

Towards Molecular Volume Imaging with Sub-cellular Resolution

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Volume imaging techniques such as cryogenic focused ion beam electron microscopy (cryo-FIB-SEM) reveal exquisite 3D biological structure of biological material [1,2]. However, there is no molecular information, which would provide powerful complementary insight. In 2017, we introduced the OrbiSIMS technology [3] bringing the performance of an Orbitrap mass spectrometer together with the high-resolution imaging capability of SIMS [4]. We were able to map the distribution of lipids and neurotransmitters in mouse brain with sub-cellular resolution. We also demonstrated the ability for single-cell metabolic profiling of macrophage cells incubated with the anti-arrhythmia drug, amiodarone, revealing strong heterogeneity of drug uptake. However, with single-cell resolution a clear correlation of drug uptake with upregulation of specific lipids was found. The unique ability of OrbiSIMS to simultaneously provide high-confidence in a molecule's location and identity has led to strong uptake in a wide range of science and technologies, with now many instruments installed worldwide.

Inspired by advances in Cryo-EM, we introduced the cryo-OrbiSIMS which allows imaging in the native biological state [5]. For example, we demonstrated the ability to undertake in-situ metabolomics of biofilm formation and in collaboration with the Francis Crick Institute we mapped the distribution of metabolites on the cuticular surface of drosophila. [6] We are now combining cryo-OrbiSIMS with an in situ cryo-FIB to develop protocols for molecular volume imaging. Initial results will be presented as well as novel routes to improve Orbitrap data analysis.[7]

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