Geneva chemistry & biochemistry days 2020

TH 16 January 2020, 09:00–17:30
FR 17 January 2020, 09:00–12:30
École de Physique – Grand Auditoire A – quai Ernest-Ansermet 24 – 1205 Genève
No registration required

Prof. Harry L. Anderson – FRS
Oxford University

Dr Laurent Blanchoin
CEA – CNRS – INRA – Université Grenoble Alpes

Prof. Clémence Corminboeuf
Prix Jaubert 2020 Lecture – École Polytechnique Fédérale de Lausanne

Prof. Luke P. Lee
University of California at Berkeley

Dr Christophe Léger
Aix-Marseille Université

Junior Speakers:

Alexander Aster • Kenji Caprice • Dalu Chang • Ewa Drab • Angelina Gigante • Kristina Jajcevic • Rania Kazan • Lyudmil Raykov • Clément Richard • Chloé Roffay • David Ruskic • Biljana Stojimirovic • Karolina Strakova • Thomas Stricker •

FACULTÉ DES SCIENCES
SECTION DE CHIMIE ET BIOCHIMIE

UNIVERSITÉ DE GENÈVE

FOREWORD

The *Section de chimie et biochimie*, University of Geneva, has the pleasure to announce the 10th edition of its "***Geneva Chemistry & Biochemistry Days***".

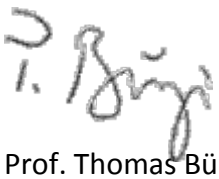
The vocation of the event is to give our students who are close to finishing their PhD studies the opportunity to present their research as attractive speed talks to an audience from academia and industry, and the steering committee is glad to welcome you in this context.

This year, five distinguished lecturers, amongst whom the recipient of the Prix Jaubert 2020, further enrich the programme. Our four departments have invited them, and they will illustrate the extent and the quality of top-level fundamental research in chemistry and biochemistry today.

Our BSc and MSc students are welcome to smell the very flavour of the research held in our School and abroad, and to learn a bit more about how to present punchy results to a scientific audience.

We expect that the event will catalyse fruitful discussions between young and advanced researchers, and give our students an opportunity to get ready for their professional career, yet offering our guests an overview of the quality of the fundamental research performed in our School.

Looking forward to meeting you at this event, we hope that you will enjoy the lectures and interactions!



Prof. Thomas Bürgi
Président de la Section de chimie et biochimie

Steering and organising committee

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PROGRAMME – THURSDAY, 16 JANUARY

SESSION 1

Chair: **Prof. Stefan Matile** (Senior Speaker)
Prof. Takuji Adachi (Junior Speakers)

09:00--09:05	**Prof. Thomas Bürgi**	Welcome message
09:05--10:05	**Prof. Harry L. Anderson** Oxford University	Synthesis of molecular wire rings: Exploring aromaticity on the nanoscale
10:05--10:20	**Alexander Aster**	Conformational control of symmetry breaking charge separation and singlet fission in bichromophores
10:20--10:35	**Karolina Strakova**	Fluorescent probes to image physical forces in living cells
10:35--10:55	Coffee break	Hall of École de Physique
10:55--11:10	**David Ruskic**	Modifier effect on differential ion mobility mass spectrometry analysis of isomeric drugs
11:10--11:25	**Lyudmil Raykov**	Identification and characterization of *D. discoideum* response factors involved in pathogen detect. and stress signal transduct.
11:25--11:40	**Ewa Drab**	Mechanism of the inhibitory interference in human antimicrobial peptides
11:40--11:45	Photo (all speakers + all chairs + committee)	Outside of École de Physique
11:45--13:45	Lunch (senior speakers + junior speakers)	Restaurant *Sole Mio*

SESSION 2

Chair: **Prof. Charlotte Aumeier** (Senior Speaker)
Dr Benjamin Doistau (Junior Speakers)
Prof. Jérôme Lacour (Prix Jaubert Speaker)

13:45--14:45	**Dr Laurent Blanchoin** CEA – CNRS – INRA – Université Grenoble Alpes	Reconstitution of the cell cytoskeleton
14:45--15:00	**Angelina Gigante**	Achieving the selectivity of the synthesis of $B_nH_m^{z-}$ boron clusters for hydrogen storage and sodium batteries
15:00--15:15	**Kenji Caprice**	Synchronized on/off switching of four binding sites for water in a molecular Solomon link
15:15--15:30	**Biljana Stojimirovic**	Silica interactions in aqueous solutions of multivalent coions
15:30--15:50	Coffee break	Hall of École de Physique
15:50--16:05	**Clément Richard**	SARA endosomes and microtubules asymmetry during asymmetric cell division in Zebrafish
16:05--16:20	**Kristina Jajcevic**	Lipid nanotubes as an organic template for nanofabrication
16:20--17:20	**Prof. Clémence Corminboeuf** Ecole Polytechnique Fédérale de Lausanne	Blending old concepts with machine learning to discover homogeneous catalysts – ***Prix Jaubert Lecture***
17:20-	*Verre de l'amitié*	Hall of École de Physique
19:30-	Dinner (senior speakers + chairs + committee)	Restaurant *la Cantine des Commerçants*

PROGRAMME – FRIDAY, 17 JANUARY

SESSION 3

Chair: **Prof. Ross Milton** (Senior Speaker)
Dr Nabil Hanna (Junior Speakers)
Prof. Kaori Sugihara (Senior Speaker)

09:00--10:00	**Dr Christophe Léger** Aix-Marseille Université	Studying and using hydrogenases
10:00--10:15	**Dalu Chang**	Bioluminescent enzymes: From a reporter to an effector
10:15--10:30	**Thomas Stricker**	Investigating the impact of electrospray adducts in liquid chromatography – mass spectrometry
10:30--10:45	**Chloé Roffay**	Cell response upon osmotic shock: Entangling the role of ion channels and cytoskeleton
10:45--11:05	Coffee break	Hall of Ecole de Physique
11:05--11:20	**Rania Kazan**	Alloying of thiolate protected gold nanoclusters
11:20--12:20	**Prof. Luke P. Lee** University of California at Berkeley	Quantum Biological Electron Tunneling (QBET) junction and its application in life science and medicine
12:20--12:25	**Prof. Nicolas Winssinger**	Awards for the best oral Junior presentations
12:25--12:30	**Prof. Thomas Bürgi**	Concluding remark

Synthesis of molecular wire rings: Exploring aromaticity on the nanoscale

Harry L. ANDERSON – FRS

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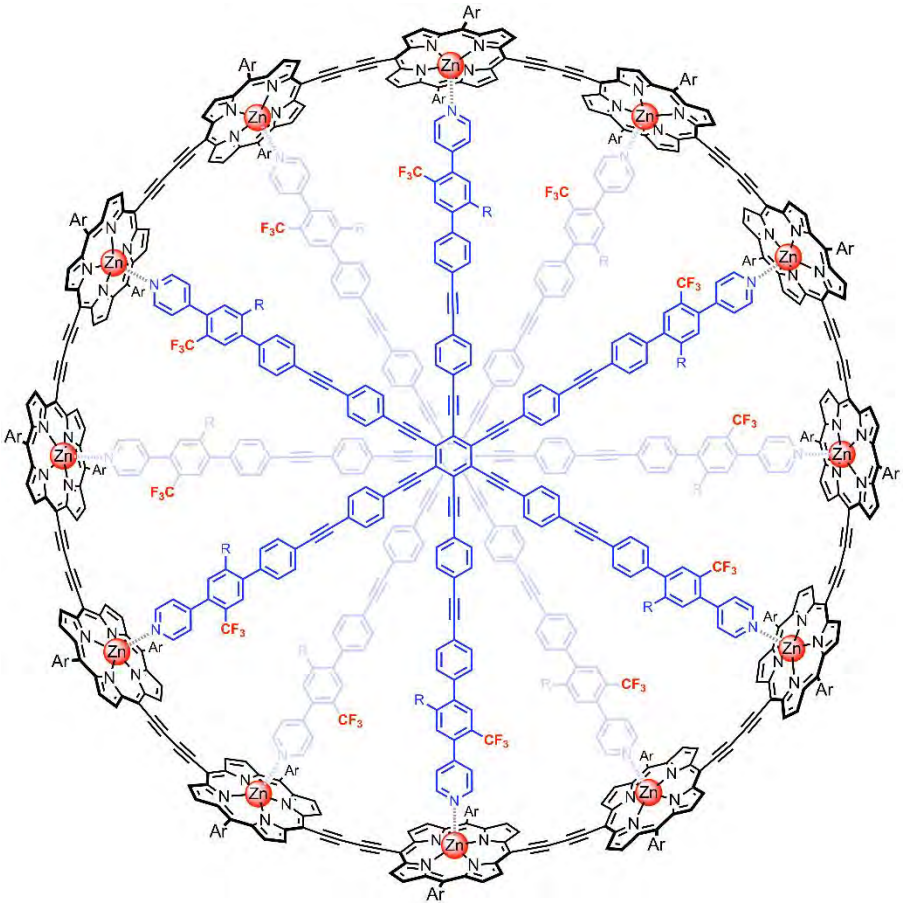
Template-directed synthesis can be used to create π-conjugated porphyrin rings that are as big as proteins.[1-3] These systems mimic the light-harvesting behavior of photosynthetic chlorophyll arrays[3] and they display global aromaticity in some oxidation states,[4] for example the 12-porphyrin nanoring template complex shown below is globally aromatic in its 6+ oxidation state with a Hückel circuit of 4n+2 = 162 π electrons.[5] Recent work on these systems will be presented.



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Reconstitution of the cell cytoskeleton

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The dynamic assembly and turnover of actin networks in cells control shape changes, migration and organelle function, as well as communication with extracellular substrates or neighbors. The intracellular actin cytoskeleton forms such complex intricate networks in cells that it is difficult to identify the principles of their dynamic self-organization. We have developed reconstituted systems *in vitro* as simplified models for the study of the cytoskeleton. Using this approach, we have established general principles on how the dynamic steady state of actin network emerges from biochemical and structural feedback.

Prix Jaubert 2020 Lecture – Blending old concepts with machine learning to discover homogeneous catalysts

Clémence CORMINBOEUF

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Sabatier's principle[1] developed in the first decades of the 20th century, states that an ideal catalyst should bind a substrate neither too strongly nor too weakly. Today, this simple idea provides the fundamental underpinning for "volcano plots", which are abundantly used in heterogeneous and electrocatalysis.[2]

Recently, we have elaborated a descriptor toolkit based on Sabatier's principle that rapidly identifies promising homogeneous catalysts.[3] We have further trained machine learning models with the aim of accelerating the catalyst discovery process.[4]

Examples of applications include prototypical classes of cross coupling reactions as well as other challenging organic processes. The massive quantity of data generated can be compiled and mined into an interactive tool, which facilitates the analysis and assists in identifying the most compatible metal/ligand family combinations and in establishing relationships between the intrinsic chemical properties of different catalysts and their overall catalytic performance.

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Quantum Biological Electron Tunneling (QBET) junction and its application in life science and medicine

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Quantum tunneling (QT) essentially involves in virtually all essential biological processes such as photosynthesis, cellular respiration, DNA repair, cellular homeostasis, and cell death. However, there is no real-time imaging method to capture biological electron tunneling in living cells to date. In this talk, I will present a quantum biological electron tunneling (QBET) junction and its application in life science and medicine. QBET junction permits to observe the behaviors of biological electron tunneling in enzymes of living cells. Using QBET spectroscopy, we obtain a real-time, *in vivo* optical imaging of electron transfer dynamics in mitochondrial cytochromes during cell life and death process. I will also discuss an *in vitro* application of QBET: the ultrafast quantum plasmonic polymerase chain reaction (PCR) for rapid precision molecular diagnostics. This quantum biological integrated circuit (QBIC) for precision medicine comprises three key elements: (1) ultrafast photonic PCR amplifications of DNA; (2) signal amplifications of proteins; (3) photonic cell lysis and sample preparation on a liquid biopsy chip, which allows a rapid sample-to-answer readout platform. Both *in vivo* and *in vitro* applications of QBET junction will open a new era in life sciences and medicine by allowing us to visualize the invisible quantum electron tunneling in enzyme reactions in living cells and to create innovative QBICs for rapid gene amplifications.

Studying and using hydrogenases

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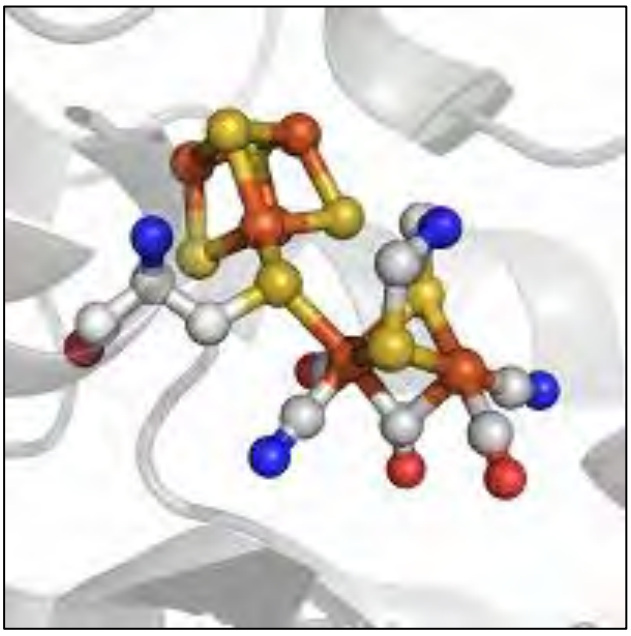
Hydrogenases are metalloenzymes that catalyze H_2 oxidation and formation at an inorganic active site. They are used in a variety of contexts, ranging from fundamental inorganic chemistry to the design of (photo)electrochemical fuel cells. Their active site is sensitive to light and small molecules such as CO and O_2. Studying the effect of inhibitors is a common approach for learning about the reactivity of enzymes' active sites; in the case of hydrogenase, understanding these reactions is particularly important because they may negatively impact the use of hydrogenase for the photoproduction of H_2. I will describe the mechanism of hydrogenases and show that combining theoretical methods, site-directed mutagenesis and electrochemical kinetics is a powerful approach for understanding at a molecular level their reactivity and to improve their resistance to inhibitors. It is also possible to embed and protect these enzymes in redox polymer films; this strategy affords new perspectives for the design of electrocatalysts of hydrogen oxidation and production.



The $[Fe_2(CO)_3(CN)_2$(dithiomethylamine)]
active site of FeFe hydrogenase.

References:

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Conformational control of symmetry breaking charge separation and singlet fission in bichromophores

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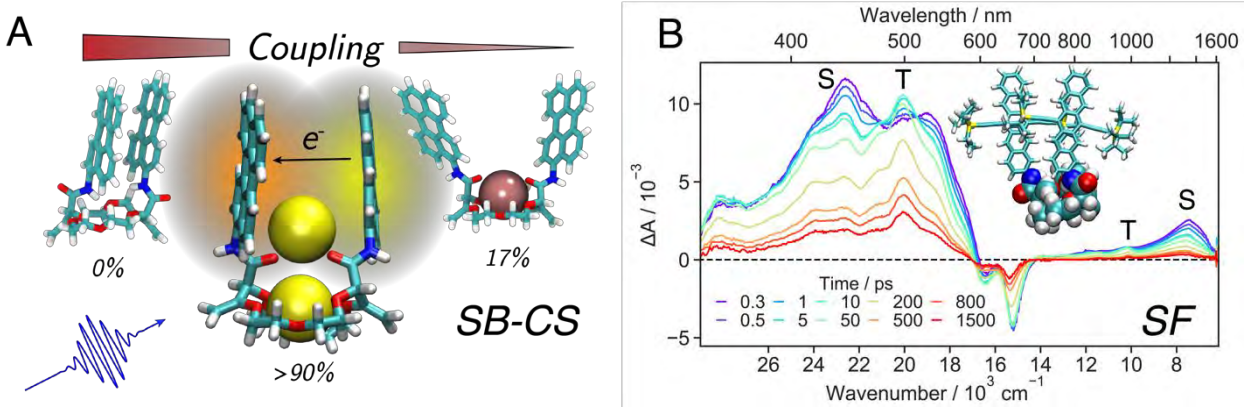
The structure-property relationship in multichromophoric systems is crucial to establish design principles in organic electronics as well as to fully comprehend how nature converts sunlight to energy. Bichromophores, consisting of two identical chromophores linked in a controlled geometry, are the model of choice to study how inter-chromophore conformation, can be used to tune the photophysical properties of a material.



In this communication, we will present two bichromophores consisting of either two perylene or two pentacene heads, connected by a crownether backbone. Even though the monomeric chromophores show similar photophysics, the processes observed in the linked dimers are completely different. Whereas the perylene dimer (Fig. A) can be used to model symmetry-breaking charge separation (SB-CS), pentacene (Fig. B) is known to undergo exothermic singlet fission (SF).

To access the impact of structure and coupling, different interchromophore conformers can be sampled by complexation of cations by the crownether backbone as shown in figure A. Transient absorption from femtosecond to microsecond and from UV to NIR is paired with molecular dynamics simulation. This allows to link the interchromophore geometries with the adiabatic dimer states formed in close proximity and the dynamics in which they are populated.

We will show that controlling the conformational restrictions can tune the SB-CS yield from zero to over 90% and enable or hinder the formation of free triplets upon SF.

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Synchronized on/off switching of four binding sites for water in a molecular Solomon link

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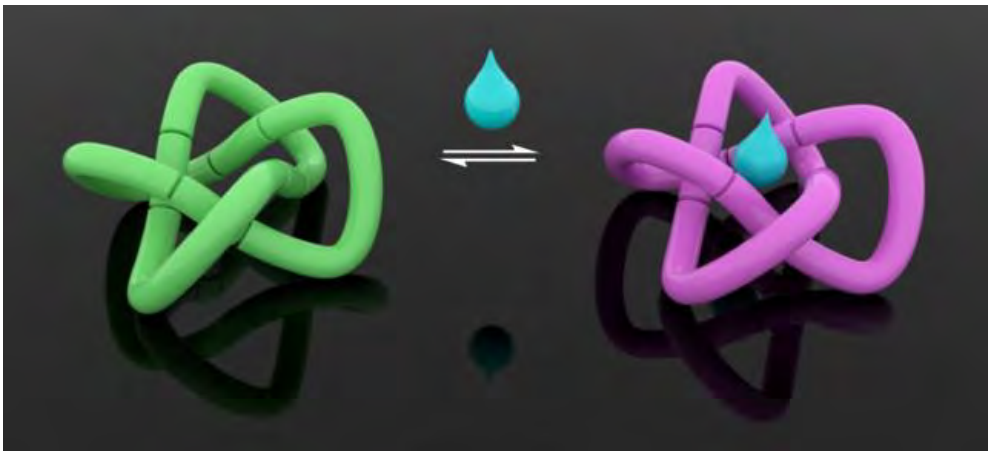
In biological systems, switching an individual binding site from one state to another often influences simultaneously or subsequently the state of neighboring binding sites.[1,2]

Here we present a molecular Solomon link[3] which adopts different conformations in acetonitrile (**1**) and in water (**2**). Contrary to expectations, the main driving force of the transformation is not the change in medium polarity, but the cooperative binding of about four molecules of water, forming a tiny droplet in the central cavity of **2**. Mechanistic studies reveal that the four binding sites can simultaneously switch between an inactive state (unable to bind water) and an active state (able to bind water) during the transformation. Spatial and temporal coordination of switching events is commonly observed in biological systems but has been rarely achieved in artificial systems. Here, the concerted activation of the four switchable sites is controlled by the topology of the whole molecule.



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Bioluminescent enzyme: From a reporter to an effector

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Bioluminescent enzymes, collectively known as luciferases, have been broadly used as reporters in biological applications ranging from cell-based assays to *in vivo* imaging.[1] Compared to conventional fluorescence imaging, bioluminescence imaging is ultrasensitive, shows high signal-to-noise ratios, because of no extraneous light required. Recently we reported a technology making use of a bioluminescent readout and smartphone quantification for specific oligonucleotide sequences detection. We demonstrated sensing of miRNA-21 sequence, a prominent cancer biomarker.

Aside from acting as a reporter, luciferase can also turn on functions in living systems.[2-3] In the second example I will show in this talk, we reported the application of luciferase to performing a biorthogonal reaction in living cells, releasing functional molecules through energy transfer to a coumarin molecule, a process termed bioluminolysis.[4] Compared to the conventional methods, this novel uncaging system requires no external light source and show fast kinetics ($t_{1/2}$ is less than 2min). We applied bioluminolysis system to release a potent kinase inhibitor, ibrutinib, in living cells, highlighting its broad utility in controlling the supply of bioactive small molecules *in vivo*.

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Mechanism of the inhibitory interference in human antimicrobial peptides

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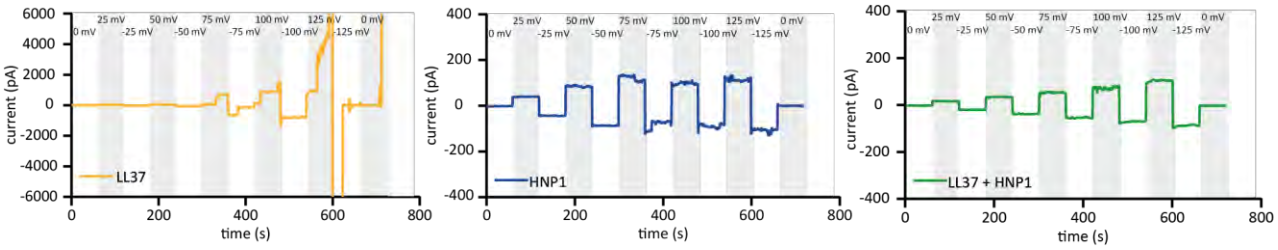
Antimicrobial peptides (AMPs) raise a great interest as an antibiotic alternative, yet their unpredictable side effects that originate from their low specificity hinder a major success as a therapeutic agent. How can we lower the peptide dosage to avoid the cytotoxicity without sacrificing their antimicrobial effects? Scientists have reported that bacteria were killed much more efficiently when two human AMPs, defensin and cathelicidin, were mixed.[1] In this work, we report that the same AMP mixture unexpectedly suppressed the cytotoxicity when incubated with eukaryotic cells. These discoveries suggest that we can "double-benefit" from mixing peptides for broadening the therapeutic window by orders of magnitudes. However, how an identical couple of peptides kills bacteria more efficiently yet reduces the cytotoxicity is left as a mystery. To tackle this open question, we characterized the cooperative function between defensin and cathelicidin, in living cells (MDCK, HUVEC, RPE1) and in synthetic bilayer systems by calcium sensitive dyes, mitochondrial staining, single channel conductance measurements, electrochemical impedance spectroscopy (EIS)[2], quartz crystal microbalance with dissipation (QCM-D), fluorescence recovery after photobleaching (FRAP)[3], isothermal titration calorimetry (ITC), circular dichroism (CD) and cryo-electron microscopy (cryo-EM)[4]. To our best knowledge, this is the first report on the inhibitory interference between defensin and cathelicidin and their mechanistic investigation at the molecular level.



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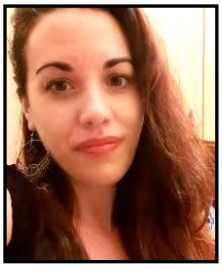
Achieving the selectivity of the synthesis of $B_nH_m^{z-}$ boron clusters for hydrogen storage and sodium batteries



Angelina GIGANTE

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Metal borohydrides $M(BH_4)_n$ have attracted a lot of interest in the past decades as candidates for solid-state hydrogen storage, leading to wealth of new compounds. Magnesium borohydride ($Mg(BH_4)_2$) has particularly caught the scientific community attention owing to its high gravimetric hydrogen content (14.8wt%).[1] Recently, it has been showed that $Mg(B_3H_8)_2{\cdot}2THF\text{-}2MgH_2$ system can be reversible hydrogenated to $Mg(BH_4)_2$ at 200°C and 50bar.[2] However, the presence of THF can affect the reaction pathways and the kinetic of the reversible hydrogenation. Until now, the synthesis methods reported in the literature have employed expensive and unfriendly routes, which require toxic chemicals like diborane B_2H_6 and mercury Hg. Our efforts are focused on the design of an efficient, cheap and eco-friendly synthesis, starting from the cheapest borohydride available on the market, namely $NaBH_4$.[3] I will show the synthesis of solvent free magnesium octahydrotriborate $Mg(B_3H_8)_2$ and its hydrogenation at 100°C with 85psi of H_2 followed by in situ solid ^{11}B NMR, *ex situ* ^{11}B liquid NMR and TPD-MS spectroscopy.[4,5]

Moreover, we have demonstrated that $B_3H_8^-$ ion is the intermediate to make the synthesis of closo-borates $B_{12}H_{12}^{2-}$ and $B_{10}H_{10}^{2-}$. Although *closo*-borates are solution processable, they are often synthesized through toxic chemicals like $B_{10}H_{14}$, hindering their development for any practical applications. Recently, a stable 3V all-solid-state batteries (ASSBs) based on the superionic conductor (1mScm^{-1} near room temperature) $Na_4B_{12}H_{12}B_{10}H_{10}$ has demonstrated excellent cycling stability.[6] Herein we developed a 5 steps, scalable and solution-based synthesis of $Na_4B_{12}H_{12}B_{10}H_{10}$. The use of the wet chemistry approach allows solution processing with high throughput and addresses the main drawbacks for this technology, specifically, the limited electrode-electrolyte contact and high cost. Furthermore, through the same process, we achieved a cost efficient synthesis for the expensive precursors $Na_2B_{10}H_{10}$ and $Na_2B_{12}H_{12}$. We investigated the mechanism of the reactions and highlighted two key parameters to tune the kinetics and selectivity: The choice of the counter cation, herein tetrae-thylammonium ($(C_2H_5)_4N^+$, TEA^+), and the solvent.[7]

References:

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Lipid nanotubes as an organic template for nanofabrication

Kristina JAJCEVIC

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The fabrication of conductive nanostructures is the key technology in semiconductor industry and has gained importance in biology for applications such as biosensors and drug delivery. There is a growing interest in the use of lipid nanotubes (LNTs) as templates in the fabrication of one-dimensional nanostructures such as gold nanowires.

The lipid 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) which is the main component of bacterial cell membranes is known to self-assemble into single-wall synthetic LNTs on polyelectrolyte-functionalized surfaces.[1-3] We have demonstrated a high-throughput approach to fabricate gold nanowires on surfaces with a LNT template. First, biotin-tagged DOPE LNTs are formed from lipid blocks in inverted hexagonal phase adsorbed on polymer-coated surfaces upon application of shear force. Streptavidin-coated gold nanoparticles were then attached to the biotin-tagged LNTs and gold nanoparticle-encapsulated LNTs were cross-linked by chemical fixation.[4] Samples were dried and particles were connected through electroless gold metal plating to form gold nanowires. Similarly, the created LNTs without the attachment of gold nanoparticles were adsorbed on polymer-coated surfaces and cross-linked by chemical fixation. These were dried and treated with high temperature in a process of pyrolysis under inert atmosphere to form connected carbon nanostructures. The created nanowires and carbon nanostructures were characterized by transmission electron microscopy, atomic force microscopy and electrical measurements.

The method is advantageous because the small size of LNTs enables the fabrication of solid nanostructures with a higher throughput without using expensive electron beam lithography. The approach can further be combined with single LNT patterning with a micromanipulator to create distinct patterns instead of random networks.

References:

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Alloying of thiolate protected gold nanoclusters

Rania KAZAN

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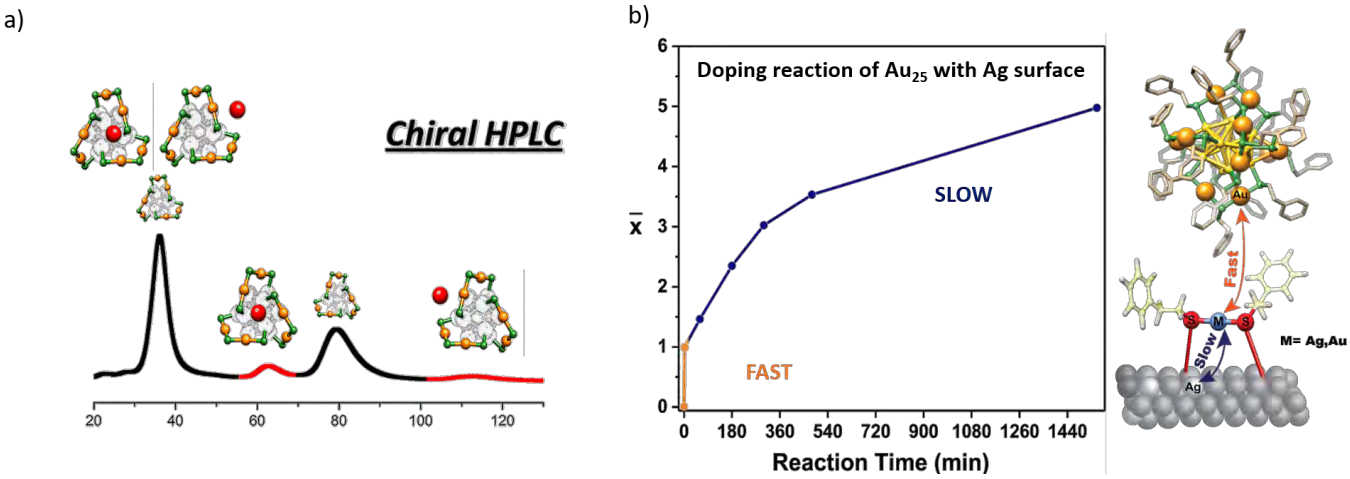
Thiolate protected gold nanoclusters have gained substantial attention due to their precise atomic composition and their well-defined structure. The composition of such clusters and as a result their physical and chemical properties can be tailored by the introduction of different metal atoms forming thus alloy nanoclusters. This can be achieved either by replacing the Au atoms in the cluster with metal heteroatoms forming doped clusters, or by simply adding the latter to the cluster thus forming adducts.[1]

In this study, a $CuAu_{38}$ bimetallic alloy was synthesized by adding a single copper atom to the chiral $Au_{38}(2\text{-PET})_{24}$ nanocluster. A separation of an alloy cluster was attained for the first time where isomers of the E2 enantiomer of the $CuAu_{38}$ adduct were successfully separated from their parent cluster using chiral HPLC and their corresponding CD spectra were recorded.[2]

Moreover, a new technique was introduced for doping gold nanoclusters by using a metal surface such as Ag, Cu and Cd as a source of heteroatoms. The importance of the thiol ligand in the doping process is examined by following the reactions with MALDI-TOF mass spectrometry in the presence and the absence of the thiols on the surface. The availability of the ligand is a crucial element for alloying where it acts as a messenger exchanging the metal atoms between the cluster and the metal surface as revealed by the XPS studies performed on the metal surfaces.[3].



(a) HPLC chromatogram showing the separation of the $CuAu_{38}$ bimetallic alloy. **(b)** Change in the average number of doped Ag atoms ($\bar{x}$) in Au_{25} cluster throughout the reaction with the Ag surface modified by 2-PET thiol (left) and the model to explain the mechanism (right).

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Identification/characterization of *D. discoideum* response factors involved in pathogen detection and stress signal transduction

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The social amoeba *Dictyostelium discoideum* is a recognized professional phagocyte model to study processes of cell-intrinsic defenses, which are conserved in professional phagocytes of the animal immune system, such as macrophages or neutrophils. We use *D. discoideum* as a host cell for the pathogenic bacterium *Mycobacterium marinum*, a close relative of *Mycobacterium tuberculosis*, to study the molecular mechanisms of the host-pathogen interactions during infection. Following uptake by the host cell, *M. marinum* inhibits host defense mechanisms such as autophagy and lysosomal-dependent degradation, to establish a permissive niche with endosomal features, where it replicates. Studies in animals showed a group of host factors involved in stress signaling transduction, pathogen detection and restriction of its intracellular proliferation, such as TRAFs, TRIMs and STATs. TRAFs are E3 ubiquitin ligases of the TNF-receptor associated factors protein family.

In mammalian cells, TRAFs are involved in a variety of immunity-related biological processes, including the decoration of intracellular pathogens and/or their vacuole with K63-linked polyubiquitin chains serving as autophagy “eat-me” signals. They also act in the regulation of the autophagy and the NF-kB proinflammatory signaling pathways. Little is known about the upstream sensors, recognizing the pathogen and promoting activation and recruitment of the TRAF proteins, and the downstream actors, relaying the stress signal and leading to differential expression of defense genes.

Therefore, to identify relevant relationships and potential partners in these immune pathways, we are exploiting and characterizing the human TRAF orthologs in *D. discoideum*. We carry out RNA-seq and RT-qPCR to track the mRNA levels of the aforementioned factors during *M. marinum* infection. In addition, we monitor by live microscopy the sub-cellular localization of these proteins tagged with fluorescent proteins expressed either as knock-in fusions or ectopically, in normal and stress conditions. Furthermore, we use intracellular growth assays and high-content confocal microscopy to quantitate mycobacterial survival within *D. discoideum* knockout cells lacking these factors. Finally, we aim at identifying relevant interaction partners by immunoprecipitation and APEX2 proximity labelling techniques.

SARA endosomes and microtubules asymmetry during asymmetric cell division in Zebrafish

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Over asymmetric cell division of Zebrafish neural precursor cells, Sara endosomes are asymmetrically inherited during directional trafficking on microtubules (MTs).[1] They carry an endocytosed pool of the cell fate determinant Notch ligand Delta, resulting in a bias in the signalling events between the two daughter cells and generation of different neuronal types.

How the asymmetric dispatch of Sara endosomes is achieved is still unclear in vertebrates. In fly's sensory organ precursor, central spindle asymmetry during anaphase induces asymmetric Sara endosomes inheritance. Patronin, a MTs-minus-end binding protein which stabilizes MTs is more present in one daughter cell; this dispatch generates a difference in MT density and their antiparallel array.[2]

Here, I study the role of its homolog in zebrafish neural precursor cells: Calmodulin-regulated spectrin-associated proteins (CAMSAPs). Preliminary assays have shown that spindle-associated-MTs have an asymmetric density between the sides of a dividing cell in anaphase for 50% of the cases whereas when CAMSAPs are knockdown by morpholinos injection, the asymmetry of MTs drops to 15%. To further understanding the mechanism of Sara endosomes asymmetric segregation during neural precursor cell division, the CRISPR/CAS9 technology is currently used to generate Knock-in mutants for GFP-Sara, and Knock-out mutants for CAMSAP2a, CAMSAP2b, and CAMSAP3a.

Therefore, the traveling of Sara endosomes is monitored according to the central spindle enrichment during neural precursor cell division in Zebrafish spinal cord. Extraction of physical parameters allows characterizing the motility and density of Sara endosomes on the spindle through space and time dimensions.

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Cell response upon osmotic shock: Entangling the role of ion channels and cytoskeleton

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Lipid membranes are auto-assembled viscoelastic bilayers separating the cells from their environment. The elastic properties of the lipid bilayers present unique features; they are very easy to bend but quite resistant to stretching. These properties strongly affect all cellular processes that require membrane remodelling. Cells have thus evolved to respond to changes of membrane tension. The genetic response to an osmotic stress has been studied extensively but its timescale is of the order of minutes, and cannot account for immediate resistance to stretch.

In order to have a quantitative description of the relationship between the membrane tension, area, volume and osmotic shocks, we perform time-resolved membrane tension measurements coupled with 3D imaging.

The observed cellular response is highly asymmetric: In hypoosmotic shocks, the volume, tension and area increase seconds after shock, and proportionally to the osmotic pressure difference. All parameters restore their initial values within minutes. In hyperosmotic shocks, the volume shrinks proportionally to the osmotic pressure difference but no recovery is observed.

However, the membrane tension changes proportionally to the change of apparent surface area, which is essentially controlled by volume changes. This suggests that the immediate response of cells to osmotic shocks is related to the membrane area changes due to cytoplasmic volume changes in accordance to osmotic equilibrium between the inside and the outside of the cell. This can be confirmed by the inhibition of cytoskeleton dynamics, leaving the immediate cell response unchanged.

Such drastic changes of volume induce drastic modification of cell crowding. The absolute variations of protein concentration are proportional to the cell volume, confirming the absence of protein exchange (endocytosis, exocytosis) on short timescales. Indeed, changing the cytoplasm crowding induces changes of nucleus volume following the cell volume changes. On long timescales, it might impact the genetic response.

Finally, inhibiting specific ion channels allows us to observe the main role of VRAC (Volume-regulated anion channel); preventing osmolytes going through the membrane leads to the explosion of the cells. This shows that ion channels are responsible for the immediate cell response.

Modifier effect on differential ion mobility mass spectrometry analysis of isomeric drugs

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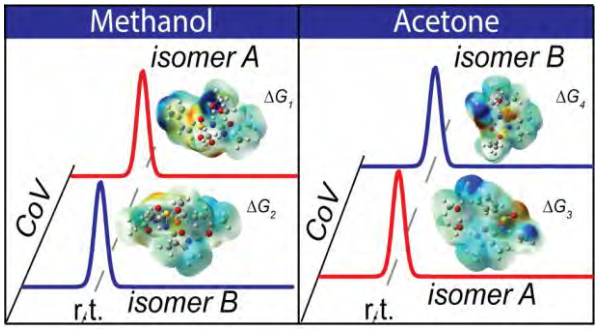
Liquid chromatography mass spectrometry is commonly used for complex matrix sample analysis for different applications. However, it often lacks selectivity, especially for isobaric/isomeric analytes or interferences that are not resolved in the chromatographic dimension. The recent availability of ion mobility devices has enabled its implementation as an additional separation dimension prior to mass analysis and detection.



Therefore, such hybrid instruments offer improved selectivity and specificity of analysis and better MS data quality. Most of the ion mobility instruments are utilising pure nitrogen or helium gas as an ion carrier or drift gas, and the ion separation is mostly done by shape to charge ratio. The special feature of the differential ion mobility is the possibility to use polar organic solvent as chemical modifier in the nitrogen carrier gas, offering specific separation mechanisms. Differential ion mobility is mainly driven by two widely accepted mechanisms, collision-deflection when pure nitrogen is used and clustering-declustering when chemical modifiers are added.[1] Cluster formation in the alternating electric field during differential ion mobility is critical for separation selectivity and is governed by two factors. One factor is the reduced mass[2] and the other factor is cluster binding energy between an ion and a neutral solvent molecule (modifier). Therefore, separations of isomeric analytes with certain modifier (the same reduced mass) can be related to the thermochemistry of the cluster formation, as subtle changes in the molecular structure will affect its charge delocalization. Consequently, the binding energy with the corresponding modifier will be different.

We have examined the relation between the calculated Gibbs free energies of the cluster formation and experimental ion mobility measurements (*i.e.* CoV dispersion plots) considering the most prominent ion-modifier interactions: Charge-dipole, dipole-dipole and charge-quadrupole. In order to explain selectivity effects due to the chosen modifier, we have selected series of positional isomers of sulfonamide drugs that were analyzed in positive and negative electrospray. Additionally, the diastereoisomers ephedrine and pseudoephedrine in positive mode. We could demonstrate a dependence of the separation selectivity of the differential mobility on the reduced mass and the Gibbs free energy of the cluster formation. These results are supported by extensive thermochemistry calculations (DFT) and interpreted by molecular modelling.
Finally, we applied a selectivity tuning of the differential ion mobility for implementation in comprehensive multidimensional LCxDMS-MS separation of sulfonamide isomers in human plasma.

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Silica interactions in aqueous solutions of multivalent coions

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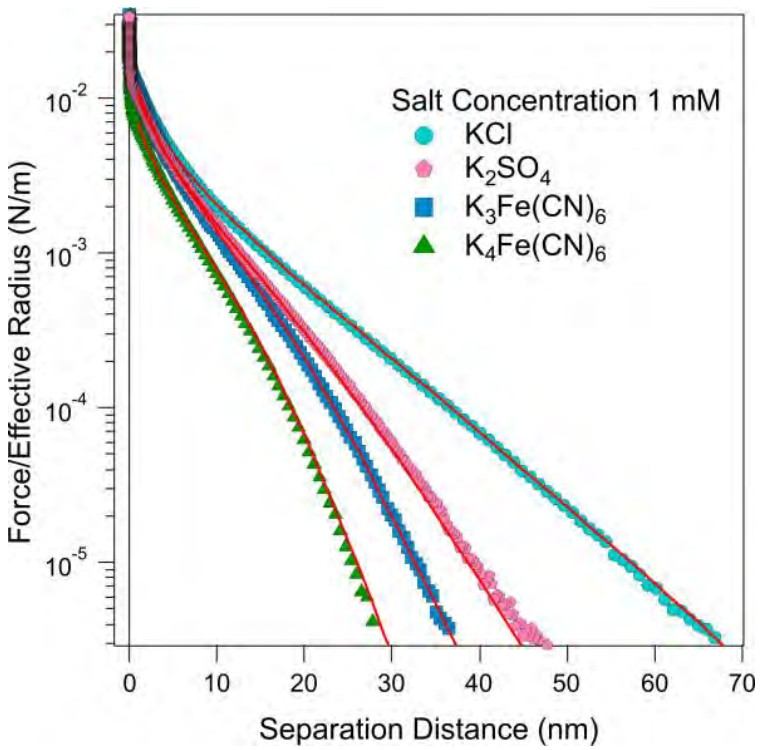
Colloidal probe technique based on atomic force microscopy was used to measure interaction forces between charged silica particles in aqueous solutions. For various concentrations of different salts: KCl, K_2SO_4, $K_3Fe(CN)_6$, and $K_4Fe(CN)_6$, the measurements are done at pH=10. These multivalent anions are coions, since the silica surface is also negatively charged. For low salt concentrations where ions hardly adsorb, forces are dominated by double layer repulsion.[1] For concentrations above 200 mM, Van der Waals attraction is observed.

The valence of coion influences the shape of force curves. For the same ionic strength, force curves in presence of multivalent coions are softer and have sigmoidal appearance in semi-logarithmic representation. The shape is explained by Poisson-Boltzmann theory. At large distances both monovalent counterions and multivalent coions are in the slit between two charged surfaces. At close proximity the multivalent ions are expelled from the slit because of the strong electrostatic repulsion.

Diffuse layer potential and regulation parameter dependencies are shifted to lower concentration with increasing coion valence, if plotted as function of concentration of salt. However, when presented as function of monovalent counterion concentration, the same profiles collapse to a master curve.



Measured force curves for 1 mM concentration of different salts at pH=10 with DLVO fits (red line).

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Fluorescent probes to image physical forces in living cells

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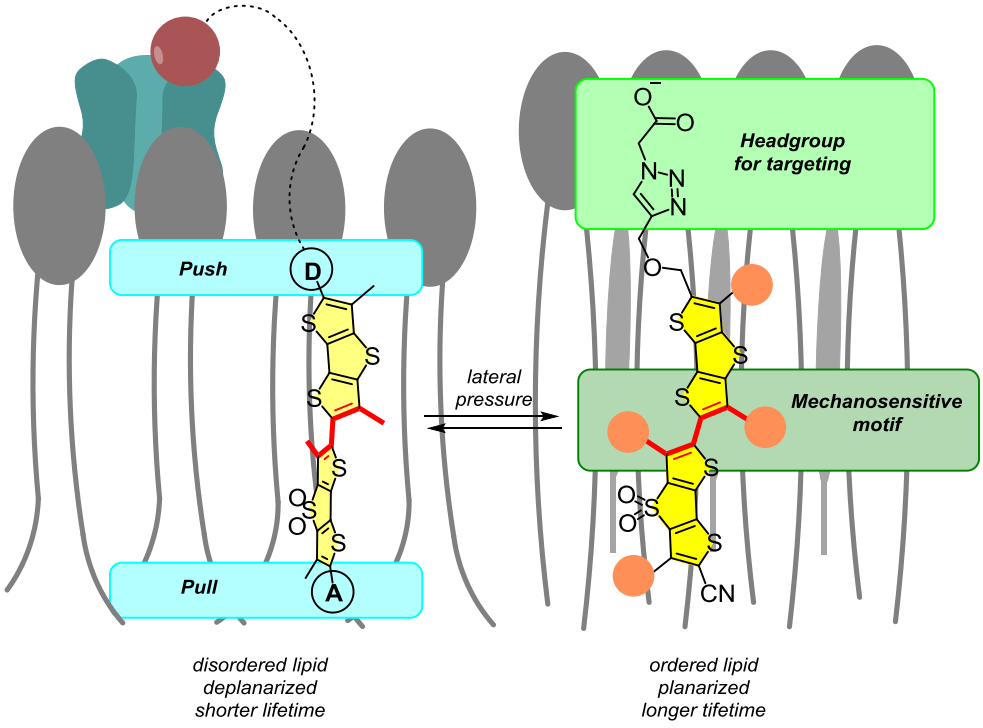
Aiming to provide better understanding of cellular membrane behavior, mechanosensitive fluorescent probes have been developed. These push-pull dithienothiophene ("flipper") dimers can respond to varying forces in membranes by a combined effect of ground state planarization and polarization, thus giving a direct fluorescent readout of tension and lateral organization of membranes.[1]

In past few years, our attention has been focused in two directions: a) improving the spectroscopic and mechanical properties of the dye and b) attaching targeting groups to specifically reach desired cellular sites. By tailoring our flippers almost atom by atom, we have gained insight on the relationship between twist extent/push-pull strength and mechanosensitivity.[2,3] Moreover, we have been able to specifically stain membranes of several cellular organelles[4] and further studies using HaloTag and streptavidin-biotin technology are ongoing.



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Investigating the impact of electrospray adducts in liquid chromatography – mass spectrometry

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The discovery of new biomarkers is essential to allow personalized medicine to establish itself in general healthcare for the development of patient-specific diagnostics, prognoses and therapies. Patient screening for disease-specific biomarkers requires the use high-throughput analytical techniques for rapid and accurate identification and quantification of target molecules. Liquid chromatography coupled to mass-spectrometry (LC-MS) has become the technique of choice for metabolite profiling. However, the high complexity of LC-MS spectral data combined with large sample cohort frequently prohibits manual data processing and interpretation. Additionally, the use of automated software solutions often results in false identification and a large overestimation of metabolites in the sample. High spectral complexity arises from the great diversity of ions commonly generated with Electrospray Ionization (ESI) sources and is known as a major cause of the aforementioned issues and is still poorly understood. Beside protonated and deprotonated ions, neutral losses, oligomers, as well as a large variety of adduct ions including sodium and potassium are regularly detected in both positive and negative mode ESI-MS. Adducts are undesirable as they not only significantly increase data complexity, but also affect reproducibility and decrease the sensitivity of quantitative assays.

Here we investigate using bioinformatics tools and high resolution mass spectrometry, the nature and occurrence of the most abundant adduct ions for three metabolite libraries of several hundreds of compounds on different analytical system and in positive mode flow injection analysis (FIA) and LC-MS. About 50% of the signal in the spectra from these three datasets could be interpreted using 14 annotations including protonation, neutral losses, sodium and potassium adducts, as well as oligomers. We present an open source annotation software (mzAdan) for metabolite identification. MzAdan was implemented for data reduction in a metabolite identification workflow. The performance of our approach is compared with two widely popular annotation software (CAMERA and FindMain) with a set of 52 metabolites and pooled urine samples. CAMERA, FindMain, mzAdan could annotate 21, 48, 44 of the 52 metabolites of a standard mix, respectively. Camera and FindMain failed to annotate target metabolites present in the pooled urine samples. MzAdan did annotate correctly 21 of the 35 target metabolites and lead to a spectral complexity reduction of 50% in the LC-MS analysis.

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