Fundamentals Interest Group and Native Mass Spectrometry Interest Group Workshop Report

The fundamentals interest group, (chaired by Rachel Ogorzalek Loo and Jim Prell) and the native mass spectrometry interest group (chaired by Carter Lantz) presented the joint workshop "When Gas Phase Biomolecular Structure Differs from Solution Phase" on Wed., June 3, 2026. The interest groups presented and discussed mass spectrometry, ion mobility, and other measurements suggesting differences between gas and solution phase structures, how differences could be rationalized, and what, if any, changes should be made in how we view ESI-generated ions. Approximately 70 participants were present.

Jim Prell opened the workshop, presenting relationships between the mass and charge of globular proteins, the relationships between collision cross sections and oligomer structures, and evidence for structural compaction via self-solvation. He also showed that reducing denatured ubiquitin precursors by up to 10 charges with cation-to-anion proton transfer consistently yielded product collision cross-sections that were independent of the initial charge state, and low charge states only slightly larger than those from native-like solutions.

Brandon Ruotolo discussed methods to interrogate protein stabilities in gas and solution phases, providing examples illustrating correlations. He expressed the need for validation methods and to further understand the "memory effects" and kinetic trapping anchoring these correlations.

Scott Quarmby described the processes involved in cryo-electron microscopy of native-sprayed, soft-landed protein complexes. He explained that proteins soft-landed onto cryogenically cooled grids are shrunken compared to plunge-frozen particles, and that ice deposition does not replace all of the missing water molecules. Subsequent laser rehydration steps do nudge soft-landed structures closer to the targeted plunge-frozen structures.

Elyssia Gallagher presented her lab's work applying molecular dynamics simulations with mobile protons to gas phase proteins and electrospray processes, showing the importance of electrostatic interactions. She showed that these simulations can predict the native charge state distributions of ions in positive and negative ion mode and even the high degree of compaction undergone by GroEL 14-mer when subjected to electrospray ionization.

Following the presentations, participants discussed gas and solution phase differences and correlations. There was discussion regarding whether or not the exact gas phase structures were important, with some attendees favoring more of an emphasis on how mass spectrometry results correlate to solution behavior. Many questions focused on soft landing procedures and developments.