Editorial and Review:
30th ASMS Sanibel Conference on Mass Spectrometry – Computational Modelling in Mass Spectrometry and Ion Mobility: Methods for Ion Structure and Reactivity Determination

Mass spectrometry (MS) is now firmly established as a widely used and versatile analytical method across the physical, chemical and life science research disciplines. Determination of accurate masses and often exact isotope patterns of atoms and molecules can be sufficient to confirm the identity of a compound. However MS comes to the forefront in structural analysis of molecules, complexes and supra- and/or bio-molecular structures. Structure determination relies traditionally on tandem-MS (MS/MS) or MS^n fragmentation, but can also include experiments under kinetic or thermodynamic control and, more recently, ion mobility (IM) to determine the gas-phase ion/neutral collision cross section. Across this wide spectrum of MS-related methods and applications in both the academic and industrial research setting, computational approaches are instrumental in interpreting the experimental data, but crucially for generating structural models of the analyte, representing its connectivity at the level of atoms as well as the overall three-dimensional structure and charge distribution.

Since the annual meeting in 2016, ASMS has offered a Fundamentals session dedicated to the subject of "molecular dynamics (MD) and quantum mechanical (QM) calculations in mass spectrometry (MS) and ion mobility (IM)". Due to its popularity and attendance, this session has continued through to the 2018 annual meeting. When we proposed a dedicated Sanibel meeting on the use of MD and QM in IM and MS, we thought it was highly timely and important to summarize the current state of this fast-moving field. The ASMS Sanibel Conference on Computational Modelling in Mass Spectrometry and Ion Mobility: Methods for Calculating Ion Structure and Reactivity Determination was organized by Iain Campuzano (Amgen, Inc.), Frank Sobott (University of Antwerp/Belgium, now Leeds/UK), and Michael van Stipdonk (Duquesne University) and took place from January 25 - 28, 2018 at the Hilton St. Petersburg Bayfront Hotel, St. Petersburg, Florida. This was a new venue for the Sanibel Meeting. The greater distance to the nearest (bay-facing) beach was more than compensated for by the proximity of the renowned Salvador Dalí Museum and the Museum of Fine Arts, which happened to have a fascinating exhibition on "Star Wars and the Power of Costume", with iconic outfits featured in the first seven films of the Star Wars saga; from Queen Amidala's lavish gowns to Darth Vader's imposing black armor.

The goal of this Sanibel meeting was to bring together different research groups performing computational calculations (MD and QM) currently being used to aid in MS and IM data interpretation. Therefore, a highly diverse group of over 100 attendees, from academia as well as from biopharma and instrument manufacturers, presented and discussed topics related to computational approaches to address a wide range of molecules, from organometallics, glycans, lipids, and nucleic acids to peptides, proteins, and protein complexes.

The opening plenary lecture on Thursday evening was given by James Cheeseman from Gaussian Inc. The Gaussian suite of software is arguably the most ubiquitously used package for QM calculations, making Jim an ideal choice to open the meeting. Jim covered a variety of topics ranging from density functional theory (DFT) background to vibration circular dichroism (VCD) and infrared (IR) spectroscopy, which were highly applicable to many subsequent talks within the meeting.

Friday morning opened with a session entitled Small Molecule and Protein Molecular Dynamics and Quantum Mechanics: The Basics. Adrian Roitberg (University of Florida) initiated the session by describing ANAKIN-ME (Accurate NeurAl networK engINe for Molecular Energies) or ANI in short. He also quoted Paul Dirac: "all models are wrong: some are useful". A very compelling MD simulation was demonstrated where CH_2 molecules spontaneously formed carbon tubules and graphene sheets, if the simulation was allowed to evolve for a long enough period of time. Adrian also described how machine learning is being applied in MD simulations. Michael Bartberger, a computational modeler from Amgen, described how molecular mechanics and quantum chemistry calculations are used in current small molecule drug design. Mike's talk also focused on using high level DFT to calculate the coordination position of various cations (Li, K, Na and Cs) with either cis- or trans-hydroxyproline and how these species can be separated by IM. Beibei Wang (University of Calgary, Canada) described the basics of the Martini course grain force field and how it can be applied to modelling of membrane proteins and complexes within a phospholipid bilayer. Using her course gain simulations, Beibei demonstrated how fluid membrane proteins are within the bilayer and suggested that too much emphasis is being applied on specific membrane protein-lipid interactions, as the bilayer is so dynamic. Lipid rafts, however, were not observed in these simulations.

The second session on Friday, Small Molecule and Peptide Molecular Dynamics and Quantum Mechanics, focused on applications of theory in diverse areas. Bela Paizs (Bangor University, UK) presented data from a cyclic drift-tube IM device, demonstrating separation of polyalanine isomers, and discussed software for the prediction of peptide fragmentation. William Hase (Texas Tech University) discussed energy transfer of peptides collisions with surfaces, in the context of surface-induced dissociation experiments, and pointed out that MD simulations show shattering of the analyte, which is not entirely explained by purely thermal activation. Lucas Hamlow (Wayne State University) followed this with data on sugar puckering and how this affects higher-order structure of modified nucleosides.

A first for the Sanibel meeting was a "Lunch-and-Learn" workshop, where Michael Bartberger (Amgen) and Carlos Larriba-Andaluz (Purdue University) demonstrated how to create geometry optimization within Gaussian and Firefly geometry files and how to subsequently calculate a theoretically derived collision cross section using the MOBCAL and IMoS suites of software. The event was well attended, but it filled the lunch break, directly leading into the afternoon session, Computational Methods for Determination of Ion Structure by Tandem Mass Spectrometry, Ion Mobility and Ion Spectroscopy. Ryan Steele (University of Utah) covered the use of molecular

dynamics to probe vibrational signatures of electronic properties for a range of molecules, Anne McCoy (University of Washington) discussed vibrational patterns and frequencies for protonated water clusters, and Bert de Jong (Lawrence Berkeley National Laboratory) expounded on the challenges of applying high-level quantum mechanical calculations to complexes that contain heavy elements such as uranium. (At that stage it became clear that the frequent rumbling sounds that shook the glass chandelier were not from the passage of a freight train, but rather just the air conditioning kicking in.) Stephen Valentine (West Virginia University) described the combination of D_2O labelling within the IM drift cell and ETD of the IM-separated peptides and the development of his Hydrogen Accessibility Scoring routine as a means of assessing both the position of peptide protonation and selection of possible peptide candidate structures from an MD simulation. Keith Richardson (Waters Corporation) gave a very interesting MS-vendor perspective of how QM calculations have been used to design a selection of glow discharge source ETD reagents. He described the evolution of the initial and serendipitously discovered compound nitrosobenzene, to the QM calculated and derived 1,4-dicyanobenzene with the concomitant improvement in Frank-Condon Factor and favorable electron affinity. Natalia Yalovenko (École Polytechnique Fédérale de Lausanne, Switzerland) described the use of the combination of IM, helium tagging in a cold trap, IR irradiation and MS, to determine the absolute gas-phase structures of the commonly used IM peptides standards GRGDS and SDGRG. Electrospray generated droplets and protein interactions within them were the topic of the talk by Styliana Consta (University of Western Ontario, Canada), who also suggested a mechanism of how polymers such as polyethylene glycol can "extrude" from droplets.

After the free afternoon, which many used to visit one of the local museums, the evening keynote lecture was given by Mark Johnson (Yale University), who discussed the exploration of shared proton vibrations, the structure of water and related systems using MS and cryogenic ion spectroscopy. Following Mark's excellent lecture was the first Poster Flash Talk session, which led into the highly interactive poster session fueled by an open bar.

Saturday morning started with the Computational Methods for Studies of Ion Chemistry session, which was kicked off in style by Peter Armentrout (University of Utah), who talked in detail about spreading samarium powder in the atmosphere and how thermochemical calculations can explain the ensuing phenomena. Lai-Sheng Wang (Brown University) discussed the use of velocity map imaging and anion photodissociation spectroscopy to measure the vibrational and electronic features of dipole-bound systems (including measuring 16 fundamental frequencies of C_{60} anions in the gas-phase produced by ESI). Robert Continetti (UC San Diego) addressed the elephant in the room - metastable ions. Daiki Asakawa (AIST, Tsukuba, Japan) presented a new method of fragmentation of an acetylated arginine peptide based on Hydrogen Attachment/Abstraction Dissociation (HAD) and mapping the reaction using ab initio QM calculations.

The next session was on Gas-Phase Structure and Reactions of Nucleic Acids and Glycans. Dan Fabris (University of Albany) described a new coarse-grain model to perform MD simulations of large nucleic acid structures. Dan also progressed on to the new Martini coarse-grain model for

nucleic acids, which they are currently implementing, and quoted Tamar Schlick: "The key in modelling is to develop and apply models that are appropriate for the questions being examined *with them".* This was followed by Benjamin Bythell (University of Missouri), who uses MS and DFT studies to predict glycosidic and cross-ring transition state energies for sodiated cellobiose and gentiobiose fragmentation to describe the formation of the y_1/b_1 and a_2 ion as a result of tandem-MS. Returning to oligonucleotides, Valerie Gabelica (IECB Bordeaux, France) described her recent MS, IM and MD research on duplex and quadruplex nucleic acid structures. She also addressed what she described as the central dogma of (native) MS: "the analyte's molecular structure is preserved in the gas phase". (Whereas Fred McLafferty would say that understanding (structural) rearrangements is key to making use of MS for structure determination.) Valeria also discussed: how do three dimensional structures evolve when analytes transfer from solution to ions in the gas phase? She suggested that we as a community should stop pretending that these structure are retained in their entirety from solution to gas-phase, but instead try to understand the relationship between experiment and model, and develop new methods to calculate instrument-derived CCS values and theoretical values. (However, during the conference, Jim Cheeseman expressed concerns about using MD simulations to derive a gas phase protein structure from a collision cross section measurements. Worries arise because the force fields employed were never intended to be used in the gas phase and have not been validated against "known" gas phase structures.)

Understanding the fundamentals of ESI is essential. Neelam Khanal (Indiana University) gave a nice summary of major glycan analytical tools. Neelam described how MS is a highly applicable analytical technique due to its speed, but largely blind to stereochemistry and MS/MS is required to assign isomers. Combining a 2m-drift tube and cold trap IR irradiation, Neelam described H_2 and N_2 ion tagging to aid structural confirmation of glycosaminoglycans, chondroitin and heparin sulphate. Both Neelam's and Natalia Yalovenko's presentations highlighted a very exciting new development in hybrid MS and IM technologies.

The second Lunch-and-Learn workshop was given on Saturday by Andy Lau and Argyris Politis from King's College (London, UK) and focused on "Macromolecular Modelling with Cross-Linking and Ion Mobility MS." Different computational strategies were discussed that allow integration of data from complementary structural proteomics approaches. The session that followed immediately targeted Protein-Ligand and Protein/Protein Complexes: Soluble and Membrane Proteins. Thanh Do (University of Illinois) started by discussing the application of MD and IM for determining structural transitions from solution to the gas-phase. Thanh showed a very interesting slide demonstrating the different gas-phase structures one can obtain by using the multiple force-fields that are available. Brandon Ruotolo (University of Michigan) followed by describing recent work where he and his group have developed an IM-MS workflow for protein complex assignment based on course-grain MD cluster analysis, tandem-MS and native-MS in the presence of chaotropic agents. Michael Marty (University of Arizona) discussed some new native-MS data of nanodiscs, which show some very interesting behavior under negative ion mode in the

presence of supercharging agents. Argyris Politis then described how the two important phospholipids PE and PI are important in modulating dimerization of the UapA purine/proton symporter. Argyris also discussed how H/D exchange data can be used to guide MD studies. Alice Walker (University of North Texas) discussed aspects of lysozyme unfolding and aggregation based on IM data and MD modelling, while Andy Lau demonstrated how cryo-EM and MS approaches combine to shed light on the structure and conformational dynamics of supercomplexes.

Perdita Barran (University of Manchester) gave the keynote lecture on Saturday evening, taking the audience on the tour de force of protein structure in the gas phase, from collapsing antibodies to shape-shifting intrinsically disordered proteins and their role in biology. She did use the phrase "memory of solution" without declaring how many dilutions her lab typically puts the samples through, or if they are shaken or stirred. This was followed by the second set of Poster Flash Talks and discussions around the posters.

Sunday morning began with the session Ion Mobility Separation Algorithms: Which One is Optimal? This proved to be a highly interactive session, since there are multiple models and algorithms that can be used to derive a theoretical collision cross section value, but there is little consensus on which one to use. Carlos Larriba-Andaluz discussed the differences between elastic specular and inelastic diffuse collisions between the ion and either the monoatomic or polyatomic drift gases and whether the quadrupole moment for the ion-N_2 integration can be incorporated into the Lennard-Jones interaction potential, thus saving expensive computational processing times. Christian Bleiholder (Florida State University) presented a novel way of calculating arrival time distributions and illustrated this method with IM data of ubiquitin, and how collision cross section distributions can be correlated with structural families. Erik Marklund (Uppsala University, Sweden) covered fast PA algorithm calculations and how they can be employed to understand macromolecular structures.

The final session of the conference was Molecular Dynamics and Quantum Mechanics in Medicinal Chemistry: Real Therapeutic Case Studies. Brian Lanman, a medicinal chemist from Amgen, presented a detailed story of how the interaction of β-catenin and its natural substrate, the TCF4 peptide, was targeted as a potential oncology therapy. Using a combination of in vitro assays, MS and MD, Brian discussed how two native cysteine residues located in the active site of β-catenin were specifically targeted for alkylation using a chloroacetamide derivative of TCF4. Brian's talk was also intentionally placed towards the end of the meeting to provide a highly valuable industrial and therapeutic perspective for what was a very fundamentals-focused meeting. This session was closed with a very interesting contribution from Steffen Lindert (Ohio State University), who showed novel ways of using surface induced dissociation (SID) data and other higher-order structure information obtained by native MS methods to drive computational modeling of protein complexes.

Since the majority of the attendees attending this meeting are using ESI to generate their gas-phase ions for subsequent MS, MS/MS, IM and IR measurements, it seemed highly appropriate that Lars Konermann (University of Western Ontario, Canada) gave the closing plenary. He presented his recent MD modelling of the ESI process, with particular emphasis on what constitutes supercharging at the molecular level and how it affects the fate of protein structures once they are liberated from the hydrated environment. As always, Lars delivered his presentation with great passion, and this generated a lively discussion afterwards.

The meeting was elegantly and jovially summarized and closed by Frank Sobott. Within Frank's presentation there were many memorable pictures and quotes, three of which stand out: the Dalí picture of Abraham Lincoln and the accompanying analogy of course grain modelling; Michael Marty's supercharged nanodisc versus a quadruply-stacked cheese and bacon burger, and Benjamin Bythell's quote: "sodium is not a proton". We certainly learned a lot from this meeting. We also want to thank the ASMS Sanibel Committee, especially Brent Watson, for all his organizational help prior to and during the meeting.

As organizers, we tried to address a large, and often seen as disparate field of theoreticians dealing with data generated by MS and IM. Bringing together all of these individuals to one meeting for three days was highly productive and generated large amounts of discussion after most presentations - some of which was very passionate. There were over 100 participants registered for this meeting (many of which were young graduate students) and everyone who requested an oral presentation was granted one, either in the form of a plenary lecture, a 30 minute main session presentation, a 15 minute hot-topic or a 3-minute poster flash talk; this was a great achievement. Also for the first time, two Lunch-and-Learn workshops were run and received positive feedback. The presenters were asked multiple times for their slide decks, which were subsequently uploaded to the Sanibel Meeting website. We wish the Sanibel 2019 Meeting all the success.

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Attendees of the 30th ASMS Sanibel Conference