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Reprint of "Enhanced Fourier transform for Orbitrap mass spectrometry"☆

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ABSTRACT

A novel method for processing of periodic signals, which combines absorption spectra presentation with magnitude spectra and finite-impulse-response filtering, is applied to image current transients acquired in Orbitrap mass spectrometry. Phasing of signal for absorption spectra is facilitated by the excitation-by-injection mechanism of forming coherent ion packets in the Orbitrap analyzer. In conjunction with extensive refinement of the trap and electronics design of the Orbitrap analyzer, this method allows completion of the excitation process and initiation of detection within a fraction of a millisecond after ejection of ions from an external storage device into the Orbitrap analyzer, thus avoiding baseline roll and large non-linear phase corrections. For most real-life analytes with limited signal decay over acquisition time, the method achieves a 2-fold increase of resolving power relative to the traditional Fourier transform processing method. For rapidly decaying signals of intact proteins, the relative increase in resolving power is reduced to about 1.4, which accords with theory. Peak shape and mass accuracy in LC/MS measurements obtained employing the novel method appear to be similar to those observed in traditional magnitude-mode FT spectra. Performance of the method was optimized using calibration mixtures and tested on different real-life samples, including complex peptide mixtures and proteins supplied to the mass spectrometer in infusion and LC/MS modes.

1. Introduction

This article is intended to serve as a bridge from the radiofrequency quadrupole technology so succinctly reviewed by Ray March and John Todd in the beginning of this special issue, to Orbitrap™ technology, which is heavily reliant on the former and at the same time markedly distinct in its principle of operation. Orbitrap technology combines orbital trapping with image current detection. The Orbitrap analyzer is the youngest among major mass analysis technologies; nevertheless, it also celebrates a small jubilee this year: 15 years since the first public presentation of its proof of principle [1]. Since then, thousands of instruments of this type have been produced and have become a common sight in laboratories around the globe, with rapidly changing succession of instrument generations providing ever increasing performance and uptime.

So, it seemed to be very appropriate that this issue will be devoted to the so-called enhanced Fourier transform (eFT™) technique, which became one of the key performance enablers in the latest representatives of three instrument families: LTQ Orbitrap™, Orbitrap Fusion™ and (Q) Exactive™ mass spectrometers. Allowing a doubling of acquisition speed for the same setting of resolving power relative to conventional processing methods, this signal processing technique drastically improved matching of acquisition times to the narrow peak widths associated with progressively faster chromatographic separation, and opened new real-world applications for Orbitrap mass spectrometry. As will be shown below, realization of its potential also required making appropriate changes to the instrumentation hardware and electronics.

Image current detection provides a time-domain transient from the output of a differential amplifier. Subsequent Fourier transformation (FT) of the time-domain transient provides a complex value for each point in the frequency domain (a complex spectrum). Complex values are usually represented as pairs of magnitude and phase or as real (Re) and imaginary (Im) components.

By making use of the phase information, an "absorption" spectrum and a "dispersion" spectrum can be calculated from the real

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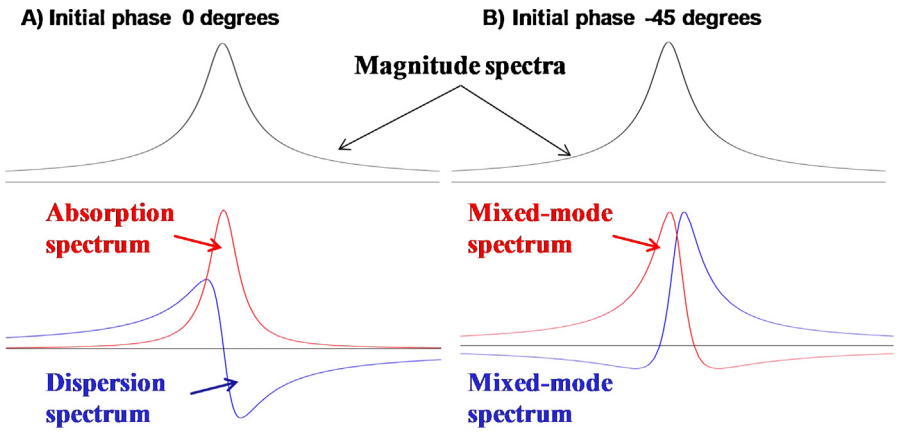

Fig. 1. (A) Absorption and dispersion spectra resulting from Fourier transformation when signal phase is 0° at the start of the transient (i.e., pure cosine), and (B) mixed-mode spectra resulting from FT when signal phase is −45° at the start of the transient [2–4]. In both cases, a transient with a substantial exponential decay was chosen in order to minimize Gibbs oscillations [4].

component and the imaginary part of the spectrum [2–4]. However, in general, real and imaginary components produce asymmetric peak shapes, except for special cases, e.g., when the phase of that peak is zero (Fig. 1). Data systems for Fourier transform mass spectrometry (FTMS) have, therefore, largely neglected the phases and used for broad mass ranges the so-called "magnitude" spectrum given by the following:

$$M(p) = \sqrt{\mathrm{Re}(p)^2 + \mathrm{Im}(p)^2} \quad (1)$$

where $M(p)$ is the magnitude value at a point p in the frequency (f) domain; Re(p) is the real component from the Fourier transformation at the point p; and Im(p) is the imaginary component from the Fourier transformation at the point p. The m/z value can be derived from the frequency f. The use of the magnitude spectrum, which amounts to disregarding the phase information, yields symmetrical peaks in frequency and mass spectra but suffers from reduced resolving power compared to the pure absorption spectrum, by a factor of between 1.4 and 2 [2]. Additional broadening of peaks may arise from further processing of spectra such as apodization, (i.e., windowing) of the transient. Apodization is commonly used as an adaptation to the finite transient measuring time, which would otherwise deteriorate the peak shape [4].

Since the early days of FTMS, researchers have been drawn to the promise of substantial resolution enhancement from correct phasing of the signal and subsequent use of absorption spectrum [5]. This proved to be a real challenge in Fourier transform ion cyclotron resonance (FTICR) mass spectrometers (the only FTMS instruments available prior to the introduction of the Orbitrap analyzer), which require excitation of ions prior to their detection. Such temporal separation of excitation and detection causes the starting phase to depend strongly on m/z [2] and results in baseline roll and other forms of spectral leakage. Phase errors then translate into mass and intensity errors. Recent improvements of ICR cells allow simultaneous excitation and detection by elaborate electronic design (e.g. capacitive nulling as exemplified in [3]) which appears to be difficult in practice. Alternatively, more elaborate phasing algorithms could be used when a large number of mass peaks are available for calibration [5–8].

2. Methods

2.1. Synchronization of ions in Orbitrap analyzers

Orbitrap mass spectrometers differ fundamentally from most FTICR mass spectrometers by their built-in excitation-by-injection mechanism [9]. In short, a quasi-continuous ion beam enters a gas-filled C-trap (an ion trap composed of rod electrodes curved concavely toward the Orbitrap entrance, depicted in Fig. 2), where ions collide with bath gas, lose energy and are stored. After the RF voltage applied to the C-trap electrodes is ramped down, a radial DC potential is applied across the electrodes, and ions are ejected

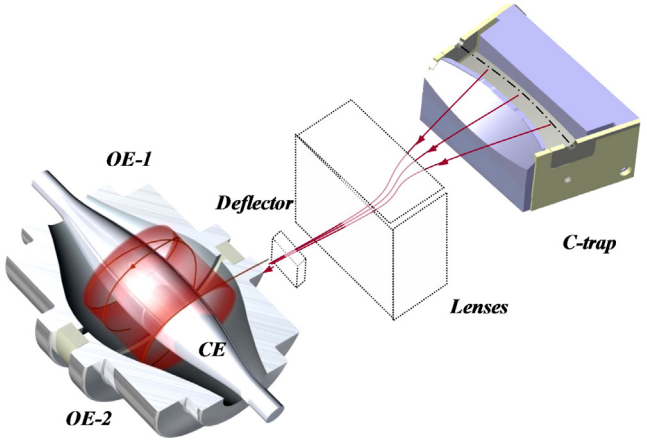

Fig. 2. Scheme of coupling of the C-trap to the Orbitrap analyzer resulting in excitation-by-injection and synchronization of ion motion. OE denotes outer electrodes and CE denotes the central electrode. Reprinted with permission of Thermo Fisher Scientific© 2014.

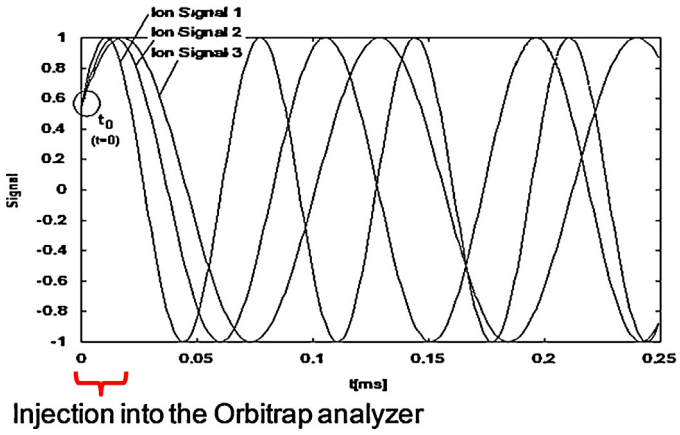

Fig. 3. Illustration of synchronization of ions of different m/z.