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A method for isolating ions in quadrupole ion traps using an excitation waveform generated by frequency modulation and mixing

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ABSTRACT

We describe a new method for isolating ions in quadrupole ion traps using an excitation waveform generated by mixing a broadband waveform generated by frequency modulation (FM) with a sine-wave at the secular frequency of the ion to be isolated. In terms of resolution and efficiency, the mixed FM method exhibits performance nearly identical to isolation using the apex of the Mathieu stability diagram. A disadvantage of the mixed FM method is that isolations require additional time relative to apex-based methods. This disadvantage is shared by other methods that involve application of multi-frequency waveforms such as stored waveform inverse Fourier transform (SWIFT). An advantage of the mixed FM technique (also shared with other tailored waveform approaches), is applicability to a much larger m/z range than apex-based methods. Indeed, the mixed FM technique performs identically to SWIFT in many respects. While the mixed FM technique is not nearly as flexible as SWIFT in terms of the frequency content of the generated waveforms, the mixed FM technique is much simpler to implement as it requires only two function generators and a frequency mixer. Tuning important parameters of the waveform such as notch frequency, notch width, and excitation bandwidth is also facilitated with the mixed FM technique.

1. Introduction

Tandem mass spectrometry [1] (MS/MS) is the process of isolating precursor ions of a specific mass-to-charge ratio (m/z), subjecting them to some physiochemical process (e.g., collision induced dissociation, electron transfer dissociation), and measuring the masses of the product ions. MS/MS is extensively used because it allows for identification and structural characterization of analytes using mass spectrometry. MS/MS also increases specificity and improves detection limits because of the reduction in chemical noise that results when monitoring product ions. Isolation is a critical step in any MS/MS workflow as it ensures that product ions are generated from the desired precursor ion. An ideal isolation method preserves all of the target precursor ions and removes all of the untargeted ions. The extent to which these things are possible depends on many factors, such as the difference in m/z between the target ion and the untargeted ion(s), the abundance of the target ion relative to the untargeted ion(s), the available time, and, of course, the isolation method.

Presently, the most extensively used ion isolation device in tandem mass spectrometry is the quadrupole mass filter [2]. Linear quadrupoles are also widely used as ion guides and as collision cells in many tandem mass spectrometer platforms. A linear quadrupole can be used to isolate ions in several ways. For example, mass filtering can be effected by appropriate application of radio frequency (RF) and DC potentials to the four rods. In this configuration, the range of m/z that is transmitted by the quadrupole can be reduced to only those ions with m/z values that fall within the tip of the Mathieu stability diagram. Ions with m/z values outside the stable range are said to be ‘filtered’ out with the low m/z and high m/z ions being ejected in orthogonal directions.

A disadvantage of the quadrupole mass filter is that, as the nominally stable m/z range is decreased (i.e., resolution is increased by approaching the tip of the stability diagram more closely), the acceptance of the device for successful transmission decreases. Since incoming ions enter the device with a range of energies, positions, and angles, the decreased acceptance results in decreased transmission efficiency even for theoretically stable ions. One way to circumvent this problem is to trap and cool the

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ions in the quadrupole operated in the RF-only mode before applying the DC potentials that raise the precursor ions to the apex of the stability diagram. We refer to this process as apex isolation [3]. The cooling narrows the position and velocity distributions such that fewer precursor ions are lost upon isolation. A disadvantage of apex isolation is that the trapping and cooling process requires more time than simply passing the ions through a quadrupole mass filter.

After the ions have been trapped and cooled in a quadrupole, several methods other than apex isolation can be used to isolate a precursor ion. These methods exploit the fact that, under these conditions, ions have m/z dependent resonant frequencies. Ions can therefore be selectively removed from the trap by applying a sinusoidal signal at the appropriate frequency across one pair of rods. Isolation can be performed by applying signals at all frequencies except for a narrow band centered on the resonant frequency of the target precursor ion. This scenario can be realized by passing a broadband waveform through a bandpass filter, which has been shown to be effective for isolating ions in a three-dimensional ion trap [4,5]. An alternative approach for generating a tailored waveform for ion isolation is the method of stored waveform inverse Fourier transform (SWIFT) [6,7]. In this method, a waveform consisting of a series of discreet signals, closely spaced in frequency, is defined in the frequency domain. Signals with frequencies nearby the ion to be isolated are removed in order to create a notch. The resulting frequency domain waveform is then inverse Fourier transformed, creating a time domain waveform that can be played back using an arbitrary waveform generator. SWIFT provides greater flexibility than the use of a broad-band waveform with a single frequency filter. For example, with SWIFT, multiple notches can be defined, allowing for simultaneous isolation at multiple m/z values. However, SWIFT requires relatively specialized equipment including software for defining the waveforms in the frequency domain and performing the inverse Fourier transform. Such software typically includes algorithms for optimizing the phases of the frequency components such that output power is maximized. The software must also be coupled to an arbitrary waveform generator used to play back the waveforms. Additionally, fine tuning of the SWIFT waveform can only be performed in the software. After each step of fine tuning, the waveform must be recompiled, inverse Fourier transformed, and downloaded to the arbitrary waveform generator for playback. Below we describe a method for isolation of ions trapped in a quadrupole that produces results similar to SWIFT, and, although it is less flexible (e.g., cannot define multiple notches), it is more straightforward to implement and fine tuning is as simple as turning a knob.

A waveform containing signals at multiple, closely-spaced frequencies can also be created using frequency modulation (FM). If a sinusoidal carrier signal with frequency f_c is modulated such that its frequency varies from $f_c - f_d$ to $f_c + f_d$ (f_d is called the frequency deviation) by a sinusoid with frequency f_m (the modulation frequency), the result is a waveform containing signals at intervals of f_m covering the frequency range $f_c - f_d$ to $f_c + f_d$. In order to create a notched waveform suitable for ion isolation, the FM signal is multiplied by another sinusoid with frequency f_n using a frequency mixer. When two signals (frequencies f_1 and f_2) are multiplied using a frequency mixer, the output is a waveform containing components at frequencies $f_1 + f_2$ and $f_1 - f_2$. When the FM signal is multiplied by f_n in this manner, the result is a waveform containing two frequency sidebands. The lower sideband contains signals at intervals of f_m spanning the frequency range $f_n - (f_c + f_d)$ to $f_n - (f_c - f_d)$. The upper sideband contains signals at intervals of f_m spanning the frequency range $f_n + (f_c - f_d)$ to $f_n + (f_c + f_d)$. The region between the two sidebands is the notch, and exists between $f_n + (f_c - f_d)$ and $f_n + (f_c + f_d)$. Fig. 1 illustrates the waveform generation process using hypothetical values for the various frequencies and Fig. 2 shows a frequency spectrum of an actual waveform generated by our apparatus.

The above discussion reveals several important points. The waveform is centered on f_n. The bandwidth covered by the waveform is $2(f_c + f_d)$. The width of the notch (also centered on f_n) is

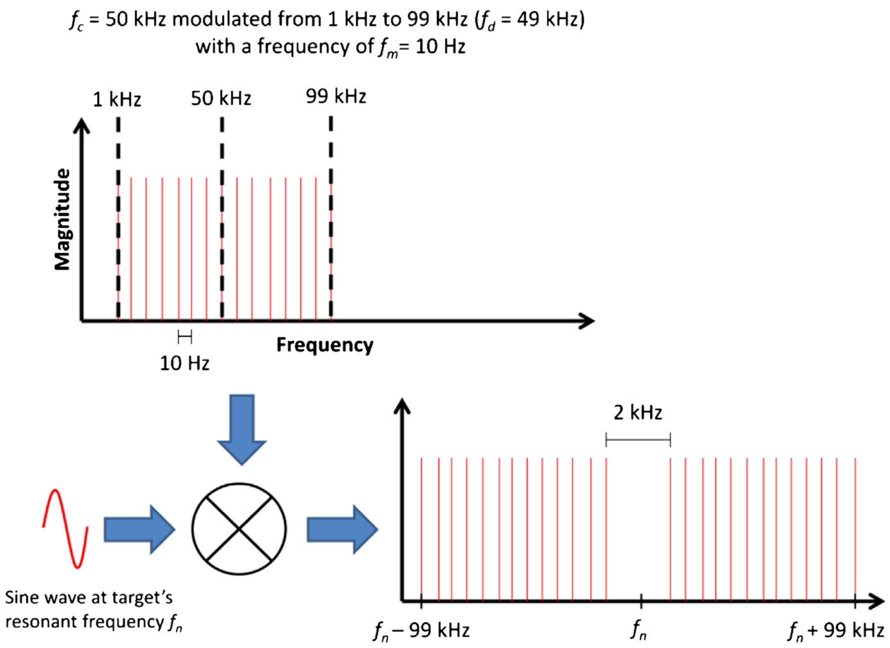

Fig. 1. Cartoon illustrating generation of a notched broadband waveform using the mixed FM technique. The internal FM function of a function generator is used to produce a broadband waveform containing signals every 10 Hz over the range 1–99 kHz. This waveform is then mixed with a sine wave at frequency f_n to produce a waveform with bands on either side of a 2 kHz wide notch.