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High-Precision Position-Specific Hydrogen Isotope Analysis of Fatty Acids via GC-Orbitrap

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Stable isotopes have become indispensable tools for deciphering complex processes in both environmental and biological systems. In biological system, isotope fractionation during metabolism offers a unique window into pathophysiology. However, conventional GC-IRMS methods are limited to molecular-average isotopic values, obscuring critical position-specific variations (δ^2H) that are highly sensitive to metabolic shifts. In this study, we developed a high-precision method for position-specific hydrogen isotope analysis of fatty acids using a custom-modified GC-Orbitrap mass spectrometer. By leveraging the high mass resolution of the Orbitrap, we achieved direct characterization of intramolecular hydrogen distributions without complex chemical degradation. Our method demonstrates exceptional sensitivity, requiring only 7.6 nmol of sample to reach experimental precisions of 5.4 ‰ for $C_4H_7O_2^+$ and 8.8 ‰ for $C_5H_9O_2^+$ (1 SD, n = 5). Validation using labelled palmitic acids conformed negligible hydrogen scrambling and a strong correlation ($R^2 = 0.991$, slope = 1.044) with whole-molecule GC-IRMS measurements across a wide composition range (-223 – 418 ‰). By resolving position-specific isotopic fingerprints, the research provides a robust tool for tracing cellular metabolic condition, offering new avenues for the early diagnosis and monitoring of metabolic disorders and cancer through naturally occurring isotopic signatures.