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Orbitrap Fourier transform isotopic ratio mass spectrometry of proteins – the coming revolution in biological MS?

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Isotopic ratio (IR) analysis is the oldest branch of biological mass spectrometry (bio-MS), preceding by decades the molecular analysis by bio-MS. In Karolinska Institutet (KI), the first IR mass spectrometer appeared in 1945, and already in 1947 the first in Europe (and second in the world) service MS laboratory was opened. For the first 20 years, this laboratory performed only one type of analysis, measuring the ratios of stable isotopes $^{13}\text{C}/^{12}\text{C}$, $^{15}\text{N}/^{14}\text{N}$, D/H and $^{18}\text{O}/^{16}\text{O}$. The first paper, published in 1948 in *Journal of Biological Chemistry*, epitomized the general approach of IR bio-MS – isotopically labeled (enriched) molecules, such as ^{15}N -glycine, were introduced in a biological system, from bacteria to humans, with a biopsy taken at a time course, converted to gases and isotopic ratios analyzed. This method gave rise to a great variety of studies, with many related to turnover rates of certain molecules, including proteins. In 1967, IR MS at KI was discontinued in favor of molecular analysis. In the 1980s the interest to IR bio-MS in the world has spiked once again, this time in the form of isotopic ecology, where IRs are natural. With the advent of interplanetary missions, IR analysis of biological molecules, such as amino acids, outside Earth has received a lot of interest. Yet the IR MS technology has remained largely the same as in the 1940s, requiring mg quantities of sample. Here we describe IR analysis of sub- μg amounts of polypeptides, with separate measurements for individual types of amino acids. The approach utilizes the high resolution of Orbitrap FTMS and its MS/MS capabilities, and provides precision comparable with standard IR MS.