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Molecular structure identification in mass spectrometry by Free-Electron Laser-based IR ion spectroscopy

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Mass spectrometry (MS) is one of the primary analytical methods in the characterization of complex mixtures, samples that contain thousands of molecular constituents in concentrations that vary by many orders of magnitude. Both sensitivity and resolving power of MS are unparalleled by other analytical methods. However, determination of molecular structures on the basis of MS data is challenging, as a single molecular weight value may correspond to many structural isomers. Tandem mass spectrometry (MS/MS) provides further molecular structure information, but relies strongly on empirical matching with previously obtained MS/MS spectra from reference standards, often collected in mass spectral libraries.

In contrast to MS, spectroscopic techniques directly probe molecular structure. The FELIX free-electron laser provides opportunities for molecular structure identification in MS, as it enables integration of MS with infrared (IR) spectroscopy. IR spectra can be recorded with the selectivity of MS, i.e. for individual components in a complex mixture [1]. The IR spectra may be related to molecular structure via reference spectra, either from actual physical reference standards, but also from IR spectra predicted in silico using density functional theory (DFT). Accurate spectral prediction is possible with DFT, thus enabling reference-free molecular structure identification.

A prominent example of complex mixture analysis involves body fluid samples of patients containing metabolites that may serve as valuable biomarkers for their pathological condition. We will show examples of how we apply this method to identify new biomarkers for inborn errors of metabolism [2] in an extensive collaboration with researchers at Radboud University Medical Centre. With accurate molecular structure information in hand, new strategies for diagnostics, e.g. in newborn screening, and therapeutics may be developed [3].

The method of infrared ion spectroscopy (IRIS) is also applicable in fields beyond metabolomics. Molecular structure identification of unknown compounds is for instance also relevant environmental studies (e.g. drinking water contaminants), pharmaceutical sciences (drug metabolism) and forensic investigations (molecular structure of uncontrolled “designer”drugs). We will present new strategies towards (partially) automated molecular structure annotation based on IRIS in combination with conventional tandem-MS approaches.

[1] J. Martens, et al., Anal. Chim. Acta, 1093, 1 (2020).
[2] R.E. van Outersterp et al., Anal. Chem. 93, 15340 (2021); J. Merx et al. Commun. Biol. 5, 997 (2022)
[3] U.F.H. Engelke, et al. J. Clin. Invest. 131, e148272 (2021)

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