled by the phase relationship between the trapping field RF and the
15
16 resonance ejection voltage when their frequencies have an integer relationship. In
17
18 a linear quadrupole ion trap, ions can additionally be scanned out either *axially*
19
20 (along the length of the trap) [49] or *radially* [50, 183] through slits in the
21
22 quadrupole electrodes. These different methods are used in commercial Thermo
23
24 and Sciex instruments, respectively. The axial ejection method takes advantage of
25
26 the coupling of ion motion in fringe fields near the ends of the trap (i.e. the “cone of
27
28 reflection”) while the latter relies on excitation along a single axis. Axial ejection can
29
30 be enhanced with auxiliary electrodes for ion extraction [184, 185], but unlike radial
31
32 ejection, added octopole fields have not been shown to increase resolution or
33
34 sensitivity [186].
35
36
37
38
39
40
41
42
43

44 Resonance ejection is typically performed at a Mathieu q_u in the vicinity of
45
46 0.88 but can also be performed at lower values of q in order to extend the mass
47
48 range [187, 188]. However, because ejection is performed away from the optimal q_u
49
50 value, resolution and sensitivity are sacrificed in order to achieve this extension.
51
52 Overtone and sideband frequencies can also be used for mass range extension,
53
54 though they require higher ac amplitudes because they are fundamentally weaker
55
56 resonances [189].
57
58
59
60
61
62
63
64
65

Resolution can further be improved by performing *double or triple resonance ejection*. Double resonance ejection has been demonstrated and incorporated into Bruker instruments [190], and it has since been adopted in miniature cylindrical ion traps [181, 191]. In a double resonance ejection scan, the resonance ejection frequency is chosen to match a nonlinear resonance point. These are most commonly the hexapolar resonances at one-third ($\beta_z = 2/3$) and one-sixth ($\beta_z = 1/3$) the rf frequency or the octopolar nonlinear resonance at one-fourth ($\beta_z = 1/2$) the rf frequency [192]. The term “double resonance” therefore refers to the co-occurrence of the dipolar resonance and the nonlinear resonance. The coupling of the two resonances is claimed to cause the rate of ion ejection to be faster than the rate encountered in typical single frequency resonance ejection, resulting in superior resolution and sensitivity. An analogous triple resonance ejection mode has been demonstrated and incorporated into Varian instruments [84]. A hexapolar field is intentionally introduced by applying an ac voltage to the endcaps 180 degrees out of phase with respect to the rf frequency. A dipolar ac frequency is chosen to match a hexapolar resonance and a low-voltage quadrupolar field is then also applied and chosen to match the lower rf sideband ($\Omega - \omega$) corresponding to the same resonance, thereby generating a triple resonance ejection scan (**Figure 7d**), which is claimed to give even better resolution than a double resonance (**Figure 7c**) scan. Care must be taken in both single and multiple frequency resonance ejection experiments to phase-lock the rf and ac waveforms in order to prevent mass peaks from splitting and to maintain mass accuracy [191, 193-195].

Multiple resonance ejection points can be used in *compressive mass spectrometry*, or *multi-resonant frequency excitation* (mFRE), illustrated on the Mathieu stability diagram in **Figure 7b** [196]. In contrast to double and triple resonance ejection, which combine multiple frequencies that correspond to *the same* Mathieu q_u parameter, this method combines frequencies that correspond to *different* Mathieu q_u parameters. As a result, multiple “holes” of instability are imposed on the stability diagram. When the rf amplitude is ramped, multiple sets of ions are detected simultaneously, reducing the time needed for mass analysis by a factor of three to six in the first particular implementation. The signal-to-noise ratio was found to be inferior when using multiple frequencies, and resolution is different for different mass/charge subranges because of the different q_{eject} values. In addition, the mass spectra must be “uncompressed.” That is, the underlying ion distribution must be calculated from the mFRE data, of which there must be multiple different measurements (i.e. a two-frequency measurement and a three-frequency measurement). Nonetheless, a reconstruction algorithm has been described [196].

Multiple frequency resonance ejection need not take place on a single pair of electrodes. *Rhombic excitation and ejection* has been implemented in a linear ion trap with simultaneous excitation in x and y [197]. Key considerations are the amplitudes and frequencies applied as well as the phase difference between them, particularly if the dimensions in x and y are different, which would cause ion secular frequencies in those dimensions to differ. Ion excitation profiles differ based on the phase difference, with a 90-degree phase shift generating rhombic ion motion and a

1
2
3
4 zero-degree phase shift generating linear excitation. The key advantage of rhombic
5
6 excitation and ejection is that as the ions are excited to higher trajectories, they
7
8 *circle* the rest of the ion cloud, reducing interactions between the ejected ions and
9
10 the rest of the ion cloud. This results in a substantial reduction in space charge,
11
12 which is known to cause peak broadening (compare **Figure 7e and f**). Space charge
13
14 can similarly be reduced by using *successive resonances* for ion ejection [194]. The
15
16 normal single resonance frequency is replaced by a dual-frequency signal with
17
18 frequencies spaced very closely (ideally this difference is equivalent to the mass
19
20 scan rate). When ions encounter the first, lower-amplitude resonance frequency,
21
22 they are excited to higher trajectories, thereby decreasing space charge induced
23
24 peak broadening when they are then ejected by the second higher-amplitude
25
26 frequency component. The successive effect can be observed in both the rf
27
28 amplitude scan and ac frequency scan (discussed later) modes.
29
30
31
32
33
34
35

36
37 Alternative methods of mass-selective ejection can be deduced from the
38
39 Mathieu parameters a_u and q_u . The parameters that can be varied in order to
40
41 accomplish a mass scan are the rf amplitude (V_{rf}), as already discussed, the DC
42
43 amplitude (U), the internal radius of the trap (r_0), and the angular rf frequency (Ω).
44
45

46
47 An uncommon method of mass analysis is to scan the rf frequency while
48
49 holding the rf amplitude constant. This method was first demonstrated by Landais
50
51 et al. [198] and is the method of choice in digital ion traps [164, 199]. The
52
53 attractiveness of this method is the ease with which a frequency can be scanned,
54
55 especially compared to a linear scan of a high voltage rf. Additionally, mass range
56
57 can be extended quite easily since the the rf voltage usually limits this range. For rf
58
59
60
61
62
63
64
65

1
2
3
4 amplitude ramps, the mass range is limited by the maximum rf voltage that can
5
6 practically be synthesized and applied without discharges and system instability.
7
8 Thus, the rf frequency scan has been particularly useful in the analysis of
9
10 microparticles [200, 201], nanoparticles [202], and large biomolecules [203-205].
11
12 According to the Mathieu parameters, mass calibration is nonlinear with a linear
13
14 frequency sweep, which is a disadvantage of the method. Digital traps, on the other
15
16 hand, are particularly appropriate devices for frequency scanning because they can
17
18 modulate the period of the trapping digital waveform [164, 199, 206-208]. Digital
19
20 traps use high-frequency switching technology to alternate between high-voltage
21
22 positive (HIGH) and negative (LOW) states, and by varying the ratio of time that the
23
24 waveform spends on each state (i.e. the duty cycle), a mass spectrum can be
25
26 recorded in the same manner that rf frequency mass spectra can be recorded.
27
28 Similarly, resonance ejection can be performed in digital traps by dividing down the
29
30 trapping digital waveform to obtain a lower-frequency and lower-amplitude dipolar
31
32 signal [165]. As the trapping waveform duty cycle varies during the mass scan, the
33
34 supplemental ac frequency will also vary and will be a constant fraction (e.g. 1/3) of
35
36 the trapping waveform, thereby keeping q_{eject} constant. More recently it has been
37
38 demonstrated that resolution may be improved by using a non-integral ratio
39
40 between the trapping and excitation waveforms, but apparent beat frequencies
41
42 force ions to be ejected at integer m/z values (assuming the beats line up with
43
44 integer m/z), which will corrupt any but the simplest mass spectra [209].
45
46
47
48
49
50
51
52
53
54
55

56 While in theory the radius of the ion trap can be altered during a mass scan
57
58 with, for example, a stepper motor or linear actuator, it is impossible in practice to
59
60
61
62
63
64
65

1
2
3
4 generate a mass spectrum using this method due to 1) changing electric field
5
6 components as the internal radius is scanned, and 2) the high precision and
7
8 accuracy that would be required from the motors. The more promising use of the r_0
9
10 parameter is in ion trap arrays, where traps of different sizes are used to mass-
11
12 select ions of different m/z while using the same set of electronics to drive each trap
13
14
15
16
17 [210].
18

19 Traps generally do not operate with DC components ($a_u = 0$); however, in
20
21 practice there are some uses for non-zero Mathieu a_u parameters. As previously
22
23 mentioned, isolation can be accomplished by using the rf/dc method [115].
24
25 However, a mass spectrum can also be recorded by using a *DC downscan (capscan)*,
26
27 a *reverse scan*, or an *anglescan* [211, 212], all nonresonance techniques. To effect a
28
29 reverse scan, the amplitude of the rf is increased to bring higher mass ions to higher
30
31 q_u values. A DC potential is then applied so that ions have nonzero Mathieu a_u
32
33 parameters. As in a typical quadrupole mass filter, the rf and dc potentials are
34
35 ramped linearly (but in the reverse direction) keeping their ratio constant, thereby
36
37 generating a mass spectrum. The DC downscan experiment shows particular
38
39 promise for analysis of high mass ions since high mass analysis generally requires
40
41 impractically high rf amplitudes (or unconventional rf frequency scanning). With
42
43 the downscan technique, the rf amplitude is held constant while the dc potential
44
45 applied to the endcaps (a capscan) or ring electrode (downscan) is ramped to eject
46
47 ions nonlinearly with time. In the anglescan experiment, which is a variant of the
48
49 downscan, the rf amplitude is decreased linearly while the dc amplitude is
50
51 increased.
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Another technique for obtaining a mass spectrum can be deduced from consideration of ion secular frequencies. Though not common, the rf frequency and amplitude can be kept constant while the frequency of the supplementary dipolar ac signal is ramped in a *secular frequency scan* [8, 114, 213]. This kind of scan may be particularly advantageous for miniature mass spectrometers, which benefit from small, power-efficient electronics. Since the rf amplitude need only be fixed (not ramped linearly in a precise manner), the electronics are simplified. Furthermore, power savings are expected because lower rf amplitudes can be used to achieve higher mass ranges [156]. “Black holes” are a concern in this method, with blank intensity profiles and split peaks at nonlinear resonance points in forward and reverse frequency scans, respectively. Although mass calibration is nonlinear because the relationship between m/z and frequency is not analytically described, a procedure which utilizes the Mathieu parameters a_u , q_u , and β_u showing <0.1% calibration error has recently been demonstrated [213]. The calibration method can be modified in order to create a custom frequency-swept waveform to give a linear relationship between m/z and time in a scan termed the “inverse Mathieu q scan” [214]. If the ac frequency is varied so that an inverse relationship exists between the ejected ion’s Mathieu q_u parameter and time, then the calibration procedure involves performing a linear fit of m/z vs. time, the same procedure that is performed for analytical rf ramp scans. An advantage of the inverse Mathieu q scan is the natural extension of mass range, since typically mass range is limited by the highest voltage that can be achieved by the rf coil without causing a discharge [215]. A further advantage of ac frequency scanning is that, when used as a method of

1
2
3
4 mass-selective excitation and combined with a fixed frequency component set on a
5
6 particular product ion, a precursor scan can be performed as a single scan using a
7
8 single ion trap. This was first demonstrated by Yost [157] but has since been
9
10 demonstrated on a miniature mass spectrometer [158]. Whether the ac frequency
11
12 scan is comparable to the rf amplitude scan in terms of simplicity, scan rate, mass
13
14 accuracy, and resolution have yet to be determined. For example, the amplitude of
15
16 the ac has so far been kept constant, but one would expect this amplitude to vary
17
18 with m/z because of potential well depth (as is the case with resonance ejection
19
20 [174]).
21
22
23
24

25
26 So far we have discussed methods of *scanning* ions out of a quadrupole ion
27
28 trap, but for targeted applications the entire ion population need not be detected.
29
30 Instead, the trap could be operated in a *non-scanning* mode. For example, a non-
31
32 scanning rectilinear ion trap for selected ion and selected reaction monitoring has
33
34 been described [216]. Ions were injected into the RIT and a DC offset on the y rods
35
36 was used for apex isolation of a particular precursor ion, which could then be
37
38 ejected axially by applying a DC pulse on one of the axial z electrodes. Thus, the
39
40 intensity of a single m/z species is monitored, and a full scan mass spectrum cannot
41
42 be collected unless the experiment is repeated for each m/z . A similar experiment
43
44 was implemented on a linear ion trap made using digital light processing technology
45
46 [217], and it has recently been calculated that a mass resolution of 1 amu should be
47
48 possible in the non-scanning mode [218].
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

3.4 Charge detection

Image charge detection of trapped ions can be classified into two types. The first type is to measure the ion image charge (or resulting induced voltage) with a charge detector coupled with the ion trap, e.g. gated electrostatic ion trap [219, 220] or a quadrupole ion trap [221, 222]. Conventional secondary electron multiplier detectors are not able to generate enough signal at low ion velocity because of low secondary electron yield; a charge detector, however, is independent of ion velocity, so it can overcome the ion detection problem of macroions like viruses and cells [223]. The second approach is to measure the ion image current by connecting a differential amplifier circuit to a pair of electrodes in the quadrupole ion trap [224], Fourier transform ion cyclotron resonance (FTICR) [225] or Orbitrap mass spectrometers [226], which we briefly discuss due to the similarities between the detection schemes between these instruments and charge detection QITs. With a Fourier transform of ion signals, high resolving power is obtained, but in the case of the ion trap great care must be taken to observe the small ion signal in the presence of the very large rf signal [227].

Gated electrostatic ion traps can measure the charge and mass-to-charge ratios of large electrosprayed ions nondestructively as shown in **Figure 8a** [219, 228]. In **Figure 8b**, by repeatedly measuring the ions within the electrostatic ion trap, the uncertainty of the charge measurement could be reduced to $\sim 0.2 e$ [220]. In **Figure 8c**, a quadrupole ion trap coupled with a charge detector was used to non-destructively measure the charge and mass-to-charge ratios of laser-induced acoustic desorbed macroions [221, 222, 229].

The mass resolution of charge-detection quadrupole ion trap instruments depends on the measurement accuracy, the mass-to-charge ratios, and also charge. The coefficient of variance of the measured individual particles' ejection points (q_{eject}) at high pressure (40 mtorr) is about 1.2%, ensuring the mass resolution is approximately 100 [230]. The accuracy in charge measurement depends on the number of charges carried by individual particles [231].

The use of ion traps with image charge (or induced current) detection circuits can result in high resolving power and mass accuracy. Guan and Marshall proposed stored waveform inverse Fourier transform (SWIFT) for broadband mass-selective excitation and ejection of ions in quadrupole ion trap and FT-ICR mass spectrometers [124, 232, 233]. **Figure 9a** shows that non-destructive ion detection with a broad-band Fourier transform quadrupole ion trap can reach a resolution of ~ 1000 at a detection bandwidth of 400 kHz [224, 234]. **Figure 9b** shows the method of trapping, excitation, and detection of ions in FT-ICR cells [225]. Unit mass resolution of high mass molecules (chondroitinase, 112 kDa) with 3 Da mass accuracy has been achieved with a 9.4 tesla FT-ICR mass spectrometer [235]. Recently, a 21 tesla FT-ICR mass spectrometer was developed and took advantage of the linear quadrupole trap for high ion capacity and ejection efficiency; a mass resolving power of 150,000 ($m/\Delta m$, 50%) was achieved for bovine serum albumin (66 kDa) for a 0.38 s detection period, and $>2,000,000$ resolving power is achieved for a 12 s detection period. However, the cost to maintain the operation of an FT-ICR instrument is high. To reduce the cost, an electrostatic ion trap device, i.e. Orbitrap [226, 236-238] or Cassinian trap [239, 240] were developed.

1
2
3
4 The Orbitrap, a first order trap, shows a resolving power of 500,000, and
5
6 mass accuracies within a few parts per million (**Figure 9c**). The Cassinian trap, a
7
8 second order trap, shows resolving powers of 53,000 for the fundamental frequency
9
10 and 140,000 for the third harmonic in 1 s. Broad-band and narrow-band waveforms
11
12 are used to de-excite/re-excite ion motion and unit mass selection is achieved by
13
14 selective de-excitation and re-excitation with narrow-band waveforms [241]. In
15
16 addition, phase-enhanced selective ion ejection based on broadband dipolar
17
18 excitation and ion ejection shows an isolation resolution of 28,400 and a mass
19
20 resolution of 100,000 with an Orbitrap [242]. By rephasing the ion packet with a
21
22 narrower axial spatial extent and frequency distribution in an Orbitrap, mass
23
24 resolutions of 124,000 to 171,000 are obtained which is a 2- to 3-fold improvement
25
26 over the resolution of 40,000 to 60,000 without rephasing [243].
27
28
29
30
31
32

33
34 High mass ions, e.g. GroEL and immunoglobulin G (IgG) can be detected by
35
36 implementing ion optics for ion transport with ion funnels and quadrupoles and
37
38 extending software detection mass range to $\sim m/z$ 20,000 [244, 245]. MS/MS of
39
40 high mass ions with an Orbitrap device is arranged in tandem-in-space method, i.e.
41
42 collisional-induced fragmentation at high pressure conditions in collision cells. MS³
43
44 is demonstrated with an Orbitrap instrument by analyzing the GroEL fragment ions
45
46 and a mass measurement accuracy of 2.3 ppm is achieved [244].
47
48
49
50
51
52

53 54 **4. Conclusion**

55
56 The quadrupole ion trap has a storied history of development over the past six and a
57
58 half decades, becoming one of the most sensitive, selective, and versatile analytical
59
60
61
62
63
64
65

1
2
3
4 devices. While complications arise from the co-occurrence of linear and higher-
5
6
7 order field resonances, they have nonetheless proved quite useful for increasing the
8
9 performance and overall versatility of these already-advantageous devices. With
10
11 new developments in multi-trap systems, QIT-FT hybrids (e.g. QIT-Orbitrap),
12
13 frequency scanning, digital ion trap technology, ion trap miniaturization and
14
15
16 multiplexing on the horizon, it will become increasingly important to further
17
18 understand ion trap resonances in order to continue to exploit them for optimized
19
20 performance.
21
22
23
24
25

26 5. Acknowledgements

27
28
29 The authors acknowledge funding from NSF (CHE 1307264) and NASA
30
31 (NNX16AJ25G) and recognize outstanding contributions from many fellow
32
33 scientists. The authors also gratefully acknowledge the contributions of Jae
34
35 Schwartz (Thermo Fisher Scientific), who reviewed the article prior to submission.
36
37 WPP thanks the support by grants from the Ministry of Science and Technology of
38
39 Taiwan (MOST 102-2112-M-259-003-MY3 and 105-2918-I-259-001) and
40
41 appreciates Prof. R.G. Cooks for the opportunity to visit his lab.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

biologically active molecules onto surfaces. His group is also responsible for the ambient ionization method desorption electrospray ionization (DESI). Most recently his interests have focused on applications of mass spectrometry to chemical synthesis in microdroplets, intrasurgical diagnostics, and origin-of-life chemistry. Cooks has authored 1,100 publications and served as thesis advisor to 130 Ph. D.'s.

7. References

- [1] R.D. Espy, M. Wlekinski, X. Yan, R.G. Cooks, Beyond the flask: Reactions on the fly in ambient mass spectrometry, *TrAC Trends in Analytical Chemistry*, 57 (2014) 135-146.
- [2] A. Colorado, D.J. Barket, J.M. Hurst, P.B. Shepson, A fast-response method for determination of atmospheric isoprene using quadrupole ion trap mass spectrometry, *Analytical Chemistry*, 70 (1998) 5129-5135.
- [3] L.H. Mielke, K.A. Pratt, P.B. Shepson, S.A. McLuckey, A. Wisthaler, A. Hansel, Quantitative determination of biogenic volatile organic compounds in the atmosphere using proton-transfer reaction linear ion trap mass spectrometry, *Anal Chem*, 82 (2010) 7952-7957.
- [4] W. Paul, H. Steinwedel, A new mass spectrometer without a magnetic field, *Z. Naturforsch. Sect. A*, 8 (1953) 448-450.
- [5] W. Paul, Electromagnetic traps for charged and neutral particles, *Reviews of modern physics*, 62 (1990) 531.
- [6] M. Welling, R.I. Thompson, H. Walther, Photodissociation of MgC60+ complexes generated and stored in a linear ion trap, *Chemical Physics Letters*, 253 (1996) 37-42.
- [7] N. Mikami, Y. Miyata, S. Sato, T. Sasaki, ION TRAP METHOD COMBINED WITH TWO-COLOR LASER SPECTROSCOPY OF SUPERSONIC MOLECULAR BEAMS-PHOTODISSOCIATION OF TRAPPED C6H5Cl+, *Chemical Physics Letters*, 166 (1990) 470-474.
- [8] M. Welling, H.A. Schuessler, R.I. Thompson, H. Walther, Ion/molecule reactions, mass spectrometry and optical spectroscopy in a linear ion trap, *Int. J. Mass Spectrom. Ion Processes*, 172 (1998) 95-114.
- [9] S. Pollack, D. Cameron, M. Rokni, W. Hill, J.H. Parks, Charge exchange and cluster formation in an rf Paul trap: interaction of alkali atoms with C60+, *Chemical Physics Letters*, 256 (1996) 101-108.
- [10] H. Hiura, T. Kanayama, Growth of hydrogenated silicon cluster ions using an ion trap, *Chemical Physics Letters*, 328 (2000) 409-414.
- [11] E.R. Lovejoy, R. Bianco, Temperature dependence of cluster ion decomposition in a quadrupole ion trap, *Journal of Physical Chemistry A*, 104 (2000) 10280-10287.

- [12] Y.S. Wang, C.H. Tsai, Y.T. Lee, H.C. Chang, J.C. Jiang, O. Asvany, S. Schlemmer, D. Gerlich, Investigations of protonated and deprotonated water clusters using a low-temperature 22-pole ion trap, *Journal of Physical Chemistry A*, 107 (2003) 4217-4225.
- [13] P.H. Hemberger, N.S. Nogar, J.D. Williams, R.G. Cooks, J.E.P. Syka, Laser Photodissociation Probe for Ion Tomography Studies in a Quadrupole Ion-Trap Mass-Spectrometer, *Chemical Physics Letters*, 191 (1992) 405-410.
- [14] C.D. Cleven, R.G. Cooks, A.W. Garrett, N.S. Nogar, P.H. Hemberger, Radial distributions and ejection times of molecular ions in an ion trap mass spectrometer: A laser tomography study of effects of ion density and molecular type, *Journal of Physical Chemistry*, 100 (1996) 40-46.
- [15] A. Steane, The ion trap quantum information processor, *Applied Physics B-Lasers and Optics*, 64 (1997) 623-642.
- [16] G.J. Milburn, S. Schneider, D.F.V. James, Ion trap quantum computing with warm ions, *Fortschritte Der Physik-Progress of Physics*, 48 (2000) 801-810.
- [17] D. Kielpinski, C. Monroe, D.J. Wineland, Architecture for a large-scale ion-trap quantum computer, *Nature*, 417 (2002) 709-711.
- [18] S. Gulde, M. Riebe, G.P. Lancaster, C. Becher, J. Eschner, H. Haffner, F. Schmidt-Kaler, I.L. Chuang, R. Blatt, Implementation of the Deutsch-Jozsa algorithm on an ion-trap quantum computer, *Nature*, 421 (2003) 48-50.
- [19] D. Porras, J.I. Cirac, Effective quantum spin systems with trapped ions, *Phys Rev Lett*, 92 (2004) 207901.
- [20] S. Seidelin, J. Chiaverini, R. Reichle, J.J. Bollinger, D. Leibfried, J. Britton, J.H. Wesenberg, R.B. Blakestad, R.J. Epstein, D.B. Hume, W.M. Itano, J.D. Jost, C. Langer, R. Ozeri, N. Shiga, D.J. Wineland, Microfabricated surface-electrode ion trap for scalable quantum information processing, *Phys Rev Lett*, 96 (2006) 253003.
- [21] J.P. Home, D. Hanneke, J.D. Jost, J.M. Amini, D. Leibfried, D.J. Wineland, Complete methods set for scalable ion trap quantum information processing, *Science*, 325 (2009) 1227-1230.
- [22] C. Monroe, J. Kim, Scaling the ion trap quantum processor, *Science*, 339 (2013) 1164-1169.
- [23] D.J. Wineland, J.C. Bergquist, W.M. Itano, J.J. Bollinger, C.H. Manney, Atomic ion Coulomb clusters in an ion trap, *Phys Rev Lett*, 59 (1987) 2935-2938.
- [24] L. Hornekaer, N. Kjaergaard, A.M. Thommesen, M. Drewsen, Structural properties of two-component coulomb crystals in linear paul traps, *Phys Rev Lett*, 86 (2001) 1994-1997.
- [25] D. Porras, J.I. Cirac, Quantum manipulation of trapped ions in two dimensional coulomb crystals, *Phys Rev Lett*, 96 (2006) 250501.
- [26] L. Schmoger, O.O. Versolato, M. Schwarz, M. Kohnen, A. Windberger, B. Piest, S. Feuchtenbeiner, J. Pedregosa-Gutierrez, T. Leopold, P. Micke, A.K. Hansen, T.M. Baumann, M. Drewsen, J. Ullrich, P.O. Schmidt, J.R. Lopez-Urrutia, Coulomb crystallization of highly charged ions, *Science*, 347 (2015) 1233-1236.
- [27] R. Schinke, *Photodissociation Dynamics: Spectroscopy and Fragmentation of Small Polyatomic Molecules*, Cambridge University Press, New York, 1993.

- [28] Y. Inokuchi, O.V. Boyarkin, R. Kusaka, T. Haino, T. Ebata, T.R. Rizzo, Ion selectivity of crown ethers investigated by UV and IR spectroscopy in a cold ion trap, *J Phys Chem A*, 116 (2012) 4057-4068.
- [29] S. Gartner, J. Krieg, A. Klemann, O. Asvany, S. Brunken, S. Schlemmer, High-resolution spectroscopy of CH₂D⁺ in a cold 22-pole ion trap, *J Phys Chem A*, 117 (2013) 9975-9984.
- [30] J.G. Redwine, Z.A. Davis, N.L. Burke, R.A. Oglesbee, S.A. McLuckey, T.S. Zwier, A novel ion trap based tandem mass spectrometer for the spectroscopic study of cold gas phase polyatomic ions, *International Journal of Mass Spectrometry*, 348 (2013) 9-14.
- [31] N.L. Burke, J.G. Redwine, J.C. Dean, S.A. McLuckey, T.S. Zwier, UV and IR spectroscopy of cold protonated leucine enkephalin, *International Journal of Mass Spectrometry*, 378 (2015) 196-205.
- [32] N.L. Burke, A.F. DeBlase, J.G. Redwine, J.R. Hopkins, S.A. McLuckey, T.S. Zwier, Gas-Phase Folding of a Prototypical Protonated Pentapeptide: Spectroscopic Evidence for Formation of a Charge-Stabilized beta-Hairpin, *J Am Chem Soc*, 138 (2016) 2849-2857.
- [33] D.A. McQuarrie, J.D. Simon, *Physical chemistry: A molecular approach*, 1997.
- [34] J.S. Brodbelt, Photodissociation mass spectrometry: new tools for characterization of biological molecules, *Chem. Soc. Rev.*, 43 (2014) 2757-2783.
- [35] R.L. Mössbauer, Kernresonanzfluoreszenz von Gammastrahlung in Ir¹⁹¹, *Zeitschrift für Physik*, 151 (1958) 124-143.
- [36] E.R. Andrew, *Nuclear magnetic resonance*, Nuclear Magnetic Resonance, by ER Andrew, Cambridge, UK: Cambridge University Press, 2009, 1 (2009).
- [37] N.M. Atherton, M. Davies, B. Gilbert, *Electron spin resonance*, Royal Society of Chemistry, 1994.
- [38] W.B. Lynch, K.A. Earle, J.H. Freed, 1-mm wave ESR spectrometer, *Review of scientific instruments*, 59 (1988) 1345-1351.
- [39] A.P. Seyranian, The swing: Parametric resonance, *Journal of Applied Mathematics and Mechanics*, 68 (2004) 757-764.
- [40] R.C. Eckardt, C.D. Nabors, W.J. Kozlovsky, R.L. Byer, Optical parametric oscillator frequency tuning and control, *J. Opt. Soc. Am. B*, 8 (1991) 646-667.
- [41] R.E. March, J.F.J. Todd, *Quadrupole ion trap mass spectrometry*, Wiley-Interscience, 2005.
- [42] P.H. Dawson, *Quadrupole mass spectrometry and its applications*, Elsevier, 2013.
- [43] R.D. Knight, The general form of the quadrupole ion trap potential, *International Journal of Mass Spectrometry and Ion Physics*, 51 (1983) 127-131.
- [44] E. Mathieu, *Math. Pure Appl. (J. Liouville)*, 13 (1868) 137.
- [45] H.G. Dehmelt, Radiofrequency spectroscopy of stored ions I: Storage, *Adv. At. Mol. Phys.*, 3 (1968) 53-72.
- [46] D.J. Douglas, A.J. Frank, D. Mao, Linear ion traps in mass spectrometry, *Mass Spectrom. Rev.*, 24 (2005) 1-29.
- [47] P.T.A. Reilly, G.F. Brabeck, Mapping the pseudopotential well for all values of the Mathieu parameter q in digital and sinusoidal ion traps, *Int. J. Mass Spectrom.*, 392 (2015) 86-90.

- [48] C. Gao, D.J. Douglas, Can the effective potential of a linear quadrupole be extended to values of the Mathieu parameter q up to 0.90?, *J Am Soc Mass Spectrom*, 24 (2013) 1848-1852.
- [49] J.C. Schwartz, M.W. Senko, J.E. Syka, A two-dimensional quadrupole ion trap mass spectrometer, *J Am Soc Mass Spectr*, 13 (2002) 659-669.
- [50] J.W. Hager, A new linear ion trap mass spectrometer, *Rapid Commun Mass Sp*, 16 (2002) 512-526.
- [51] M.E. Bier, J.E.P. Syka, Ion trap mass spectrometer system and method, in, Finnigan Corporation, United States, 1995.
- [52] E.R. Badman, R. Graham Cooks, Miniature mass analyzers, *J. Mass Spectrom.*, 35 (2000) 659-671.
- [53] J.E. Fulford, R.E. March, R.E. Mather, J.F.J. Todd, R.M. Waldren, The cylindrical ion trap - a theoretical and experimental study, *Can. J. Spectrosc.*, 25 (1980) 85-97.
- [54] E.R. Badman, R.C. Johnson, W.R. Plass, R.G. Cooks, A miniature cylindrical quadrupole ion trap: simulation and experiment, *Anal. Chem.*, 70 (1998) 4896-4901.
- [55] J.M. Wells, E.R. Badman, R.G. Cooks, A quadrupole ion trap with cylindrical geometry operated in the mass-selective instability mode, *Anal. Chem.*, 70 (1998) 438-444.
- [56] G.E. Patterson, A.J. Guymon, L.S. Riter, M. Everly, J. Griep-Raming, B.C. Laughlin, Z. Ouyang, R.G. Cooks, Miniature Cylindrical Ion Trap Mass Spectrometer, *Anal. Chem.*, 74 (2002) 6145-6153.
- [57] W.-W. Lee, C.-H. Oh, P.-S. Kim, M. Yang, K. Song, Characteristics of cylindrical ion trap, *International Journal of Mass Spectrometry*, 230 (2003) 25-31.
- [58] Z. Ouyang, G. Wu, Y. Song, H. Li, W.R. Plass, R.G. Cooks, Rectilinear ion trap: concepts, calculations, and analytical performance of a new mass analyzer, *Anal. Chem.*, 76 (2004) 4595-4605.
- [59] S.A. Lammert, W.R. Plass, C.V. Thompson, M.B. Wise, Design, optimization and initial performance of a toroidal rf ion trap mass spectrometer, *Int. J. Mass Spectrom.*, 212 (2001) 25-40.
- [60] S.A. Lammert, A.A. Rockwood, M. Wang, M.L. Lee, E.D. Lee, S.E. Tolley, J.R. Oliphant, J.L. Jones, R.W. Waite, Miniature toroidal radio frequency ion trap mass analyzer, *J Am Soc Mass Spectr*, 17 (2006) 916-922.
- [61] N. Taylor, D.E. Austin, A simplified toroidal ion trap mass analyzer, *Int. J. Mass Spectrom.*, 321-322 (2012) 25-32.
- [62] J.M. Higgs, D.E. Austin, Simulations of ion motion in toroidal ion traps, *International Journal of Mass Spectrometry*, 363 (2014) 40-51.
- [63] D.E. Austin, M. Wang, S.E. Tolley, J.D. Maas, A.R. Hawkins, A.L. Rockwood, H.D. Tolley, E.D. Lee, M.L. Lee, Halo ion trap mass spectrometer, *Anal. Chem.*, 79 (2007) 2927-2932.
- [64] B.A. Collings, D.J. Douglas, Observation of higher order quadrupole excitation frequencies in a linear ion trap, *J Am Soc Mass Spectr*, 11 (2000) 1016-1022.
- [65] B.A. Collings, M. Sudakov, F.A. Londry, Resonance shifts in the excitation of the $n = 0$, $K = 1$ to 6 quadrupolar resonances for ions confined in a linear ion trap, *J Am Soc Mass Spectr*, 13 (2002) 577-586.
- [66] J. Franzen, The non-linear ion trap. Part 5. Nature of non-linear resonances and resonant ion ejection, *Int. J. Mass Spectrom. Ion Processes*, 130 (1994) 15-40.

- [67] M. Sudakov, Effective potential and the ion axial beat motion near the boundary of the first stable region in a nonlinear ion trap, *Int. J. Mass Spectrom.*, 206 (2001) 27-43.
- [68] Q. Wu, Y. Tian, A. Li, D.E. Austin, Simulations of electrode misalignment effects in two-plate linear ion traps, *International Journal of Mass Spectrometry*, 393 (2015) 52-57.
- [69] W. Xu, W.J. Chappell, R.G. Cooks, Z. Ouyang, Characterization of electrode surface roughness and its impact on ion trap mass analysis, *J Mass Spectrom*, 44 (2009) 353-360.
- [70] X. Huo, F. Tang, J. Chen, X. Zhang, X. Wang, Characterization of the impact of the ejection slit on miniature rectilinear ion trap analysis, *International Journal of Mass Spectrometry*, 399-400 (2016) 44-50.
- [71] M. Chattopadhyay, A.K. Mohanty, Approximate multipole coefficients of RF ion traps as functions of aperture size, *International Journal of Mass Spectrometry*, 295 (2010) 49-59.
- [72] The non-linear ion trap. Part 3. Multipole components in three types of practical ion trap.
- [73] P.H. Dawson, N.R. Whetten, Non-linear resonances in quadrupole mass spectrometers due to imperfect fields. II. the quadrupole mass filter and the monopole mass spectrometer, *Int. J. Mass Spectrom. Ion Phys.*, 3 (1969) 1-12.
- [74] P.H. Dawson, N.R. Whetten, Non-linear resonances in quadrupole mass spectrometers due to imperfect fields I. The quadrupole ion trap, *Int. J. Mass Spectrom. Ion Phys.*, 2 (1969) 45-59.
- [75] W.R. Plass, Theory of dipolar dc excitation and dc tomography in the rf quadrupole ion trap, *Int. J. Mass Spectrom.*, 202 (2000) 175-197.
- [76] C. Weil, J.M. Wells, H. Wollnik, R.G. Cooks, Axial ion motion within the quadrupole ion trap elucidated by dc pulse tomography, *International Journal of Mass Spectrometry*, 194 (2000) 225-234.
- [77] Y. Wang, Z. Huang, Y. Jiang, X. Xiong, Y. Deng, X. Fang, W. Xu, The coupling effects of hexapole and octopole fields in quadrupole ion traps: a theoretical study, *J. Mass Spectrom.*, 48 (2013) 937-944.
- [78] S. Sevugarajan, A.G. Menon, Field imperfection induced axial secular frequency shifts in nonlinear ion traps, *International Journal of Mass Spectrometry*, 189 (1999) 53-61.
- [79] X. Zhou, C. Xiong, S. Zhang, N. Zhang, Z. Nie, Study of nonlinear resonance effect in Paul trap, *J Am Soc Mass Spectrom*, 24 (2013) 794-800.
- [80] C.Q. Xiong, X.Y. Zhou, N. Zhang, L.P. Zhan, Y.T. Chen, Z.X. Nie, Nonlinear Ion Harmonics in the Paul Trap with Added Octopole Field: Theoretical Characterization and New Insight into Nonlinear Resonance Effect, *Journal of the American Society for Mass Spectrometry*, 27 (2016) 344-351.
- [81] J.E. Fulford, D. Nhu-Hoa, R.J. Hughes, R.E. March, R.F. Bonner, G.J. Wong, Radio-frequency mass selective excitation and resonant ejection of ions in a three-dimensional quadrupole ion trap, *J. Vac. Sci. Technol.*, 17 (1980) 829-835.
- [82] J.N. Louris, R.G. Cooks, J.E.P. Syka, P.E. Kelley, G.C. Stafford, J.F.J. Todd, Instrumentation, applications, and energy deposition in quadrupole ion-trap tandem mass-spectrometry, *Anal. Chem.*, 59 (1987) 1677-1685.

- [83] G.C. Stafford, P.E. Kelley, J.E.P. Syka, W.E. Reynolds, J.F.J. Todd, Recent improvements in and analytical applications of advanced ion trap technology, *Int. J. Mass Spectrom. Ion Proc.*, 60 (1984) 85-98.
- [84] M. Splendore, E. Marquette, J. Oppenheimer, C. Huston, G. Wells, A new ion ejection method employing an asymmetric trapping field to improve the mass scanning performance of an electrodynamic ion trap, *Int. J. Mass Spectrom.*, 191 (1999) 129-143.
- [85] A.A. Makarov, Resonance ejection from the Paul trap: a theoretical treatment incorporating a weak octapole field, *Anal. Chem.*, 68 (1996) 4257-4263.
- [86] S. Sevugarajan, A.G. Menon, Frequency perturbation in nonlinear Paul traps: a simulation study of the effect of geometric aberration, space charge, dipolar excitation, and damping on ion axial secular frequency, *International Journal of Mass Spectrometry*, 197 (2000) 263-278.
- [87] J.D. Williams, K.A. Cox, R.G. Cooks, S.A. McLuckey, K.J. Hart, D.E. Goeringer, Resonance ejection ion-trap mass-spectrometry and nonlinear field contributions - the effect of scan direction on mass resolution, *Anal. Chem.*, 66 (1994) 725-729.
- [88] X.-G. Wu, Ion dynamics in non-perfect quadrupole traps, *International Journal of Mass Spectrometry*, 263 (2007) 59-65.
- [89] Q. Dang, F. Xu, X. Huang, X. Fang, R. Wang, C.F. Ding, Linear ion trap with added octopole field component: the property and method, *J Mass Spectrom*, 50 (2015) 1400-1408.
- [90] Y. Wang, X. Zhang, Y. Feng, R. Shao, X. Xiong, X. Fang, Y. Deng, W. Xu, Characterization of geometry deviation effects on ion trap mass analysis: A comparison study, *International Journal of Mass Spectrometry*, 370 (2014) 125-131.
- [91] J.M. Wells, W.R. Plass, G.E. Patterson, Z. Ouyang, E.R. Badman, R.G. Cooks, Chemical Mass Shifts in Ion Trap Mass Spectrometry: Experiments and Simulations, *Anal. Chem.*, 71 (1999) 3405-3415.
- [92] J.M. Wells, W.A. Plass, R.G. Cooks, Control of chemical mass shifts in the quadrupole ion trap through selection of resonance ejection working point and rf scan direction, *Anal. Chem.*, 72 (2000) 2677-2683.
- [93] D. Guo, Y. Wang, X. Xiong, H. Zhang, X. Zhang, T. Yuan, X. Fang, W. Xu, Space charge induced nonlinear effects in quadrupole ion traps, *J Am Soc Mass Spectrom*, 25 (2014) 498-508.
- [94] K.A. Cox, C.D. Cleven, R.G. Cooks, Mass shifts and local space-charge effects observed in the quadrupole ion-trap at higher resolution, *Int. J. Mass Spectrom. Ion Proc.*, 144 (1995) 47-65.
- [95] H. Qiao, C. Gao, D. Mao, N. Kononkov, D.J. Douglas, Space-charge effects with mass-selective axial ejection from a linear quadrupole ion trap, *Rapid Commun Mass Sp*, 25 (2011) 3509-3520.
- [96] P. Mandal, S. Das, D. De Munshi, T. Dutta, M. Mukherjee, Space charge and collective oscillation of ion cloud in a linear Paul trap, *International Journal of Mass Spectrometry*, 364 (2014) 16-20.
- [97] M.J. Charles, S.A. McLuckey, G.L. Glish, Competition between Resonance Ejection and Ion Dissociation during Resonant Excitation in a Quadrupole Ion-Trap, *Journal of the American Society for Mass Spectrometry*, 5 (1994) 1031-1041.

- [98] M.A. Mabud, M.J. Dekrey, R.G. Cooks, Surface-induced dissociation of molecular ions, *Int. J. Mass Spectrom. Ion Processes*, 67 (1985) 285-294.
- [99] J.E. Syka, J.J. Coon, M.J. Schroeder, J. Shabanowitz, D.F. Hunt, Peptide and protein sequence analysis by electron transfer dissociation mass spectrometry, *Proceedings of the National Academy of Sciences of the United States of America*, 101 (2004) 9528-9533.
- [100] J.C. Schwartz, High-q Pulsed Fragmentation In Ion Traps, in: U. States (Ed.), Thermo Finnigan LLC, United States, 2005.
- [101] W.D. Bowers, S.S. Delbert, R.L. Hunter, R.T. McIver, Fragmentation of oligopeptide ions using ultraviolet laser radiation and Fourier transform mass spectrometry, *Journal of the American Chemical Society*, 106 (1984) 7288-7289.
- [102] D.P. Little, J.P. Speir, M.W. Senko, P.B. O'Connor, F.W. McLafferty, Infrared Multiphoton Dissociation of Large Multiply Charged Ions for Biomolecule Sequencing, *Analytical Chemistry*, 66 (1994) 2809-2815.
- [103] B.A. Collings, W.R. Stott, F.A. Londry, Resonant excitation in a low-pressure linear ion trap, *Journal of the American Society for Mass Spectrometry*, 14 (2003) 622-634.
- [104] A.G. Baker, A. Alexander, M.V. Novotny, Narrow-band collisional activation technique for ion trap mass spectrometers, *Anal Chem*, 71 (1999) 2945-2950.
- [105] J.W. Hager, Off-resonance excitation in a linear ion trap, *J Am Soc Mass Spectr*, 20 (2009) 443-450.
- [106] R. Alheit, S. Kleineidam, F. Vedel, M. Vedel, G. Werth, Higher order non-linear resonances in a Paul trap, *Int. J. Mass Spectrom. Ion Processes*, 154 (1996) 155-169.
- [107] X.Z. Chu, M. Holzki, R. Alheit, G. Werth, Observation of high-order motional resonances of an ion cloud in a Paul trap, *Int. J. Mass Spectrom. Ion Processes*, 173 (1998) 107-112.
- [108] J.C. Schwartz, J.N. Louris, Method of detecting ions in an ion trap mass spectrometer, in, Google Patents, 1994.
- [109] D.M. Eades, R.A. Yost, Black Canyons for Ions Stored in an Ion-trap Mass Spectrometer, *Rapid Commun Mass Sp*, 6 (1992) 573-578.
- [110] F. Guidugli, P. Traldi, A Phenomenological Description of a Black Hole for Collisionally Induced Decomposition Products in Ion-trap Mass Spectrometry, *Rapid Commun Mass Sp*, 5 (1991) 343-348.
- [111] K.L. Morand, S.A. Lammert, R.G. Cooks, Concerning 'Black Holes' in Ion-trap Mass Spectrometry, *Rapid Commun Mass Sp*, 5 (2005) 491.
- [112] D.M. Eades, J.V. Johnson, R.A. Yost, Nonlinear resonance effects during ion storage in a quadrupole ion trap, *J Am Soc Mass Spectr*, 4 (1993) 917-929.
- [113] V.M. Doroshenko, R.J. Cotter, Losses of Ions During Forward and Reverse Scans in a Quadrupole Ion Trap Mass Spectrometer and How to Reduce Them, *J Am Soc Mass Spectr*, 8 (1997) 1141-1146.
- [114] D.T. Snyder, C.J. Pulliam, J.S. Wiley, J. Duncan, R.G. Cooks, Experimental characterization of secular frequency scanning in ion trap mass spectrometers, *J Am Soc Mass Spectr*, 27 (2016) 1243-1255.
- [115] S.A. McLuckey, D.E. Goeringer, G.L. Glish, Selective ion isolation/rejection over a broad mass range in the quadrupole ion trap, *J Am Soc Mass Spectr*, 2 (1991) 11-21.

- [116] J.E. Fulford, R.E. March, A new mode of operation for the three-dimensional quadrupole ion store (QUISTOR): The selective ion reactor, *Int. J. Mass Spectrom. Ion Phys.*, 26 (1978) 155-162.
- [117] P.E. Kelley, J.E.P. Syka, P.C. Ceja, G.C. Stafford, J.N. Louris, H.F. Grutzmacher, D. Kuck, J.F.J. Todd, in: *Proceedings of the 34th Conference on Mass Spectrometry and Allied Topics*, Cincinnati, 1986, pp. 963.
- [118] R.E. Kaiser Jr., R.G. Cooks, J.E.P. Syka, G.C. Stafford Jr., Collisionally Activated Dissociation of Peptides Using a Quadrupole Ion-Trap Mass Spectrometer, *Rapid Commun Mass Sp*, 4 (1990) 30-33.
- [119] J.C. Schwartz, I. Jardine, High Resolution Parent-ion Selection/Isolation Using a Quadrupole Ion-trap Mass Spectrometer, *Rapid Commun Mass Sp*, 6 (1992) 313-317.
- [120] F. Vedel, M. Vedel, R.E. March, New schemes for resonant ejection in r.f. quadrupolar ion traps, *Int. J. Mass Spectrom. Ion Processes*, 99 (1990) 125-138.
- [121] D.T. Snyder, R.G. Cooks, Ion isolation and multigenerational collision-induced dissociation using the inverse Mathieu q scan.
- [122] F. Vedel, M. Vedel, R.E. March, A sensitive method for the detection of stored ions by resonant ejection using a wide-band signal, *Int. J. Mass Spectrom. Ion Processes*, 108 (1991) R11-R20.
- [123] L. Chen, A.G. Marchall, Stored waveform simultaneous mass-selective ejection/excitation for Fourier transform ion cyclotron resonance mass spectrometry, *Int. J. Mass Spectrom. Ion. Processes*, 79 (1987) 115-125.
- [124] S. Guan, General phase modulation method for stored waveform inverse Fourier transform excitation for Fourier transform ion cyclotron resonance mass spectrometry, *J. Chem. Phys.*, 91 (1989) 775-777.
- [125] S. Guan, A.G. Marshall, Stored waveform inverse Fourier transform axial excitation/ejection for quadrupole ion trap mass spectrometry, *Anal. Chem.*, 65 (1993) 1288-1294.
- [126] J. Julian, R. K., R.G. Cooks, Broad-Band Excitation in the Quadrupole Ion Trap Mass Spectrometer Using Shaped Pulses Created with the Inverse Fourier Transform, *Anal. Chem.*, 65 (1993) 1827-1833.
- [127] M.H. Soni, R.G. Cooks, Selective Injection and Isolation of Ions in Quadrupole Ion Trap Mass Spectrometry Using Notched Waveforms Created Using the Inverse Fourier Transform, *Anal. Chem.*, 66 (1994) 2488-2496.
- [128] D.T. Snyder, R.G. Cooks, Ion isolation in a linear ion trap using dual resonance frequencies, *J Am Soc Mass Spectr.*
- [129] J.N. Louris, D.M. Taylor, Method and apparatus for ejecting unwanted ions in an ion trap mass spectrometer, in: *Google Patents*, 1994.
- [130] R.T. Hilger, R.E. Santini, C.A. Luongo, B.M. Prentice, S.A. McLuckey, A method for isolating ions in quadrupole ion traps using an excitation waveform generated by frequency modulation and mixing, *Int. J. Mass Spectrom.*, 377 (2015) 329-337.
- [131] D.V. Kenny, P.J. Callahan, S.M. Gordon, S.W. Stiller, Simultaneous Isolation of Two Different m/z Ions in an Ion-trap Mass Spectrometer and their Tandem Mass Spectra Using Filtered-noise Fields, *Rapid Commun Mass Sp*, 7 (1993).

- [132] D.E. Goeringer, K.G. Asano, S.A. McLuckey, D. Hoekman, S.W. Stiller, Filtered Noise Field Signals for Mass-Selective Accumulation of Externally Formed Ions in a Quadrupole Ion-Trap, *Analytical Chemistry*, 66 (1994) 313-318.
- [133] K. Miseki, Ion trap mass spectrometer, in: U. States (Ed.), Shimadzu Corporation, United States, 2002.
- [134] G. Wells, C. Huston, High-Resolution Selected-Ion Monitoring in a Quadrupole Ion-Trap Mass-Spectrometer, *Analytical Chemistry*, 67 (1995) 3650-3655.
- [135] F.L. Brancia, B. McCullough, A. Entwistle, J.G. Grossmann, L. Ding, Digital asymmetric waveform isolation (DAWI) in a digital linear ion trap, *J Am Soc Mass Spectrom*, 21 (2010) 1530-1533.
- [136] R. Singh, V. Jayaram, P.T.A. Reilly, Duty cycle-based isolation in linear quadrupole ion traps, *Int. J. Mass Spectrom.*, 343-344 (2013) 45-49.
- [137] G.F. Brabeck, P.T.A. Reilly, Mapping ion stability in digitally driven ion traps and guides, *International Journal of Mass Spectrometry*, 364 (2014) 1-8.
- [138] G.F. Brabeck, H.J. Chen, N.M. Hoffman, L. Wang, P.T.A. Reilly, Development of MSn in Digitally Operated Linear Ion Guides, *Analytical Chemistry*, 86 (2014) 7757-7763.
- [139] G.F. Brabeck, H. Koizumi, E. Koizumi, P.T.A. Reilly, Characterization of quadrupole mass filters operated with frequency-asymmetric and amplitude-asymmetric waveforms, *International Journal of Mass Spectrometry*, 404 (2016) 8-13.
- [140] P.A. Chrisman, S.J. Pitteri, S.A. McLuckey, Parallel ion parking: improving conversion of parents to first-generation products in electron transfer dissociation, *Anal Chem*, 77 (2005) 3411-3414.
- [141] R.G. Cooks, *Collision Spectroscopy*, Plenum Press, New York and London, 1978.
- [142] Q. Dang, F. Xu, L. Wang, X. Huang, X. Dai, X. Fang, R. Wang, C.F. Ding, Theoretical Study of Dual-Direction Dipolar Excitation of Ions in Linear Ion Traps, *J Am Soc Mass Spectrom*, 27 (2016) 596-606.
- [143] J.C. Schwartz, J.E.P. Syka, S.T. Quarmby, in: *The 53rd ASMS Conference on Mass Spectrometry and Allied Topics*, San Antonio, TX, 2005.
- [144] C. Cunningham, Jr., G.L. Glish, D.J. Burinsky, High amplitude short time excitation: a method to form and detect low mass product ions in a quadrupole ion trap mass spectrometer, *J Am Soc Mass Spectr*, 17 (2006) 81-84.
- [145] J. Murrell, D. Despeyroux, S.A. Lammert, J.L. Stephenson, D.E. Goeringer, "Fast excitation" CID in a quadrupole ion trap mass spectrometer, *J Am Soc Mass Spectr*, 14 (2003) 785-789.
- [146] J. Qin, B.T. Chait, Matrix-assisted laser desorption ion trap mass spectrometry: efficient isolation and effective fragmentation of peptide ions, *Anal. Chem.*, 68 (1996) 2108-2112.
- [147] O.L. Collin, M. Beier, G.P. Jackson, Dynamic collision-induced dissociation of peptides in a quadrupole ion trap mass spectrometer, *Anal. Chem.*, 79 (2007) 5468-5473.
- [148] U.A. Laskay, O.L. Collin, J.J. Hyland, B. Nichol, G.P. Jackson, S.P. Pasilis, D.C. Duckworth, Dynamic collision-induced dissociation (DCID) in a quadrupole ion trap

- using a two-frequency excitation waveform: II. Effects of frequency spacing and scan rate, *J Am Soc Mass Spectr*, 18 (2007) 2017-2025.
- [149] U.A. Laskay, J.J. Hyland, G.P. Jackson, Dynamic collision-induced dissociation (DCID) in a quadrupole ion trap using a two-frequency excitation waveform: I. Effects of excitation frequency and phase angle, *J Am Soc Mass Spectr*, 18 (2007) 749-761.
- [150] U.A. Laskay, G.P. Jackson, Resonance excitation and dynamic collision-induced dissociation in quadrupole ion traps using higher-order excitation frequencies, *Rapid Commun Mass Sp*, 22 (2008) 2342-2348.
- [151] A.R. Dongre, A. Somogyi, V.H. Wysocki, Surface-induced dissociation: an effective tool to probe structure, energetics and fragmentation mechanisms of protonated peptides, *J. Mass Spectrom.*, 31 (1996) 339-350.
- [152] S.A. Lammert, R.G. Cooks, Surface-induced dissociation of molecular ions in a quadrupole ion trap mass spectrometer, *J Am Soc Mass Spectr*, 2 (1991) 487-491.
- [153] B.M. Prentice, R.E. Santini, S.A. McLuckey, Adaptation of a 3-D quadrupole ion trap for dipolar DC collisional activation, *J Am Soc Mass Spectrom*, 22 (2011) 1486-1492.
- [154] B.M. Prentice, S.A. McLuckey, Dipolar DC collisional activation in a "stretched" 3-D ion trap: the effect of higher order fields on rf-heating, *J Am Soc Mass Spectr*, 23 (2012) 736-744.
- [155] L. Wang, F. Xu, C.F. Ding, Dipolar direct current driven collision-induced dissociation in a digital ceramic-based rectilinear ion trap mass spectrometer, *Anal Chem*, 85 (2013) 1271-1275.
- [156] T. Evans-Nguyen, L. Becker, V. Doroshenko, R.J. Cotter, Development of a low power, high mass range mass spectrometer for Mars surface analysis, *Int. J. Mass Spectrom.*, 278 (2008) 170-177.
- [157] J.V. Johnson, R.E. Pedder, R.A. Yost, Ms Ms parent scans on a quadrupole ion trap mass-spectrometer by simultaneous resonant excitation of multiple ions, *Int. J. Mass Spectrom. Ion Processes*, 106 (1991) 197-212.
- [158] D.T. Snyder, C.J. Pulliam, R.G. Cooks, Single analyzer precursor scans using an ion trap, *Rapid Commun Mass Sp*, 30 (2016) 800-804.
- [159] M.H. Sonl, R.G. Cooks, Selective injection and isolation of ions in quadrupole ion trap mass spectrometry using notched waveforms created using the inverse fourier transform, *Anal. Chem.*, 66 (1994) 2488-2496.
- [160] S. Guan, A.G. Marshall, Stored waveform inverse Fourier transform (SWIFT) ion excitation in trapped-ion mass spectrometry - theory and applications, *Int. J. Mass Spectrom. Ion Processes*, 157/158 (1996) 5-37.
- [161] D.T. Snyder, R.G. Cooks, Multigenerational broadband collision-induced dissociation of precursor ions in a linear ion trap, *J Am Soc Mass Spectr*.
- [162] D.T. Snyder, P.W. Fedick, R.G. Cooks, Multigenerational collision-induced dissociation for characterization of organic compounds, *Anal. Chem.*, 88 (2016) 9572-9581.
- [163] L.L. Lopez, P.R. Tiller, M.W. Senko, J.C. Schwartz, Automated strategies for obtaining standardized collisionally induced dissociation spectra on a benchtop ion trap mass spectrometer, *Rapid Commun Mass Sp*, 13 (1999) 663-668.

- [164] L. Ding, M. Sudakov, F.L. Brancia, R. Giles, S. Kumashiro, A digital ion trap mass spectrometer coupled with atmospheric pressure ion sources, *J. Mass Spectrom.*, 39 (2004) 471-484.
- [165] F.X. Xu, L. Wang, X.H. Dai, X. Fang, C.F. Ding, Resonance Activation and Collision-Induced-Dissociation of Ions Using Rectangular Wave Dipolar Potentials in a Digital Ion Trap Mass Spectrometer, *Journal of the American Society for Mass Spectrometry*, 25 (2014) 556-562.
- [166] F.X. Xu, Q.K. Dang, X.H. Dai, X. Fang, Y.Y. Wang, L. Ding, C.F. Ding, Characteristics of Ion Activation and Collision Induced Dissociation Using Digital Ion Trap Technology, *Journal of the American Society for Mass Spectrometry*, 27 (2016) 1351-1356.
- [167] H.F. Wu, J.S. Brodbelt, Effects of collisional cooling on ion detection in a quadrupole ion trap mass-spectrometer, *Int. J. Mass Spectrom. Ion Processes*, 115 (1992) 67-81.
- [168] D.M. Black, A.H. Payne, G.L. Glish, Determination of cooling rates in a quadrupole ion trap, *J Am Soc Mass Spectrom*, 17 (2006) 932-938.
- [169] A.M. Tabert, M.P. Goodwin, R.G. Cooks, Co-occurrence of boundary and resonance ejection in a multiplexed rectilinear ion trap mass spectrometer, *J Am Soc Mass Spectrom*, 17 (2006) 56-59.
- [170] J.C. Schwartz, J.E. Syka, I. Jardine, High resolution on a quadrupole ion trap mass spectrometer, *J Am Soc Mass Spectr*, 2 (1991) 198-204.
- [171] D.E. Goeringer, W.B. Whitten, J.M. Ramsey, S.A. Mcluckey, G.L. Glish, Theory of high-resolution mass-spectrometry achieved via resonance ejection in the quadrupole ion trap, *Anal. Chem.*, 64 (1992) 1434-1439.
- [172] C.G. Yang, M.E. Bier, Investigation of the rapid scan on an electrospray ion trap mass spectrometer, *Anal Chem*, 77 (2005) 1663-1671.
- [173] G. Dobson, J. Murrell, D. Despeyroux, F. Wind, J.C. Tabet, Investigations into the use of a reverse scan in a quadrupole ion trap mass spectrometer, *Rapid Commun Mass Sp*, 17 (2003) 1657-1664.
- [174] V.M. Doroshenko, R.J. Cotter, Linear mass calibration in the quadrupole ion-trap mass-spectrometer, *Rapid Commun Mass Sp*, 8 (1994) 766-776.
- [175] L.A. Gill, J.M. Wells, G.E. Patterson, J.W. Amy, R.G. Cooks, Resolution of isobaric and isomeric ions using chemical shifts in an ion trap mass spectrometer, *Analytical Chemistry*, 70 (1998) 4448-4452.
- [176] J.M. Wells, W.R. Plass, G.E. Patterson, O.Y. Zheng, E.R. Badman, R.G. Cooks, Chemical mass shifts in ion trap mass spectrometry: Experiments and simulations, *Anal. Chem.*, 71 (1999) 3405-3415.
- [177] E.P. Sheretov, O.W. Rozhkov, D.W. Kiryushin, A.E. Malutin, Mass selective instability mode without a light buffer gas, *International Journal of Mass Spectrometry*, 191 (1999) 103-111.
- [178] W. Xu, Q. Song, S.A. Smith, W.J. Chappell, Z. Ouyang, Ion trap mass analysis at high pressure: a theoretical view, *J Am Soc Mass Spectr*, 20 (2009) 2144-2153.
- [179] Q. Song, W. Xu, S.A. Smith, L. Gao, W.J. Chappell, R.G. Cooks, Z. Ouyang, Ion trap mass analysis at high pressure: an experimental characterization, *J. Mass Spectrom.*, 45 (2010) 26-34.

- [180] W.B. Whitten, P.T. Reilly, J.M. Ramsey, High-pressure ion trap mass spectrometry, *Rapid Commun Mass Sp*, 18 (2004) 1749-1752.
- [181] K.H. Blakeman, D. Wolfe, C. Cavanaugh, J.M. Ramsey, High pressure mass spectrometry: The generation of mass spectra at operating pressures exceeding 1 torr in a microscale cylindrical ion trap, *Anal. Chem.*, 88 (2016) 5378-5384.
- [182] A.N. Kotana, A.K. Mohanty, A modified auxiliary excitation signal for achieving unidirectional ion ejection in quadrupole ion trap mass spectrometers operating in the resonance ejection mode, *International Journal of Mass Spectrometry*, 386 (2015) 15-23.
- [183] F.A. Londry, J.W. Hager, Mass selective axial ion ejection from a linear quadrupole ion trap, *Journal of the American Society for Mass Spectrometry*, 14 (2003) 1130-1147.
- [184] M. Guna, T.A. Biesenthal, Performance enhancements of mass selective axial ejection from a linear ion trap, *J Am Soc Mass Spectrom*, 20 (2009) 1132-1140.
- [185] M. Sugiyama, H. Hasegawa, Y. Hashimoto, Mass-selective axial ejection from a linear ion trap with a direct current extraction field, *Rapid Commun Mass Spectrom*, 23 (2009) 2917-2922.
- [186] A. Moradian, D.J. Douglas, Mass selective axial ion ejection from linear quadrupoles with added octopole fields, *J Am Soc Mass Spectrom*, 19 (2008) 270-280.
- [187] R.E. Kaiser, J.N. Louris, J.W. Amy, R.G. Cooks, Extending the mass range of the quadrupole ion trap using axial modulation, *Rapid Commun Mass Sp*, 3 (1989) 225-229.
- [188] R.E. Kaiser, R.G. Cooks, G.C. Stafford, J.E.P. Syka, P.H. Hemberger, Operation of a quadrupole ion trap mass-spectrometer to achieve high mass charge ratios, *Int. J. Mass Spectrom. Ion Proc.*, 106 (1991) 79-115.
- [189] C.S. Creaser, J.W. Stygall, A comparison of overtone and fundamental resonances for mass range extension by resonance ejection in a quadrupole ion trap mass spectrometer, *International Journal of Mass Spectrometry*, 191 (1999) 145-151.
- [190] J. Franzen, R. Gabling, G. Heinen, G. Weiss, Method of mass analyzing a sample by use of a quistor, in, *The United States of America as represented by the Secretary of the Army, U.S.*, 1989.
- [191] J. Moxom, P.T. Reilly, W.B. Whitten, J.M. Ramsey, Double resonance ejection in a micro ion trap mass spectrometer, *Rapid Commun Mass Sp*, 16 (2002) 755-760.
- [192] J. Franzen, The non-linear ion trap. Part 4. Mass selective instability scan with multipole superposition, *Int. J. Mass Spectrom. Ion Processes*, 125 (1993) 165-170.
- [193] V.M. Doroshenko, R.J. Cotter, Effect of phase locking AC and RF voltages for high mass analysis in a quadrupole ion trap mass spectrometer, *Rapid Commun Mass Sp*, 10 (1996) 1921-1926.
- [194] D.T. Snyder, R.G. Cooks, Successive resonances for ion ejection at arbitrary frequencies in an ion trap.
- [195] F.A. Londry, R.E. March, Systematic Factors Affecting High Mass-Resolution and Accurate Mass Assignment in a Quadrupole Ion-Trap, *International Journal of Mass Spectrometry and Ion Processes*, 144 (1995) 87-103.

- [196] E.X. Chen, M. Gehm, R. Danell, M. Wells, J.T. Glass, D. Brady, Compressive mass analysis on quadrupole ion trap systems, *J Am Soc Mass Spectr*, 25 (2014) 1295-1304.
- [197] X. Zhang, Y. Wang, L. Hu, D. Guo, X. Fang, M. Zhou, W. Xu, Reducing space charge effects in a linear ion trap by rhombic ion excitation and ejection, *J Am Soc Mass Spectr*, 27 (2016) 1256-1262.
- [198] B. Landais, C. Beaugrand, L. Capron-Dukan, M. Sablier, G. Simonneau, C. Rolando, Varying the radio frequency: a new scanning mode for quadrupole analyzers, *Rapid Commun Mass Sp*, 12 (1998) 302-306.
- [199] L. Ding, M. Sudakov, S. Kumashiro, A simulation study of the digital ion trap mass spectrometer, *Int. J. Mass Spectrom.*, 221 (2002) 117-138.
- [200] Z. Nie, F. Cui, M. Chu, C.-H. Chen, H.-C. Chang, Y. Cai, Calibration of a frequency-scan quadrupole ion trap mass spectrometer for microparticle mass analysis, *Int. J. Mass Spectrom.*, 270 (2008) 8-15.
- [201] Y. Cai, W.P. Peng, S.J. Kuo, H.C. Chang, Calibration of an audio-frequency ion trap mass spectrometer, *Int. J. Mass Spectrom.*, 214 (2002) 63-73.
- [202] W.P. Peng, Y. Cai, Y.T. Lee, H.C. Chang, Laser-induced fluorescence/ion trap as a detector for mass spectrometric analysis of nanoparticles, *Int. J. Mass Spectrom.*, 229 (2003) 67-76.
- [203] I.C. Lu, J.L. Lin, S.H. Lai, C.H. Chen, Frequency-scanning MALDI linear ion trap mass spectrometer for large biomolecular ion detection, *Anal. Chem.*, 83 (2011) 8273-8277.
- [204] U.P. Schlunegger, M. Stoeckli, R.M. Caprioli, Frequency scan for the analysis of high mass ions generated by matrix-assisted laser desorption/ionization in a Paul trap, *Rapid Commun Mass Sp*, 13 (1999) 1792-1796.
- [205] Z. Zhu, C. Xiong, G. Xu, H. Liu, X. Zhou, R. Chen, W.P. Peng, Z. Nie, Characterization of bioparticles using a miniature cylindrical ion trap mass spectrometer operated at rough vacuum, *Analyst*, 136 (2011) 1305-1309.
- [206] L. Ding, S. Kumashiro, Ion motion in the rectangular wave quadrupole field and digital operation mode of a quadrupole ion trap mass spectrometer, *Rapid Commun Mass Sp*, 20 (2006) 3-8.
- [207] A. Berton, P. Traldi, L. Ding, F.L. Brancia, Mapping the stability diagram of a digital ion trap (DIT) mass spectrometer varying the duty cycle of the trapping rectangular waveform, *J Am Soc Mass Spectrom*, 19 (2008) 620-625.
- [208] D. Wang, F.H. van Amerom, T. Evans-Nguyen, High-speed digital frequency scanning ion trap mass spectrometry, *Anal. Chem.*, 85 (2013) 10935-10940.
- [209] B. Xue, L. Ma, L. Sun, W. Gao, P. Cheng, L. Ding, Z. Huang, Z. Zhou, Resonance ejection mass scan using dipole excitation with a non-integer frequency ratio in a digital linear ion trap mass spectrometer, *Rapid Commun Mass Sp*, 30 (2016) 1985-1990.
- [210] E.R. Badman, R.G. Cooks, Cylindrical ion trap array with mass selection by variation in trap dimensions, *Anal. Chem.*, 72 (2000) 5079-5086.
- [211] B.M. Prentice, S.A. McLuckey, Analysis of high mass-to-charge ions in a quadrupole ion trap mass spectrometer via an end-cap quadrupolar direct current downscan, *Anal Chem*, 84 (2012) 7562-7569.

- [212] J.F.J. Todd, A.D. Penman, R.D. Smith, Some Alternative Scanning Methods for the Ion Trap Mass-Spectrometer, *International Journal of Mass Spectrometry and Ion Processes*, 106 (1991) 117-135.
- [213] D.T. Snyder, C.J. Pulliam, R.G. Cooks, Calibration procedure for secular frequency scanning in an ion trap, *Rapid Commun Mass Sp*, 30 (2016) 1190-1196.
- [214] D.T. Snyder, C.J. Pulliam, R.G. Cooks, Linear mass scans in quadrupole ion traps using the inverse Mathieu q scan, *Rapid Commun Mass Sp*, 30 (2016) 2369-2378.
- [215] D.T. Snyder, C.J. Pulliam, R.G. Cooks, Extending the mass range of a miniature mass spectrometer using the inverse Mathieu q scan.
- [216] C. Zhang, H. Chen, A.J. Guymon, G. Wu, R.G. Cooks, Z. Ouyang, Instrumentation and methods for ion and reaction monitoring using a non-scanning rectilinear ion trap, *International Journal of Mass Spectrometry*, 255-256 (2006) 1-10.
- [217] B. Brkić, S. Giannoukos, N. France, R. Murcott, F. Siviero, S. Taylor, Optimized DLP linear ion trap for a portable non-scanning mass spectrometer, *International Journal of Mass Spectrometry*, 369 (2014) 30-35.
- [218] A. Janulyte, Y. Zerega, J. Andre, B. Brkic, S. Taylor, Performance Assessment of a Portable Mass Spectrometer Using a Linear Ion Trap Operated in Non-Scanning Mode, *Rapid Commun Mass Spectrom*, (2016).
- [219] W.H. Benner, A gated electrostatic ion trap to repetitiously measure the charge and m/z of large electrospray ions, *Analytical Chemistry*, 69 (1997) 4162-4168.
- [220] D.Z. Keifer, D.L. Shinholt, M.F. Jarrold, Charge Detection Mass Spectrometry with Almost Perfect Charge Accuracy, *Anal Chem*, 87 (2015) 10330-10337.
- [221] W.P. Peng, H.C. Lin, H.H. Lin, M. Chu, A.L. Yu, H.C. Chang, C.H. Chen, Charge-monitoring laser-induced acoustic desorption mass spectrometry for cell and microparticle mass distribution measurement, *Angew Chem Int Edit*, 46 (2007) 3865-3869.
- [222] W.P. Peng, H.C. Lin, M.L. Chu, H.C. Chang, N.H. Lin, A.L. Yu, C.H. Chen, Charge monitoring cell mass spectrometry, *Anal. Chem.*, 80 (2008) 2524-2530.
- [223] W.-P. Peng, S.-W. Chou, A.A. Patil, Measuring masses of large biomolecules and bioparticles using mass spectrometric techniques, *Analyst*, 139 (2014) 3507-3523.
- [224] M. Soni, V. Frankevich, M. Nappi, R.E. Santini, J.W. Amy, R.G. Cooks, Broad-Band Fourier Transform Quadrupole Ion Trap Mass Spectrometry, *Anal. Chem.*, 68 (1996) 3314-3320.
- [225] A.G. Marshall, C.L. Hendrickson, G.S. Jackson, Fourier transform ion cyclotron resonance mass spectrometry: A primer, *Mass Spectrometry Reviews*, 17 (1998) 1-35.
- [226] R.H. Perry, R.G. Cooks, R.J. Noll, Orbitrap mass spectrometry: Instrumentation, ion motion and applications, *Mass Spectrometry Reviews*, 27 (2008) 661-699.
- [227] M. Soni, V. Frankevich, M. Nappi, R.E. Santini, J.W. Amy, R.G. Cooks, Broad-Band Fourier Transform Quadrupole Ion Trap Mass Spectrometry, *Anal. Chem.*, 68 (1996) 3314-3320.
- [228] S.D. Fuerstenau, W.H. Benner, J.J. Thomas, C. Brugidou, B. Bothner, G. Siuzdak, Mass spectrometry of an intact virus, *Angew Chem Int Edit*, 40 (2001) 542-544.

- [229] Z. Nie, F. Cui, Y.K. Tzeng, H.C. Chang, M. Chu, H.C. Lin, C.H. Chen, H.H. Lin, A.L. Yu, High-speed mass analysis of whole erythrocytes by charge-detection quadrupole ion trap mass spectrometry, *Anal. Chem.*, 79 (2007) 7401-7407.
- [230] Z. Nie, F. Cui, M. Chu, C.H. Chen, H.C. Chang, Y. Cai, Calibration of a frequency-scan quadrupole ion trap mass spectrometer for microparticle mass analysis, *International Journal of Mass Spectrometry*, 270 (2008) 8-15.
- [231] S.-W. Chou, G.-R. Shiu, H.-C. Chang, W.-P. Peng, Wavelet-Based Method for Time-Domain Noise Analysis and Reduction in a Frequency-Scan Ion Trap Mass Spectrometer, *Journal of The American Society for Mass Spectrometry*, 23 (2012) 1855-1864.
- [232] S. Guan, A.G. Marshall, Stored waveform inverse Fourier transform axial excitation/ejection for quadrupole ion trap mass spectrometry, *Anal. Chem.*, 65 (1993) 1288-1294.
- [233] S. Guan, A.G. Marshall, Stored waveform inverse Fourier transform (SWIFT) ion excitation in trapped-ion mass spectrometry: Theory and applications, *International Journal of Mass Spectrometry and Ion Processes*, 157 (1996) 5-37.
- [234] M. Nappi, V. Frankevich, M. Soni, R.G. Cooks, Characteristics of a broad-band Fourier transform ion trap mass spectrometer, *International Journal of Mass Spectrometry*, 177 (1998) 91-104.
- [235] N.L. Kelleher, M.W. Senko, M.M. Siegel, F.W. McLafferty, Unit resolution mass spectra of 112 kDa molecules with 3 Da accuracy, *Journal of the American Society for Mass Spectrometry*, 8 (1997) 380-383.
- [236] A. Makarov, Electrostatic Axially Harmonic Orbital Trapping: A High-Performance Technique of Mass Analysis, *Anal. Chem.*, 72 (2000) 1156-1162.
- [237] M. Hardman, A.A. Makarov, Interfacing the Orbitrap Mass Analyzer to an Electrospray Ion Source, *Anal. Chem.*, 75 (2003) 1699-1705.
- [238] A. Makarov, E. Denisov, A. Kholomeev, W. Balschun, O. Lange, K. Strupat, S. Horning, Performance Evaluation of a Hybrid Linear Ion Trap/Orbitrap Mass Spectrometer, *Anal. Chem.*, 78 (2006) 2113-2120.
- [239] C. Köster, Twin Trap or Hyphenation of a 3D Paul- and a Cassinian Ion Trap, *Journal of The American Society for Mass Spectrometry*, 26 (2015) 390-396.
- [240] C. Köster, The concept of electrostatic non-orbital harmonic ion trapping, *International Journal of Mass Spectrometry*, 287 (2009) 114-118.
- [241] Q. Hu, A.A. Makarov, R.G. Cooks, R.J. Noll, Resonant ac Dipolar Excitation for Ion Motion Control in the Orbitrap Mass Analyzer, *The Journal of Physical Chemistry A*, 110 (2006) 2682-2689.
- [242] Q. Hu, R.G. Cooks, R.J. Noll, Phase-enhanced selective ion ejection in an orbitrap mass spectrometer, *Journal of the American Society for Mass Spectrometry*, 18 (2007) 980-983.
- [243] R.H. Perry, Q. Hu, G.A. Salazar, R.G. Cooks, R.J. Noll, Rephasing ion packets in the orbitrap mass analyzer to improve resolution and peak shape, *Journal of the American Society for Mass Spectrometry*, 20 (2009) 1397-1404.
- [244] M.E. Belov, E. Damoc, E. Denisov, P.D. Compton, S. Horning, A.A. Makarov, N.L. Kelleher, From Protein Complexes to Subunit Backbone Fragments: A Multi-stage Approach to Native Mass Spectrometry, *Anal. Chem.*, 85 (2013) 11163-11173.

- [245] S. Rosati, R.J. Rose, N.J. Thompson, E. van Duijn, E. Damoc, E. Denisov, A. Makarov, A.J.R. Heck, Exploring an Orbitrap Analyzer for the Characterization of Intact Antibodies by Native Mass Spectrometry, *Angewandte Chemie International Edition*, 51 (2012) 12992-12996.
- [246] J.J. Barroso, M.O. Terra, Beam transport in a quadrupole electrostatic system, *Brazilian Journal of Physics*, 34 (2004) 1598-1601.
- [247] Y. Wang, J. Franzen, K.P. Wanczek, The non-linear resonance ion trap. Part 2. A general theoretical analysis, *Int. J. Mass Spectrom. Ion Processes*, 124 (1993) 125-144.
- [248] D.T. Snyder, C.J. Pulliam, Z. Ouyang, R.G. Cooks, Miniature and fieldable mass spectrometers: Recent advances, *Anal. Chem.*, 88 (2016) 2-29.
- [249] R.K. Julian, R.G. Cooks, Broad-band excitation in the quadrupole ion-trap mass-spectrometer using shaped pulses created with the inverse fourier-transform, *Anal. Chem.*, 65 (1993) 1827-1833.

Figures

Figure 1: (a) Cross-section of quadrupole rods and equipotential contours created by a quadrupole potential [246], (b) Mathieu stability diagram with iso- β (i.e. β_r and β_z) and nonlinear resonance lines [247], and (c) pseudopotential well depth in r and z directions in a 3D quadrupole ion trap (SIT = sinusoidal ion trap) [47].

Figure 2: Evolution of ion trap mass analyzers. Adapted from ref. [248].

Figure 3: Frequency domain analysis of ions in (a) pure quadrupole field, (b) quadrupole field with 20% hexapole field superposition, and (c) quadrupole field with 20% octopole field superposition [66].

Figure 4: Effect of higher order fields on ion trap operation: (a) ion motion frequency shift with added hexapole and octopole fields [77], (b) effect of frequency shift on sensitivity and resolution in forward (top) and reverse (bottom) resonance ejection [87], (c) resolution as a function of electrode angular displacement (inducing nonlinear fields) [90], (d) chemical mass shift as a function of trap radius (i.e. higher-order field contribution) [176], (e) intensity of product ion m/z 111 produced from collision-induced dissociation of 1,2-dichlorobenzene as a function of the product ion's q_u value, indicating loss of product ions at nonlinear resonance

points [111], and (f) blank intensity profile for m/z 284 when placed on a nonlinear resonance line, observed using a secular frequency scan [114].

Figure 5: Methods of isolation in a quadrupole ion trap: (a) and (b) synthesis of SWIFT waveform and conversion from frequency domain to time domain [249], (c) broadband excitation with frequency modulation and mixing [130], (d) filtered noise field frequency spectrum [132], (e) and (f) isolation in a digital ion trap using digital asymmetric waveforms [135].

Figure 6: Methods of activation in a quadrupole ion trap: (a) conventional resonance excitation compared to (d) "fast excitation" CID [145], (b) simulation of ion temperature with rhombic (dual direction) ion excitation (red) compared to single direction excitation (blue) [142], (c) pulsed Q dissociation [100, 143], (e) dynamic collision-induced dissociation excitation waveform from superposition of

171 and 172 kHz [149], and (f) multigenerational collision-induced dissociation (Wideband Activation) [162].

Figure 7: Methods of ion ejection in quadrupole ion traps: (a) resonance ejection and (b) compressive mass spectrometry [196], (c) double and (d) triple resonance ejection [84], (e) mass spectrum from resonance ejection with inset ion motion [197], and (f) mass spectrum from rhombic ejection with inset ion motion [197].

Figure 8: Image charge detection (induced voltages): a) schematic diagram of the gated electrostatic ion trap [219]; b) charge detection mass spectrometry, inset a) time domain signal, inset b) Fourier transform of time domain, giving ion frequencies of motion and hence m/z [220]; c) experimental setup of charge detection quadrupole ion trap mass spectrometer with laser-induced acoustic desorption source [221].

Figure 9: Image charge detection (induced currents): a) the time domain signal and background transients (A, B) and their FFTs (C, D) in a quadrupole ion trap [224]; b) incoherent ion cyclotron orbital motion (top left) is converted to coherent motion (top right) by the application of a rotating electric field and at the ICR frequency of the ions of a given m/z value. The electronic circuitry is shown in the bottom diagram [225]; c) a resonant ac waveform applied 180° with respect to ion oscillation, inset (a) schematic depiction of outer electrode polarity required to achieve 180° phase relative to a positive ion by SIMION. The outer electrode is split at the equator, the central plane in the Orbitrap ($z = 0$), inset (b) SIMION simulation results for axial position vs. time for a single ion undergoing resonant ac excitation. Inset (c) ITSIM simulation results of peak intensity as a function of number of cycles of applied ac for a single ion system [241].