Development of Ion Mobility-Mass Spectrometry as a High-throughput Approach for Structural Genomics

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The field of structural genomics is ultimately concerned with determining high-resolution structures for all the functional macromolecules within living cells and tissues and one of the chief bottle-necks in this ambitious endeavour is the technology available for determining the structures of multi-protein assemblies. Ion mobility-mass spectrometry (IM-MS) is an attractive approach for assessing protein topology, as measurements can be acquired for transient assemblies, at low concentrations and in the context of complex mixtures. Recent efforts in our laboratory have been aimed at generating high-throughput IM-MS methods that are capable of determining the topology, organization, and stability of disease-associated protein complexes in an automated fashion. A rate-limiting step in the acquisition of IM-MS data for protein complexes is the identification of optimal parameters, both in solution and in the gas-phase, for attaining the maximum number of IM measurements that can be related easily to solution-phase dimensions and distances. Often, the optimal conditions for topology model generation represent several distinct solution conditions and instrument settings that must be discovered after a protracted period of trial and error. Here, we describe an extensive, ongoing screen of solution additives and ion-molecule reaction chemistries aimed at modulating ion charge state, improving gas-phase structural stability, and maximizing the intensity of protein sub-assemblies for down-stream model building. We will also describe our recent efforts to develop these screens into basic rules and best-practices that can be used to automate protein topology assignment from IM-MS data in a high-throughput framework.