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From Transient to Isotope Ratio: Targeted Signal Processing Strategies for Compound-Specific Isotope Analysis by Orbitrap MS

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High-resolution Orbitrap mass spectrometry is emerging as a powerful platform for compound-specific stable isotope analysis of intact molecules. However, achieving the precision required for isotopic applications remains challenging in complex natural matrices. In Fourier transform mass analyzers, ion motion is detected as a time-domain transient (FID) and converted to mass spectra via frequency estimation and calibration [1,2]. Because image-current frequency is sensitive to ion population, localized space-charge interactions induce small but systematic frequency shifts. In conventional high-resolution omics applications, sub-ppm shifts typically introduce negligible quantitative bias. In isotope ratio measurements, however, even a ~1% relative intensity distortion between isotopologues can propagate to errors on the order of 10‰, rendering standard optimized “black-box” processing insufficient for high-precision isotope applications.

Here we directly access and reprocess raw Orbitrap transients to systematically evaluate how signal processing and calibration strategies affect isotopologue ratio stability. Organic acids were analyzed in synthetic standards and complex produced water matrices by ESI-Orbitrap-MS. We examine how FID-to-spectrum conversion (including frequency estimation, peak definition, centroid determination, and calibration mapping) interacts with localized space-charge-induced frequency shifts to influence measured M0/M+1 intensity ratios. Particular emphasis is placed on calibration strategy: conventional broadband calibration is compared to targeted narrow-window approaches, including lock-mass correction and two-point calibration anchored exclusively to the monoisotopic (M0) and heavy (M+1) isotopologues. Constraining calibration to the isotopologue pair of interest reduces local frequency-to-mass mapping asymmetry, thereby mitigating differential centroid displacement between M0 and M+1 peaks under varying ion population regimes. This framework enables clearer discrimination between instrumental artifacts and true matrix-driven isotope effects

Traditional IRMS achieves high precision through analyte-specific tuning of simple combustion products (e.g., CO_2, N_2). In contrast, Orbitrap instruments are designed for multiplexed, untargeted analysis of hundreds to thousands of species. We propose that high-precision isotope ratio applications similarly require analyte-directed signal processing strategies. Establishing targeted FID reprocessing workflows represents an essential step toward robust Orbitrap-based compound-specific isotope analysis in complex geochemical systems.

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[2]M.Scigelova and A.Makarov, *Orbitrap Mass Analyzer - Overview and Applications in Proteomics*, in *Proteomics* (2006).