A “molecular uncertainty principle” – can we simultaneously identify and localize molecules with high confidence?

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Nuclear magnetic resonance (NMR) and high-performance liquid chromatography mass spectrometry (HPLC-MS) are the “gold standards” for molecular identification. However, they have limited spatial information. A multitude of mass spectrometry methods with different probes have been developed to attain high spatial resolution but this has been achieved with the sacrifice of mass spectrometry performance. Generally, from an analytical perspective, this creates what can be termed the “Metabolite Uncertainty Principle”, where the more certain we are about a metabolite’s identity, the less certain we are about its localization. This is a frustrating barrier for measurements at the frontiers of scientific discoveries and for next generation technologies.

In 2017, we introduced the OrbiSIMS technology [1] bringing the mass spectrometry (MS) performance found in high-end proteomics laboratories to UHV surface and interface analysis studies at the mico (spatial) and nanoscale (depth). The OrbiSIMS, uses a hybrid approach where the high mass resolution of the Orbitrap MS, but slow speed, complements the high-speed, but low mass spectrometry performance, of a time-of-flight (ToF) MS. The OrbiSIMS was originally designed for single-cell metabolomic studies to reduce drug attrition and improve drug efficacy in pharmaceutical research and development. Since then, the ability to escape the confines of the “molecular uncertainty principle” has enabled many laboratories around the world to push scientific boundaries from in situ protein identification in biomaterials [2] to the design of new photoresists in next-generation Extreme Ultra-Violet Photo-Lithography [3].

The capability of the OrbiSIMS will be illustrated for metabolite imaging with sub-celluar spatial resolution and nanoscale depth resolution for organic electronic and inorganic semiconductors. The next generation Cryo-OrbiSIMS will be introduced for native state biological imaging preserving cellular structure and chemical integrity as well as new detection concepts for improved signal to noise.

[1] Passarelli, M., Pirkl, A., Moellers, R. et al. Nat Methods 14, 1175–1183 (2017).
[2] Kotowska, A.M., Trindade, G.F., Mendes, P.M. et al. Nat Commun 11, 5832 (2020).
[3] Spampinato, V., Franquet, A., De Simone, D., Pollentier, I., Pirkl, A., Oka, H. and van der Heide, P. Analytical Chemistry 2022 94 (5), 2408-2415.