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FOCUS: MASS SPECTROMETRY AS A PROBE OF HIGHER ORDER PROTEIN STRUCTURE: EDITORIAL

Focus on Mass Spectrometry as a Probe of Higher Order Protein Structure, Honoring Prof. Brian T. Chait, Recipient of the 2015 ASMS Award for a Distinguished Contribution in Mass Spectrometry

Editorial: A Turning Point for Biological Mass Spectrometry

Professor Brian T. Chait of the Rockefeller University received the 2015 ASMS Award for a Distinguished Contribution in Mass Spectrometry at the 63rd Conference on Mass Spectrometry and Allied Topics in St. Louis. Brian received B.Sc. degrees in natural sciences (1969) and physics (1970) from the University of Cape Town, and in 1976 was awarded the D. Phil. degree in nuclear physics from the University of Oxford. After postdoctoral study at the University of Manitoba, he joined the Rockefeller University in 1979, where he is now a Camille and Henry Dreyfus Professor and Head of the Laboratory of Mass Spectrometry and Gaseous Ion Chemistry. Brian has received numerous awards, including the Newcombe-Cleveland Prize, Bijvoet Medal (Utrecht University), Field and Franklin Award, HUPO Discovery Award in Proteomics Sciences, and the Pehr Edman Award.

Throughout his career, Brian has made internationally recognized contributions advancing analytical chemistry and biochemistry. He is a pioneer in mass spectrometry, instrumentation, and proteomics. His seminal work on plasma desorption MS and MALDI-MS brought mass spectrometry to the forefront of biomedical research. However, the ASMS Distinguished Contribution Award focuses on his achievement in recognizing and demonstrating the link between electrospray ionization spectra and protein conformation.

Brian's discovery that a protein's solution-phase conformation dramatically impacts its electrospray ionization mass spectrometry (ESI-MS) charge state distribution (CSD) destroyed the barriers isolating mass spectrometry from physical biochemistry and fostered a continuing wealth of applications of MS to noncovalent assemblies, hydrogen/deuterium exchange, probes of gas phase protein structure, and ultimately "native mass spectrometry."

The interpretation of ESI-MS and MS/MS data for proteins examined from native solutions often begins today from NMR or crystal structures, based on assumptions that the gas-phase structure will be closely related. But in 1990 there was no expectation that relationships from higher order solution structure could be retained in the gas phase and any such assumption would have been unfounded. Brian and his co-workers opened the world to this possibility, first by demonstrating that electrosprayed cytochrome *c* molecules assumed about twice as much charge when sprayed from pH 2.6 than from pH 5.2 aqueous solutions [1], by probing conformational changes in proteins via hydrogen/deuterium exchange [2], and by monitoring solution-phase thermal denaturation processes by ESI-MS [3].

Figure 1. ASMS President Jennifer Brodbelt presenting the Award for a Distinguished Contribution in Mass Spectrometry to Brian Chait

Brian's achievement must be viewed from the perspective of mass spectrometry 25 years ago. Few scientists were able to spray 100% aqueous solutions back then, nor did they see its need or potential value. For some researchers, an organic sheath solvent sufficiently reduced surface tension to complete the analyses; others simply added methanol directly. Chowdhury and Chait [4], however, demonstrated that electropolished needles could electrospray water at voltages sufficiently below those inducing dielectric breakdown. The ability to electrospray aqueous solutions—without organic

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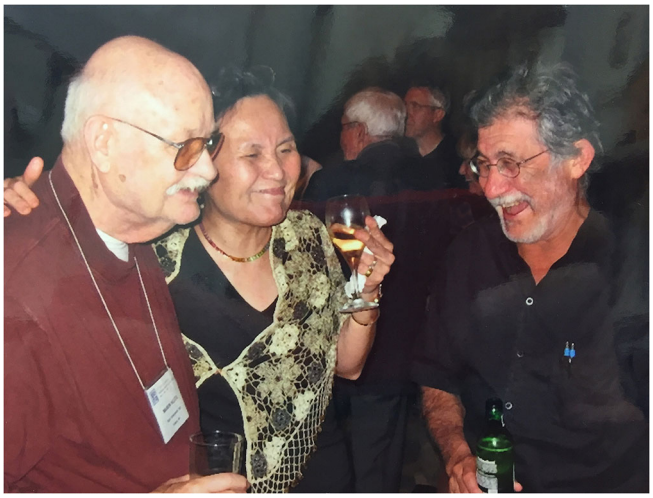

Figure 2. Marvin and Christine Vestal and Brian Chait at the 2010 ASMS Conference in Philadelphia

Figure 3. Brian relaxing in October 2015 after delivering the keynote address for the Asilomar Conference on Native Mass Spectrometry-Based Structural Biology

solvents—was key to observing the charge state distribution differences associated with natively folded proteins. Equally important was Brian's ability to rationalize and verify that the source of the observed CSD difference was solution-phase structure.

Our understanding of electrospray ionization continues to advance at a rapid pace, yet remains remarkably incomplete; however, the ideas that Brian precisely articulated 25 years ago about the electrospray CSD/conformation relationship represent a major turning point—a quantum leap—for biological mass spectrometry.

This Special Focus of *JASMS* highlights work devoted to the advancement of mass spectrometry as a probe of higher order protein structure. This issue begins with an insightful *Account and Perspective* article by the awardee and coworkers, which is followed by 14 contributions from colleagues and friends:

(1) *Account and Perspective*: "Revealing Higher Order Protein Structure Using Mass Spectrometry" by Brian T. Chait, Martine Cadene, Paul Dominic Olinares, Michael P. Rout, and Yi Shi.
(2) *Account and Perspective*: "The Evolving Contribution of Mass Spectrometry to Integrative Structural Biology" by Marco Faini, Florian Stengel, and Ruedi Aebersold.
(3) *Critical Insight*: "Salt Bridge Rearrangement (SaBRe) Explains the Dissociation Behavior of Noncovalent Complexes" by Rachel R. Ogorzalek Loo and Joseph A. Loo.
(4) "Differential Mobility Spectrometry-Hydrogen Deuterium Exchange (DMS-HDX) as a Probe of Protein Conformation in Solution" by Shaolong Zhu, J. Larry Campbell, Igor Chernushevich, J C. Yves Le Blanc, and Derek J. Wilson.
(5) "Examining the Heterogeneous Genome Content of Multipartite Viruses BMV and CCMV by Native Mass Spectrometry" by Michiel van de Waterbeemd, Joost Snijder, Irina B. Tsvetkova, Bogdan G. Dragnea, Jeroen J. Cornelissen, and Albert J. R. Heck.
(6) "Human Islet Amyloid Polypeptide N-Terminus Fragment Self-Assembly: Effect of Conserved Disulfide Bond on Aggregation Propensity" by Alexandre I. Ilitchev, Maxwell J. Giammona, Thanh D. Do, Amy G. Wong, Steven K. Buratto, Joan-Emma Shea, Daniel P. Raleigh, and Michael T. Bowers.
(7) "Real-time HD Exchange Kinetics of Proteins from Buffered Aqueous Solution with Electrothermal Supercharging and Top-Down Tandem Mass Spectrometry" by Catherine C. Going, Zijie Xia, and Evan R. Williams.
(8) "Acquiring Structural Information on Virus Particles With Charge Detection Mass Spectrometry" by David Z. Keifer, Tina Motwani, Carolyn M. Teschke, and Martin F. Jarrold.
(9) "'Wet' versus 'Dry' Folding of Polyproline" by Liuqing Shi, Alison E. Holliday, Brian C. Bohrer, Doyong Kim, Kelly A. Servage, David H. Russell, and David E. Clemmer.
(10) "Hydrogen Exchange Mass Spectrometry of Related Proteins with Divergent Sequences: A Comparative Study of HIV-1 Nef Allelic Variants" by Thomas E. Wales, Jerrod A. Poe, Lori Emert-Sedlak, Christopher R. Morgan, Thomas E. Smithgall, and John R. Engen.
(11) "Structural Characterization of Missense Mutations Using High Resolution Mass Spectrometry: A Case Study of the Parkinson's-Related Protein, DJ-1" by Gili Ben-Nissan, Almog Chotiner, Mark Tarnavsky, and Michal Sharon.
(12) "Substrate and Substrate-Mimetic Chaperone Binding Sites in Human α-Galactosidase A Revealed by Affinity-Mass Spectrometry" by Adrian Moise, Stefan Maeser, Stephan Rawer, Frederike Eggers, Mary Murphy, Jeff Bornheim, and Michael Przybylski.
(13) "Unfolding and Folding of the Three-helix Bundle Protein KIX in the Absence of Solvent" by Moritz Schennach, Eva-Maria Schneeberger, and Kathrin Breuker.
(14) "Selective Covalent Chemistry via Gas-Phase Ion/ion Reactions: An Exploration of the Energy Surfaces Associated with N-Hydroxysuccinimide Ester Reagents and Primary Amines and Guanidine Groups" by Jiexun Bu,

Christine M. Fisher, Joshua D. Gilbert, Boone M. Prentice, and Scott A. McLuckey.

(15) "Negative Ions Enhance Survival of Membrane Protein Complexes" by Idlir Liko, Jonathan T.S. Hopper, Timothy M. Allison, Justin L.P. Benesch, and Carol V. Robinson.

This *JASMS* Special Focus clearly highlights the extraordinarily valuable role of mass spectrometry in characterizing the richness and diversity of protein structure. Moreover, although the progress and achievements have been dramatic, these manuscripts underscore the intriguing questions and analytical challenges of future research. On behalf of the Editors of *JASMS* and the members of ASMS, we congratulate Brian for his profound contributions to this exciting field, and we look forward to his continuing innovations, insights, and accomplishments.

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