

Native MS Workshop, June 2023, Houston

Native MS: new approaches to enable discovery in academia and industry

Native MS is recognized as a cutting-edge approach in the molecular characterization of protein targets and therapeutics, and their interactions. It can provide information on assembly stoichiometry, structural integrity, ligand and drug binding, all with unrivalled mass resolution and accuracy. As research targets in academia and industry become more challenging, there is an increasing need to push the limits of native MS in terms of the samples it can address, the ease in which it does so, and how it can integrate with orthogonal technologies.

We are witnessing a continuing growth in native MS and associated methodologies. Exciting developments have been made in the ability to deliver samples of greater inherent complexity, and from “dirty” sources, as well as big steps forward in online delivery and throughput. At the same time, there is continued effort at the interfaces with other MS-based or structural biology methods.

This workshop highlighted the cutting edge of native MS technology development, focusing on disseminating the newest approaches in the field that are breaking down barriers for examining previously intractably complex samples. This workshop, in an informal style, therefore was tasked with demystifying the state-of-the-art topic and will be valuable both for newcomers to the individual topics as well as those already proficient in the native MS field.

Speakers

Marius Kostelic (Ohio State University) - *Online buffer exchange*

Kiani Jeacock (University of Edinburgh/Michigan) - *Isotope depletion*

Jérôme Castel (Université- de Strasbourg) - *Mass photometry*

Stephan Rauschenbach (University of Oxford) - *Soft-landing*

Chae Kyung Jeon (University of Michigan) - *Computational tools*

Varun Gadkari (University of Minnesota) - *Nucleic acids*

Summary of workshop themes and discussion:

The workshop gave a set of six speakers, the majority of which are early career researchers, an opportunity to highlight their method-development work on innovations that are coupled to native mass spectrometry to provide new levels of information on protein structure, dynamics, and function. Marius Kostelic and Jérôme Castel described work using online buffer exchange via size-exclusion chromatography, enabling native MS analysis from samples that may not be stable for long in ammonium acetate, and the prospect of higher-throughput, automated measurements. Jérôme Castel also highlighted the complementarity of mass photometry for measuring protein assembly, with a focus on membrane proteins solubilised in detergent. Kiani Jeacock described the utility of using proteins made in ¹³C- and ¹⁵N-depleted media, due the resulting

signal-to-noise improvement arising from a narrower isotope pattern. Stephan Rauschenbach showed recent data that demonstrate how high-resolution cryoEM reconstructions can be obtained from prepared via soft-landing within the mass spectrometer. Chae Kyung Jeon described the evolution of computational methods that enable in particular the unfolding trajectories of proteins to be examined and compared through ion mobility measurements. coupled to native MS. And Varun Gadkhari described new work on using native MS to examine nucleic acids, and their interactions with small molecules.

The native MS workshop has long supported collaboration and knowledge transfer between academia and industry. The session was well attended, and questions on all the talks were diverse. The discussion highlighted the increasing use of these approaches in both theatres, with a clear driver towards both increasing throughput and confidence in the extracted information.

Next year's organisers will be Kristine Parson and Arthur Laganowsky