XXIV^{èmes} Rencontres du Club Jeune de la SFSM

Ecole de printemps

Club Jeune
SFSM

18 au 22 mars 2019
Auberge des Dunes
Saint-Pierre-Quiberon (56)

programme

Programme détaillé

	LUNDI	MARDI	MERCREDI	JEUDI	VENDREDI
8h30					**Libérer les chambres avant 8h30**
		C1A -Métabolomique **(C. Junot)** **1h30**	**C2B - Traitement de données** **(Y. Guitton)** **2h**	**C3B – Modes de fragmentation** **(S. Alves)** **2h**	**Sponsors** **Session 5** **6 communications** **1h30**
		Pause café	*Pause café*	*Pause café*	*Pause café*
		Session 1 **6 communications** **1h30**	**C3A – Modes de fragmentation** **(S. Alves)** **2h**	**Session 3** **4 communications**	**Session 6** **6 communications** **1h30**
12h30		**Sponsors**		**Sponsors**	
		REPAS	**Sponsors**	*REPAS*	Départ des participants en car
14h			*REPAS*		
		C1B - Métabolomique **(C. Junot)** **1h30**		**C4A – Analyse polymères** **(J. De Winter)** **1h30**	Arrivée à Auray aux alentours de **13h50**
	16h30 - Départ en car de la gare d'AURAY	*Pause café*		*Pause café*	
		C2A- Traitement de données **(Y. Guitton)** **2h**	**Après-midi récréative**	**C4B – Analyse polymères** **(J. De Winter)** **1h30**	
	Accueil des participants sur le site	**Session 2** **2 communications**		**Session 4** **4 communications**	
18h30					
19h30					
	REPAS	*REPAS*	*REPAS*	*REPAS*	
	Soirée d'accueil			**Soirée à thème**	

Mardi 19 mars

Modératrice : Thaïs Hautbergue

C1A 8h30 – 10h00 :

« Métabolomique »
Christophe Junot
LEMM - CEA

Ehan kafeta

Session 1 : 10h30 – 12h00

10h30 **O1** – " *Metabolomic Profiling in Aortic Valve Stenosis* "

Cynthia Al Hageh – LAU (Liban)

10h45 **O2** – " Direct insertion probe and atmospheric pressure ionization coupled to high-resolution mass spectrometry for the description of lignocellulosic biomass "

Clément Castilla – COBRA Rouen

11h00 **O3** – " A MALDI mass spectrometry study of the segregation of lignocellulosic structures in several maize stems with contrasted degradability in biorefinery "

Bastien Arnaud – INRA Nantes

11h15 **O4** – " Détection et caractérisation des entérotoxines staphylococciques dans les aliments par couplage chromatographique liquide- spectrométrie de masse "

Donatien Lefebvre – CEA Saclay

11h30 **O5** – " Analyse métabolomique non ciblée du méconium par LC/HRMS "

Nihel Bekhti – CEA Saclay

11h45 **O6** – " Red cabbage anthocyanins: equilibria and chemical stability in neutral conditions "

Julie-Anne Fenger – Université Avignon

12h00 – 12h30 :

Présentations partenaires industriels :

Etienne Maout (Shimadzu)

Catherine Balthasar (Cluzeau)

Mardi 19 mars

Modérateur : Nicolas Eskenazi

C1B 14h00 – 15h30 :

« Métabolomique»
Christophe Junot
LEMM - CEA

Ehan kafeta

C2A 16h00 – 18h00 :

« Introduction au traitement de données de LC-HRMS pour la métabolomique »
Yann Guitton
LABERCA - ONIRIS

Session 2 : 18h00 – 18h30

18h00 **O7** – " Collision cross sections of chemical warfare related compounds by ion mobility spectrometry - mass spectrometry "
Valentin Baillet – COBRA Rouen

18h15 **O8** – " KIT QUANTA - standardization kit for absolute protein quantitation: monitoring of methionine oxidation induced by liquid chromatography separation "
France Baumans – LSM Liège

Mercredi 20 mars

Modératrice : Julie-Anne Fenger

C2B 8h30 – 10h30 :

« Introduction aux méthodes statistiques pour la métabolomique »
Yann Guitton
LABERCA - ONIRIS

Ehan kafeta

C3A 11h00 – 13h00 :

« Tandem mass spectrometry »
Sandra Alves
CSOB - IPCM

Présentation partenaire industriel :

Sabine Jourdain (Bruker)

Après-midi récréative

Jeudi 21 mars

Modérateur : Emmanuel Colson

C3B 8h30 – 10h30 :

« Tandem mass spectrometry »
Sandra Alves
CSOB - IPCM

Ehan kafeta

Session 3 : 11h00 – 12h00

11h00 **O9** – " Dommages de la centrine 2 humaine soumise à un stress oxydant : identification et caractérisation structurale des produits d'oxydation par spectrométrie de masse "
Anouchka Gatin – LCP Orsay

11h15 **O10** – " Development of Ion Mobility Spectrometry –Mass Spectrometry (IMS-MS) for high throughput and large scale metabolomic analyses "
Aurélie Delvaux – UPMC Paris

11h30 **O11** – " Stools lipid profiling by HILIC LC-MS/MS "
Justine Hustin – LSM Liège

11h45 **O12** – " Emergence de biopolymères de complexité contrôlée dans les scénarios d'origine de la Vie "
Lise Bedoin – Jussieu Paris

12h00 – 12h30 :

Présentation partenaire industriel :

Philippe Firmin - Nicolas Salle (Agilent)

Jeudi 21 mars

Modération : à définir

C4A 14h00 – 15h30 :

« Probing the Primary and Secondary Structures of Synthetic Polymers, how far can we go with mass spectrometry? »
Julien de Winter
UMONS


Ehan kafeta


C4A 16h00 – 17h30 :

« Probing the Primary and Secondary Structures of Synthetic Polymers, how far can we go with mass spectrometry? »
Julien de Winter
UMONS

Session 4 : 17h30 – 18h30

17h30 **O13** – " Identification de métabolites secondaires de souches de levures par LCMSMS "
Olivier Perruchon – COBRA Rouen

17h45 **O14** – " Dispersion of the mass accuracy in a MALDI image (TOF-TOF analyser) "
Sophie Rappe – LSM Liège

18h00 **O15** – " Tuning the hemolytic activity of Horse Chestnut saponins by molecular engineering "
Emmanuel Colson – UMONS Belgique

18h15 **O16** – " Contribution of electron-based fragmentation methods for study of synthetic polymers by tandem mass spectrometry "
Inès Aloui – LAMBE Evry

And last but not least...

Jeudi 21 mars

(Avec) Modération

Repas
&
Soirée à thème

No marinière,
No service

Thème de la soirée
La Bretagne

Vendredi 22 mars

Modération : à définir

8h30 – 9h00 :

Bilan des RCJSM et
présentation des activités du CJSM

Présentation partenaire industriel :

Freddy Drouyé (Waters)

Session 5 : 9h00 – 10h30

9h00 **O17** – " Analyse simultanée d'hormones et de perturbateurs endocriniens par couplage de la chromatographie liquide à la spectrométrie de masse : un challenge analytique "
Elodie Mirmont – LNE Paris

9h15 **O18** – " Structural study of analogues of Titan's haze by trapped ion mobility coupled with a Fourier transform ion cyclotron mass spectrometer "
Julien Maillard – COBRA Rouen

9h30 **O19** – " UHPLC-IMS-MS as a new tool for the characterization of the membrane lipids of Pseudomonas aeruginosa "
Estelle Deschamps – COBRA Rouen

9h45 **O20** – " Identification of cell-penetrating peptides interaction partner by affinity photocrosslinking coupled to mass spectrometry "
Leila Bechtella – Sorbonne Paris

10h00 **O21** – " Collision cross sections of phosphoric acid cluster anions and their use as calibrants for Traveling Wave Ion Mobility "
Valentina Calabrese – COBRA Rouen

10h15 **O22** – " Distribution study of paracetamol and its metabolites in rat whole body after on-tissue chemical derivatization by MALDI Mass Spectrometry Imaging "
Mira Merdas – Protim Rennes

Ehan kafeta

Vendredi 22 mars

Modération : à définir

Session 6 : 11h00 – 12h30

11h00 **O23** – " Electrospray Ionization and co-elution in Meta-metabolomics: a biomarker or a suppressed ion? "
Hikmat Ghosson – CRIOBE Perpignan

11h15 **O24** – " Analyse d'oxylipines par LC-MRM "
Déborah Lefèvre – Gustave Roussy

11h30 **O25** – " nanoLC-MS/MS of glycoproteoforms and proteolytic glycopeptides combined with glycan fingerprinting: a powerful strategy for glycoprotein characterization "
Nicolas Eskenazi – SMBP Paris

11h45 **O26** – " Combining tandem mass spectrometry with ion mobility spectrometry to decrypt information encoded in sequence-defined poly(alkoxyamine phosphodiester)s "
Jean-Arthur Amalian – ICR Marseille

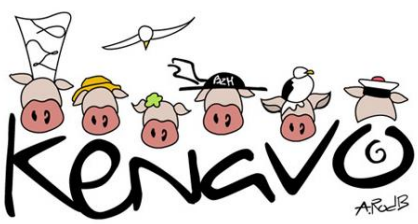
12h00 **O27** – " HPTLC (High Performance Thin Layer Chromatography) coupled with LA-ICP-MS (Laser Ablation Inductively Coupled Plasma Mass Spectrometry) and LDI/MALDI-FTICR-MS (Laser Desorption Ionization Fourier Transform Ion Cyclotron Resonance Mass Spectrometry) to study asphaltenes "
Rémi Moulian – IPREM Pau

12h15 **O28** – " Characterization of polar lipids in Brewer's spent grains"
Ali Zaiter – LCPA2MC Metz

Départ en car

Arrivée prévue en gare d'Auray à 13h50

Repas distribués dans le car



partenaires industriels

Remerciements

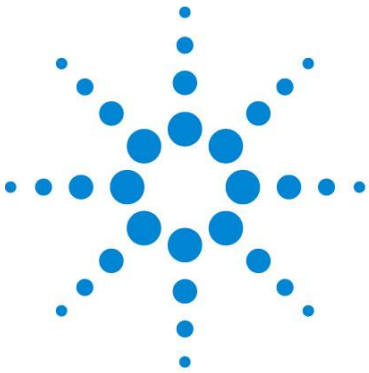
UN GRAND MERCI !

Aux entreprises et laboratoires qui ont soutenu le Club Jeune pour ces rencontres.

Nous remercions en particulier les fabricants de spectromètres de masse (**Bruker**, **Agilent**, **Shimadzu** et **Waters**), de venir partager leur expertise dans le domaine, et **Cluzeau info labo** qui commercialise notamment des accessoires d'analyse chromatographique.

Nous remercions également **Ionbench** qui fabrique des supports spécifiques pour spectromètres de masse, ainsi que **Eurisotop** qui élabore des standards et kits de quantification pour MS, marqueurs isotopiques et solvants.

Un grand merci aux entreprises locales, l'école doctorale **Matière Molécules et Matériaux** et le laboratoire **SQPOV** pour leur précieux soutien, ainsi que la **Gazette du Laboratoire** pour sa collaboration !



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Etienne MAOUT

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Freddy Drouyé

MS Specialists Team Manager

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Communications orales

O1 - Metabolomic Profiling in Aortic Valve Stenosis

Cynthia Al Hageh[1], Dr Dominique Gauguier[2], Dr Rony Khnayzer[1], Dr Pierre Zalloua[1]

[1] *Department of Natural Sciences, Lebanese American University, Chouran, Beirut 1102-2801, Lebanon*
[2] *University Paris Descartes, 15 rue de l'Ecole de Médecine, 75006 Paris, France*

Funded by CNRS-L

The idiopathic Aortic Valve Stenosis (AVS) results from the calcification and degeneration of aortic leaflets. AVS affects the elderlies and to date there are no effective pharmacological treatments. However, aortic valve replacement is the only way to remove the obstruction. Human biofluids are highly rich in metabolites which constitute the end-point of gene expression. Thus, metabolomics offer an unparalleled opportunity to identify biomarker(s). The latter aids in understanding the molecular origin of AVS and subsequently facilitates the development of new therapeutic approaches. To this end, untargeted and targeted metabolomic profiling was deployed. 90 urine and plasma samples were acquired and segregated between cases and controls. All samples were extracted using optimized published methods. GC/MS and MALDI-TOF/MS measurements were performed to identify and quantify the metabolites present in each sample. Hundreds of metabolites were confidently identified and quantified in the various samples using high-throughput data analysis. Preliminary results revealed general metabolomic profiling from the GC-MS chromatograms and more specific lipidomic profiling using MALDI-TOF/MS spectra.

O2 - Direct insertion probe and atmospheric pressure ionization coupled to high-resolution mass spectrometry for the description of lignocellulosic biomass

Clément Castilla, Christopher Rüger, Hélène Lavanant, Carlos Afonso

Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA, 76000 Rouen, France

Lignocellulosic biomass, in particular wood, is a complex mixture containing cellulose, hemicellulose, lignin, and other traces compounds. Chemical analysis of these biomasses, especially lignin components is a challenge. Lignins are highly reticulated polymers that are poorly soluble and usually require chemical, enzymatic or thermal degradation for their analysis. We chose to emulate evolved gas analysis (EGA) by studying the thermal degradation of lignocellulosic biomass using a direct insertion probe (DIP). Here we used and compared DIP with two ionization sources: atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) coupled to high resolution mass spectrometry.

Source and transmission parameters were first optimized to avoid space charge in the analyzer. A resolving power of roughly 200 000 was achieved at m/z 400 with a transient length of 0.699 s. For the two sources, two main ion distributions were observed, that most likely corresponded to lignin monomeric and dimeric degradation products. A time-resolved analysis revealed the steps of the pyrolysis process, with first the formation of low mass volatile compounds then molecules of higher mass.

Comparison of APPI and APCI showed these reproducible molecular attributions were dominated by oxygenated series from CxHyO2 to CxHyO7, in both sources. Classical marker species, such as paracoumaryl, coniferyl, and sinapyl alcohol were found among these oxygenated molecules. Van Krevelen plots revealed aliphatic compounds to be more abundant for APCI whereas APPI revealed predominantly unsaturated/aromatics compounds.

The comparison of the three feed sample types (oak, maple, and beech) with APCI showed molecular level differences in the distribution of oxygenated components and aromaticity of the volatilized species.

O3 - A MALDI mass spectrometry study of the segregation of lignocellulosic structures in several maize stems with contrasted degradability in biorefinery

Bastien Arnaud[1,2], Sylvie Durand[1], Mathieu Fanuel[1], Fabienne Guillon[1], Valérie Méchin[2], Hélène Rogniaux[1]

[1] UR1268, Biopolymers Interactions Assemblies, INRA Nantes, France
[2] UMR 1318, Institut Jean-Pierre Bourgin, INRA-AgroParisTech, CNRS, Université Paris-Saclay, Versailles, France

To offset the exhaustion of fossil fuels without competing with food productions, second-generation biofuels deriving from the lignocellulosic biomass are under development. Maize stems are good candidates for a future industrial production, but the yield of their enzymatic conversion remains low. The factors involved are not fully understood and need to be hierarchized.

The purpose of the work presented in this communication is the determination of the molecular structures - in connection with tissues degradability - of the lignocellulosic compounds in stems. To get this, different enzymes against lignocellulosic compounds were applied on sections of maize stems. Various genotypes at various stages of development were studied. To get at the same time spatial and chemical information, stalks were imaged by MALDI mass spectrometry.

Hemicelluloses were targeted first. The obtained results highlighted that the chemical structure of hemicelluloses varies according to the stem cross - section region: arabinoxylans (AX) were observed in the center of the stem, while methylglucuronoxylans (MGX) were more peripheral. Cellulosic products could also be seen with a peripheral distribution. Variation of the hemicellulose derived compounds according to development stages and genotypes was also investigated, and a relationship could be established with the degradability of the tissues.

The detection and visualization of hydroxycinnamic acids, another key compound of lignocellulosic structures, will be the future lead to complete the results of this study.

O4 - Détection et caractérisation des entérotoxines staphylococciques dans les aliments par couplage chromatographie liquide-spectrométrie de masse

Donatien Lefebvre, Yacine Nia, François Becher

Commissariat d'Energie Atomique (CEA) de Saclay
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)

Les toxi-infections alimentaires collectives (TIAC) à staphylocoques sont causées par l'ingestion d'aliments contaminés par des entérotoxines staphylococciques (ES), produites par certaines souches de staphylocoques à coagulase positive. À ce jour, 27 ES sont décrites dans la littérature mais seules cinq types, SEA à SEE, sont détectables en routine via la norme EN ISO 19020. Cette méthode, basée sur le principe ELISA (Enzyme-Linked Immunosorbent Assay) peut détecter qualitativement ces cinq ES sans les distinguer. Lors de l'investigation de nombreux foyers humains, il arrive régulièrement qu'aucune ES de type SEA-SEE ne soit retrouvée alors qu'une symptomatologie typique d'intoxication à staphylocoque a été identifiée, et que des souches codants pour d'autres gènes type *seg, seh, sei, ser*… ont été isolées de produits suspectés être à l'origine de TIACs. Il est donc impératif de disposer d'outils d'analyse et de confirmation capable de viser une large gamme de toxines. Dans ce projet, nous proposons de développer la méthode de spectrométrie de masse (SM) pour la quantification et la caractérisation des ES. En effet, cette technique apporte une grande spécificité d'analyse pour distinguer des séquences homologues dans un milieu complexes et ne nécessite pas la production d'anticorps spécifiques de chaque toxine. Ainsi, la SM apparait comme une alternative pertinente, particulièrement pour la quantification des ES connues ou récemment décrites pour lesquelles il n'existe pas d'anticorps spécifiques.

O5 - Analyse métabolomique non ciblée du méconium par LC/HRMS

Nihel Bekhti, François Fenaille, Florence Castelli, Blanche Guillon, Christophe Junot, Karine Adel-Patient

Service de Pharmacologie et d'Immuno-analyse, UMR CEA-INRA, CEA-Saclay 91191

Les allergies alimentaires sont en constante augmentation depuis plus de 20 ans, notamment chez le jeune enfant. A l'origine de ces allergies alimentaires : une réponse immunitaire inappropriée, excessive, contre des constituants (protéines) de certains aliments. Cette réponse est la conséquence d'une maturation incorrecte du système immunitaire qui commence in utero. Différents facteurs dont des facteurs environnementaux (alimentation, milieu de vie, contaminants, polluants, médicaments…) auxquels la mère est exposée pendant la grossesse pourrait interférer sur cette maturation in utero, prédisposant ainsi l'enfant au développement d'allergie alimentaire plus tard dans la vie.

Afin d'étudier l'effet de ces expositions sur le fœtus et le développement de la santé de l'enfant, j'analyse le méconium. Il s'agit des premières matières fécales excrétées par le nouveau-né, une matrice inerte qui se forme dès le deuxième mois de grossesse et qui s'accumule jusqu'à la naissance.

Mes travaux de thèse visent ainsi à établir une cartographie individuelle de la composition du méconium, incluant des analyses métabolomiques et protéomiques non ciblées, ainsi que des analyses du microbiote intestinal fœtal. Lors de cette rencontre, je me focaliserai sur l'analyse et le traitement des données métabolomiques non ciblées du méconium par LC/HRMS.

Cette caractérisation partielle de l'exposome du nouveau-né pourrait permettre d'identifier des biomarqueurs précoces d'un devenir allergique et des outils diagnostics associés, afin de mieux comprendre les mécanismes physiopathologiques précoces menant au développement d'une allergie alimentaire.

O6 - Red cabbage anthocyanins: equilibria and chemical stability in neutral conditions

J.-A. Fenger[1], R. Robbins[2], T. Collins[2], O. Dangles[1]

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A series of anthocyanins from red cabbage was investigated for their potential as food colorants. These flavonoids have a common 3-O-□-sophorosyl-5-O-□-glucosyl-cyanidin chromophore that can be substituted on the sophorosyl (Glc-□-1,2-Glc) moiety by one or two hydroxycinnamic acid (HCA) residues. Three pigments were selected to assess the impact of acylation type, number and position on their chemical stability: one non-acylated (Peak A), one acylated by a p-coumaric residue (P1), and one diacylated with a p-coumaric and a sinapic acid residues (P4).

At neutral pH, each pigment is present under several forms in equilibrium (Ref.). A mild thermal degradation was applied to the pigments (pH7, 50°C for 24h). The degradation products were analyzed by UPLC coupled with either DAD-ESI-ion trap MS or ESI-QToF. Our results show irreversible degradation pathways that are common to all anthocyanins, independently of their acylation degree. The major degradation routes include nucleophilic additions (by water, hydrogen peroxide or the bisulfite ion) to the flavylium ion, autoxidation of the anionic base and/or chalcone forms, followed by cleavage of the central ring or elimination of the catechol ring. Among the degradation products, coumarin and acylsophorose derivatives, , a phloroglucinaldehyde derivative, protocatechuic acid and 2,4,6-trihydroxyphenylacetic acid were identified.

Other structural modifications occur on acylated anthocyanins. They show a massive rearrangement of their acyl moieties by transesterification. The role of iron ions and hydrogen peroxide in the stability of neutral anthocyanin solutions was evidenced by the formation of hydrogen peroxide adducts and the detection of oxidation products in higher concentration after Fe2+ addition. These analyses open ways to stabilization strategies, involving chelating agents and antioxidants.

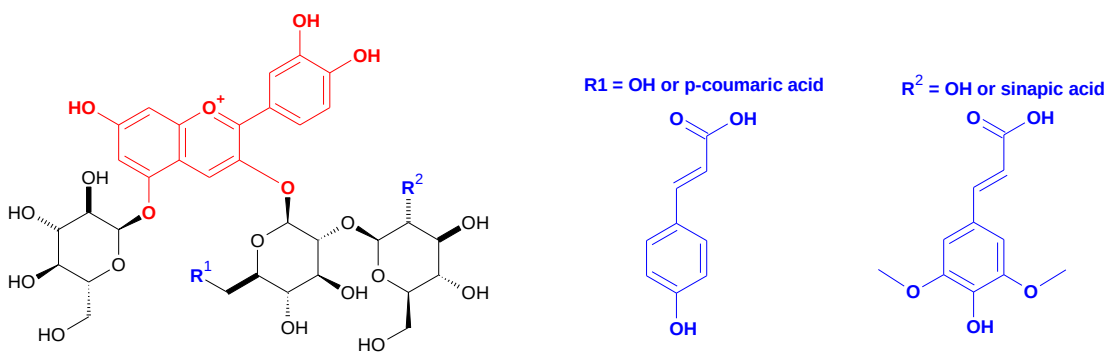

Figure. Structure of the red cabbage anthocyanins studied. R1 = R2 = OH: Peak A, R1 p-coumaric acid, R2 = OH: P1; R1 p-coumaric acid, R2 = sinapic acid: P4

Reference: Moloney M., Robbins R.J., Collins T.M., Kondo T., Yoshida K., Dangles O. Red cabbage anthocyanins: The influence of D-glucose acylation by hydroxycinnamic acids on their structural transformations in acidic to mildly alkaline conditions and on the resulting color. Dyes & Pigment 2018, 158, 342–352.

O7 - Collision cross sections of chemical warfare related compounds by ion mobility spectrometry - mass spectrometry

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The analysis of Chemical Warfare Agents (CWA), is of great interest because of the threats they represent and the need to maintain monitoring capabilities.[1] For several years, ion mobility spectrometry (IMS) has emerged as a reference technique for the characterization of numerous compounds related to the Chemical Weapons Convention (CWC).[2] More recently, the coupling of this technique with mass spectrometry (MS) can afford a more complete and reliable analysis including the determination of collision cross sections (CCS) which is a structural descriptors, characteristics of the detected ions.

In this study, we explore the use of IMS-MS coupling for the analysis of various compounds related to CWC. The analyzes were performed using a hybrid quadrupole-ion mobility-time of flight instrument (Waters, Synapt G2). The determination of experimental CCS was obtain using tetra-alkylammonium and poly-glycines as CCS calibrants. In order to obtain information on the accuracy and robustness of the results, IMS parameters such as wave height and wave speed have been modified and adjusted. Our CCS measurements were then confronted with calculated values from theoretical structures.

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2. Mäkinen, M. A.; Anttalainen, O. A.; Sillanpää, M. E. T., Ion Mobility Spectrometry and Its Applications in Detection of Chemical Warfare Agents. Analytical Chemistry 2010, 82 (23), 9594-9600.

O8 - KIT QUANTA - standardization kit for absolute protein quantitation: monitoring of methionine oxidation induced by liquid chromatography separation

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In the context of biomarker discovery and their absolute quantification in complex samples, a standardization strategy aiming to control the entire sample preparation process before LC-MS analysis would be extremely valuable. Our approach involves the use of a chimeric protein and different levels of its heavy peptides spiked at opportune moment in the sample during sample processing. Among these peptides, some containing a methionine are inserted. Methionine oxidation is a well-known protein modification occurring in vivo but also in vitro and may result in structural and functional protein alteration. Controlling this artefactual modification is then of great interest and will be possible thanks to our strategy

To address the origin of methionine oxidation, we sought differential oxidation levels comparing direct infusion, LC-MS using new columns and LC-MS using old ones.

The direct infusion of pure synthetic peptides in a Q Exactive™ Hybrid Quadrupole-Orbitrap™ showed a low percentage of oxidized peptide (less than 2%). Once injected onto the LC system coupled online with the Q Exactive, this percentage jumps to higher value (50-60% dependant of the peptide injected). The same peptides have been injected on the same LC system on which both trapping and analytical columns were replaced by new ones. Methionine oxidation in this case, was as low as in the direct infusion, meaning that the previous use of columns has a huge influence on the oxidation of methionine in pure synthetic peptides. This effect is certainly due to the presence of metal ions in the columns that promote methionine oxidation during chromatography separation. The same effect was observed on complex samples ((i.e. commercial HeLa protein digest and plasma digest). Indeed, the percentage of oxidized peptides varies from 1 to 8% when using the new columns and increases to 20% to 80% when the same samples were injected on the old columns.

The use history of a column greatly impacts the oxidation degree of peptides and has to be taken into account when studying methionine oxidation. Future works will be dedicated to the implementation of strategies that could stabilize the oxidation during chromatography separation.

O9 - Dommages de la centrine 2 humaine soumise à un stress oxydant : identification et caractérisation structurale des produits d'oxydation par spectrométrie de masse

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La centrine 2 humaine a été observée comme extrêmement sensible aux rayonnements ionisants. En effet, pour des concentrations en radicaux oxydants de l'ordre du micromolaire, elle s'oligomérise via sa tyrosine terminale. De par son implication dans les processus de duplication des centrosomes[1] et de réparation de l'ADN[2] , l'intérêt d'une compréhension des modifications radio-induites engendrées apparait comme évident.

Pour évaluer sa sensibilité aux radiations, la centrine 2 humaine a d'abord été étudiée dans sa totalité: cela a permis de montrer qu'elle présente un rendement de dimérisation supérieur à celui de la tyrosine seule[3]. C'est pourquoi l'influence de la structure a été abordée en considérant des fragments de tailles croissantes. La quantification du processus de dimérisation a été réalisée par HPLC et gels SDS, permettant la mise en évidence d'une séquence protéique minimale nécessaire à une dimérisation efficace.

Outre l'oligomérisation, d'autres modifications ont lieu et une tentative d'identification exhaustive de ces dernières a été menée. Plusieurs catégories de produits d'oxydation ont été mises en évidence par une séparation LC puis caractérisées par leur fragmentation (LC-MS/MS) et leur profil de mobilité ionique (LC-IMS-MS). Des isomères ont notamment pu être identifiés. Au vu du nombre de dégradations observées, la complexité des processus d'oxydation confronte la spectrométrie de masse à un enjeu analytique de taille.

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O10 - Development of Ion Mobility Spectrometry –Mass Spectrometry (IMS-MS) for high throughput and large scale metabolomic analyses

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Metabolomics is the study of low-molecular weight molecules (<1000Da) produced by cells and transformed during various regulatory pathways (Chouinard et al., 2018; Zhang et al., 2018). The whole metabolome of a biological sample can be analyzed without bias to detect and identify as many metabolites as possible. Metabolomics therefore permits to study or reveal perturbations in a biological system.

To conduct these studies many analytical techniques are currently used but Nuclear magnetic Resonnance (NMR) spectroscopy and Mass Spectrometry (MS) are the top two employed platforms nowadays. NMR spectroscopy is a quantitative, reproducible technique but NMR spectroscopy suffers from low sensitivity (estimated at 1nmol metabolite for 1H NMR in (Harry et al., 2008)). On the other hand, MS is more sensitive than NMR and permits to detect more metabolites in a complex mixture. But in MS studies, a separation step is usually used such as Liquid Chromatography (LC) to increase the sensitivity and the metabolome coverage. But the chromatographic separation drastically lengthens the analysis time and does not permit to distinguish many isomers. Direct Infusion MS (DIMS) approaches were successfully tested with some limitations such as matrix effects or unefficient isomer separation (Habchi et al., 2018; Rathahao-Paris et al., 2018).

Ion mobility spectrometry (IMS) is a technique to separate ionised compounds in the gas phase where an electric field is applied. Charged species shift differently according to their Collisional Cross Sections (CCS) a parameter linked to their size and charge (Kliman et al., 2011; Paglia and Astarita, 2017). IMS (usually coupled with MS for the detection) presents high capacities for the separation of isomers compared to oher MS based methods. We can mention the work of (Wu et al., 2000) displaying separations of isomeric peptides with differences in CCS as small as 2.5% and partial separations of isomeric ions differing by 1.1% in CCS. As well as (Hofmann et al., 2015) who analysed six carbohydrate anomers and were able to distinguish isomers that differ in composition (type of monosaccharide building block), in connectivity (position of the glycosidic bond) or in configuration (stereochemistry of the glycosidic bond).

Therefore, IMS-MS studies are really promising for metabolomics as they permit to distinguish some unsolved isomers and to shorten the time of analysis compared to other hyphenated methods such as LC MS.

Our research project aims to the development of a high throughput metabolomics approach based on a Trapped Ion Mobility (TIMS) coupled with a TOF analyser for large scale analysis. We first investigated instrumental parameters for trapping and detecting small metabolites (since TIMS usually traps ions with m/z > 300). The influence of other analytical conditions on the TIMS response was also examined such as the effects of compound concentrations. Finally, a mixture of oestrogen derivates containing 5 couples of isomers were studied to explore the potential of the TIMS for isomer separation. The goal is to study how the TIMS dissociate different types of isomers such as enantiomers or position isomers. Analyses parameters (additives, mobility resolution etc …) were also studied to determine the best conditions to successfully separate isomers.

O11 - Stools lipid profiling by HILIC LC-MS/MS

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The rapid profiling of lipids from human stools is an attractive method to evaluate their microbiome status. Such validated correlations were already reported to be powerful tools for the diagnosis of various pathologies. In the context of the Eurlipids project, the rapid quantification of the lipid biomarkers in mice stools using advanced chromatography and mass spectrometry methods is developed. Lipid extraction procedures, tuning of the HILIC-LC-MS(/MS) analytical systems and data treatment are presented as well as lipid profiling of biological samples.

Three different extraction procedures (MTBE/MeOH, MeOH/CHCl3 and MeOH/CH2Cl2) have been tested on solubilized stools, on freeze-dried and grinded stools, and compared. The optimization of the HILIC-LC separation has been performed using SPLASH® Lipidomix® standard (Avanti Polar Lipids). Separation of these lipids have been monitored with two types of mass spectrometers, a triple quadrupole using parent ion, neutral loss and precursor ion scans and an Orbitrap with data dependent MS/MS.

We demonstrated that MTBE/MeOH extraction on the freeze-dried and grinded stools allowed the detection of the widest range of lipids present in the standard. Because of the low MTBE density, the organic phase containing the lipids is on the top of the aqueous phase. This is not only convenient for the collection of the lipid fraction, but also for a future automation. All the lipids from SPLASH® Lipidomix® were properly found in positive electrospray mode except the phosphatidic acid and the monoglyceride as expected.

To resolve families of lipids, we choose HILIC columns to perform efficient lipid separation according to their polar head. Nine of the thirteen lipid families are separated on the HILIC column and detected in positive ionization mode. The four last were not detected, probably due to their poor ionization ratio in positive electrospray. Mice stools lipids were extracted and analyzed under the same conditions. About 240 lipids were identified on the basis of a mass accuracy better than 3ppm for the precursor ions, and validated by the interpretation of their MS/MS spectra. The change from LC to nano-LC is currently evaluated to perform nano-LC MALDI.

O12 - Emergence de biopolymères de complexité contrôlée dans les scénarios d'origine de la Vie

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La matière vivante se caractérise par la présence de biopolymères non aléatoires dont la fonction biologique dépend de la séquence en monomères. Ainsi, la séquence primaire constituant une protéine détermine les fonctions de celle-ci. Pour comprendre les origines de la vie, il est essentiel d'expliquer l'émergence de polymères non aléatoires dans un monde où les cellules vivantes n'existaient pas. Ceci constitue un des enjeux majeurs de la chimie prébiotique.

Grâce à une détection en ultra haute résolution accessible sur une instrumentation FT-ICR, nous avons montré que l'activation thermique d'un couple d'acides aminés sur surface de silice déclenche une condensation en oligopeptides jusqu'aux octamères avec des indications d'une polymérisation non aléatoire. On observe par exemple la production privilégiée du trimère GluLeu2 à partir de la condensation de l'acide glutamique (Glu) et de la leucine (Leu), en tenant compte de la discrimination inhérente à l'étape d'ionisation. Des oligomères aussi longs n'étaient observés jusqu'à présent que pour un dépôt des acides aminés à partir de la phase gazeuse, ce qui est peu réaliste du point de vue de la chimie prébiotique.

Au-delà de la détermination de la stœchiométrie des peptides, nous avons déjà obtenu certains résultats concernant la production de séquences privilégiées en étudiant les fragmentations des oligomères via des expériences MS/MS.

O13 - Identification de métabolites secondaires de souches de levures par LCMSMS

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Les levures sont des champignons unicellulaires. De par leur capacité à réaliser la fermentation, leur métabolisme secondaire peut amener à la synthèse biologique de composés bioactifs potentiellement intéressants dans les domaines pharmaceutique ou agroalimentaire. Notre étude porte sur l'identification des métabolites secondaires de souches de levure exotiques non explorées à ce jour. Ainsi, les étapes de préparation, d'analyse et de traitement de données sont optimisées.

La technique employée est une méthode chromatographique couplée à la spectrométrie de masse en approche non ciblée, UHPLC-MS/MS. L'appareillage utilisé est une chaîne UHPLC Dionex couplée à un spectromètre de masse hybride QTOF (SYNAPT G2 HDMS, Waters), équipé d'une source ESI. Les échantillons, mélanges complexes extraits des cultures par solvant organique, sont analysés en mode Survey, c'est-à-dire une approche non-ciblée fragmentant à chaque scan les ions les plus intenses.

Les spectres MS/MS servent ensuite à la construction de réseaux moléculaires grâce à la plateforme Global Natural Products Social Molecular Networking. Les molécules structurellement proches ont des spectres de fragmentation proches et peuvent être visualisées sous la forme de nœuds et de grappes grâce au logiciel Cytoscape. Cet outil informatique innovant permet d'obtenir une cartographie des métabolites connus et inconnus. Nous avons mis en place le workflow de conversion et d'analyse de données, adapté aux données waters. Les résultats permettent de fournir des structures originales comme sources de molécules bioactives, permettant ainsi une sélection plus efficace des souches prometteuses.

O14 - Dispersion of the mass accuracy in a MALDI image (TOF-TOF analyser)

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Mass spectrometry (MS) coupled with matrix assisted laser desorption ionization (MALDI) is a powerful technique which allows spatial localization of ions of interest. Indeed, MALDI imaging (MSI) leads to the acquisition of an image of a sample deposited on a conductive slide where each "pixel" contains a mass spectrum. An "average" spectrum results from the compilation of the individual mass spectra. Mass selected (m/z) images can be reconstructed by software.

The aim of this work is to develop a fast method to read lipids in dried blood spots by MALDI imaging. The RapifleX™ (Bruker Daltonics) is a MALDI-TOF-TOF spectrometer specially designed for MSI. It allows a faster image acquisition than previous MALDI MSI generations. Single spectra usually provide narrow peak width but the mass accuracies mainly depend on the location of the sample on the conductive slide. This results in an apparent loss of mass resolving power and mass accuracy in the averaged spectrum, decreasing so the efficiency of lipid identification. Full image acquisition is then affected and shows a significant dispersion of the resolving power and mass accuracy depending on the topology of the analyzed surface.

The ionization of the molecules of interest requires the presence of small organic molecules able to absorb the wavelength of the laser, called matrix. The mode of deposition (e.g. spray or sublimation), the nature of the matrix, the composition of the solvents, and the temperature greatly affect the shape of the matrix crystals. The homogeneity of matrix deposition assures a steady mass accuracy.

We used MALDI images to map the dispersion of the mass accuracy according to the dimensions of the crystals. This allows a rapid evaluation of the best operating conditions to reach an optimum mass accuracy and resolving power on the whole image.

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O15 - Tuning the hemolytic activity of Horse Chestnut saponins by molecular engineering

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In the last decades, pharmaceutical sciences are facing huge new challenges. Micro-organisms are always developing resistance to common and original antibiotics. To overcome this health issue, the pharmaceutical societies are seeking for new solutions and focus their researches on “green” drugs, i.e. bio-sourced molecules. Saponins are currently extensively targeted for their huge biological potential against bacteria, fungi and even against certain forms of cancer. Saponins are glycosidic compounds that arise from the condensation of an oligosaccharide chain onto an aglycone moiety of steroidal or triterpenoidic nature. Due to their huge diversity, structural characterization of saponins is challenging and we are developing mass spectrometry-based approaches, mostly by combining liquid chromatography, tandem mass spectrometry and ion mobility, to tackle the composition of saponin extracts. When envisaging saponins as drug candidates, their intrinsic toxicity must also be care. The bioactivity as well as the toxicity of saponins arise from their amphiphilic natures, making them membranolytic. In other words, the use of saponins in the pharmaceutical world requires balancing their toxicity versus their pharmaceutical activity. This definitively requires to establish the structure/activity relationship. Amongst the principal targets of saponins as toxic compounds are the red blood cells. Consequently, the toxicity of saponins is often assayed based on the determination of the hemolytic activity of saponin extracts. We are interested in saponins from the Horse Chestnut seeds. These molecules, called Escins, possess closely related structures even if some minor differences generate a huge complex of isomeric and stereoisomeric molecules. The diversity comes mainly from the side chains present on the aglycone. The toxicity of HC saponins is well-known. In the present study, we slightly modified their structures by partial microwave-assisted hydrolysis to tune their membranolytic activity. Based on MS methods, we completely describe the saponin content before and after hydrolysis. Finally, the toxicity is evaluated on red blood cells by in vitro and in silico methods.

O16 - Contribution of electron-based fragmentation methods for study of synthetic polymers by tandem mass spectrometry

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Synthetic polymers are used throughout many areas such as health industry, energy, or communication. The physicochemical properties of synthetic polymers are closely dependent on their structure. Their characterization is often delicate because a polymer is generally a heterogeneous mixture, since polymerization reactions lead to the formation of molar masses distributions. Polymers can exhibit a chemical heterogeneity, various topologies, (linear, grafted, cyclic, star-shaped...). In this context, it is necessary to develop powerful analytical techniques. Mass spectrometry of synthetic polymers can be performed to obtain characteristic information of each macromolecular chains individually present in a polymer sample. Characterization of synthetic polymers can be performed by single-stage mass spectrometry but tandem mass spectrometry is required for more detailed information.

In order to obtain detailed structural information, tandem mass spectrometry, which consists in deliberately inducing gas phase decomposition reactions from previously selected precursor ion, is necessary. The main technique used to perform tandem mass spectrometry analysis is collision-induced dissociation[1] (CID). Other activation techniques have been developed more recently such as electron-transfer dissociation[2,3] (ETD) and irradiation of trapped ions[4,5] (ultraviolet wavelengths UV). Whereas the ETD activation conditions require the transfer of one electron from a radical anion to a positively charged precursor ion, the irradiation of trapped ions (UV) is a process in which an electron is emitted from a positively charged precursor ion.

In this work, CID, ETD and UV experiments were carried out in order to evaluate the information produced by each activation techniques for the study of synthetic polymers from different model polymers. Activation techniques based on electron transfer generate fragmentation pathways different by comparison to the results generated by classical CID. Electron based fragmentation methods creates new opportunities for the characterization of synthetic polymers.

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O17 - Analyse simultanée d'hormones et de perturbateurs endocriniens par couplage de la chromatographie liquide à la spectrométrie de masse : un challenge analytique

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Depuis les années 1990, la thématique de la perturbation endocrinienne est une préoccupation centrale au niveau politique, réglementaire et sociétal. Selon la définition proposée par l'OMS/IPCS un perturbateur endocrinien est une substance ou un mélange exogène altérant les fonctions du système endocrinien et induisant en conséquence des effets nocifs sur la santé d'un organisme intact, de ses descendants ou (sous-) populations.

Dans le domaine de l'environnement, de nombreuses études ont révélé une pollution des sphères aquatiques par des hormones stéroïdiennes naturelles ou synthétiques. Elles ont la particularité de provoquer des effets néfastes à partir de concentrations inférieures au ng.L-1. Par ailleurs, en hormonologie, de faibles variations de leurs niveaux peuvent être à l'origine de diverses maladies et affections chroniques : diabètes, troubles du système reproducteur…

Pour mieux appréhender cette problématique les enjeux sont doubles : la caractérisation de l'exposome et l'évaluation de ses effets au travers de biomarqueurs pertinents. L'objectif est de garantir la quantification fiable des substances sélectionnées à des concentrations auxquelles elles sont susceptibles d'avoir des effets dans des matrices environnementales (eaux) et biologiques (plasmas). Cette communication se propose de discuter des challenges analytiques existant pour la détection et la séparation de molécules d'intérêt commun en santé et en environnement.

Le couplage de la chromatographie en phase liquide à la spectrométrie de masse en tandem a été choisi dans le but de doser simultanément des hormones stéroïdiennes appartenant à 4 classes : estrogènes, progestatifs, androgènes et corticoïdes. Ceci se heurte cependant à divers verrous qui seront discutés : co-élutions, contributions spectrales, comportements différents par famille de molécules, intérêt et apport de la dérivation…

O18 - Structural study of analogues of Titan's haze by trapped ion mobility coupled with a Fourier transform ion cyclotron mass spectrometer

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Titan, the largest moon of Saturn, has a thick atmosphere which presents similarities with the one thought to be on Earth at its beginning. The study of Titan's photochemical haze is thus a precious tool in gaining knowledge of the primitive atmosphere of Earth. The chemistry occurring in Titan's atmosphere and the exact processes at act in the formation of the hazes remain largely unknown. The production of analogs samples on Earth has proved to be a useful tool to improve our knowledge of the aerosols formation on Titan. Such solid organic analogs samples, named tholins, were produced with the PAMPRE experiment (French acronym for Aerosols Microgravity Production by Reactive Plasma).

In this work, this incredibly complex mixture was firstly described by trapped ion mobility spectrometry coupled to ultra-high resolution mass spectrometry (FT-ICR MS). Electrospray ionization revealed the characteristic CHNx-class components, with CHN5-6 and DBE 6-7 most abundant. Deploying specialized visualization, enabled by the exact mass measurement and elemental composition assignment, the adapted Kendrick mass defect analysis highlights the C2H3N homolog series, whereas the nitrogen-modified Van Krevelen diagram is exhibiting a clear trend towards H/C 1.5 and N/C 0.5. More interestingly, the representation of m/z versus collision cross section (CCS) allowed hypothesizing a ramified N-PAH structural motive. IMS will not be able to resolve the isomeric continuum of ultra-complex mixtures; thus peak parameter different as CCS are explored. As such, analysing the peak width versus m/z allows suggesting a lowering increase of isomeric complexity with increasing size of the N-PAH-like structure. Due to the tremendous complexity, these structural insights are only to be revealed by TIMS FTMS.

O19 - UHPLC-IMS-MS as a new tool for the characterization of the membrane lipids of Pseudomonas aeruginosa

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Pseudomonas aeruginosa is a bacterium classified as critical priority for the R&D of new antibiotics by the World Health Organization. In order to develop efficient antibiotics against this bacterium, a better knowledge about its membrane cell composition is required.

In this study, the membrane lipids of *P. aeruginosa* were analysed by liquid chromatography- ion mobility spectrometry–mass spectrometry (UHPLC-IMS-MS). In addition to the classical lipidomics workflow, IMS was coupled to LC-MS as a third dimension of separation and for the experimental determination of Collision Cross Section (CCS) values. Indeed, CCS values are helpful molecular descriptors for structural elucidation or molecular modelling -which can eventually lead to antibiotics R&D.

Four chemical classes of phospholipids (phosphatidylethanolamines (PE), phosphatidylcholines (PC), phosphatidylglycerols (PG), diphosphatidyldiglycerol (dPG –known as cardiolipins)) were identified after LC gradient, ESI, IMS and MS/MS parameters optimization. MS/MS spectra showed that the membrane phospholipids of *P. aeruginosa* were composed of saturated or monounsaturated fatty acyl chains from 14 to 18 carbons numbers.

Experimental CCS values of the lipids were determined testing three different calibrants (polyalanine, dextran and phospholipids) in order to cover the whole m/z and CCS range required of dPGs. As published phospholipids CCSs were mostly obtained from eukaryote sourcing, few published phospholipids were common with the ones of the sample and none were for dPGs. Nonetheless, the common phospholipids CCS values were used as references to verify our calibration.

Herein, we implemented the knowledge about the membrane phospholipids of *P. aeruginosa* and complemented the prokaryote CCS database, especially for dPGs which were lacking in the literature.

O20 - Identification of cell-penetrating peptides interaction partner by affinity photocrosslinking coupled to mass spectrometry

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Cell-penetrating peptides (CPP) can cross cell membranes and deliver biologically active molecules into cells. They are usually positively charged peptides, and often amphipathic. Understanding their internalization mechanisms is of first interest for an appropriate use in the medical field or for biotechnological applications. Affinity photocrosslinking coupled to mass spectrometry (MS), using benzophenone-functionalized peptides, was used to study the interaction of CPPs and lipids at a molecular level, using model membranes.[1]

Upon irradiation, CPP peptide sequences functionalized with a benzophenone photoprobe can be covalently bound to lipid fatty acid chains in their immediate environment.[2] Optimisation of this method was performed using different CPP sequences and liposomes of controlled composition containing phosphatidylglycerol phospholipids (negatively charged polar heads) with various fatty acid chains, saturated or unsaturated.

By improving affinity photocrosslinking protocol and MS detection parameters, we significantly increase photocrosslinking yields, and ions production and detection of the covalent complexes CPP/fatty acids, resulting in high signal-to-noise MS spectra. Using MALDI-TOF and ESI-Orbitrap MS, we revealed in a single MS analysis, the site of the covalent insertion of the CPP (at the atomic level) on the fatty acyl chain in the lipid membrane. This was possible by the careful identification of highly informative secondary reactions involving benzophenone and UV irradiation.

This work highlights the complexity of the benzophenone photorereactivity in a 2D crowded environment of lipid membranes: redox photoreactions, ROS-induced oxidation reactions and “unconventional” covalent bond formation (and rupture).

Careful analysis of the MS spectra allowed to characterise the depth of insertion of the CPP in the lipid membranes and to confirm that these CPPs favour interaction with fluid disordered regions of the membrane and do not insert deeply.[3]

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O21 - Collision cross sections of phosphoric acid cluster anions and their use as calibrants for Traveling Wave Ion Mobility

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Non-linear electric field ion mobility mass spectrometry usually uses a calibration, for which reference compounds are needed, to determine the collision cross sections. Since 2014, we study the hydrogen bonded cluster anions produced by ESI from phosphoric acid, an easily accessible and inexpensive compound, to investigate their potential as calibrants.

The absence of other non-covalent interactions in the clusters allows to pay closer attention on the behavior of the labile hydrogen bonds. In this regard, their high sensitivity to activating experimental parameters and their fragility can be turned to an advantage because it makes them good candidates to monitor pre- and post-IMS conditions and improve both instrument parameters and calibration.

Phosphoric acid solutions (5 mM in water/acetonitrile) were analyzed with an electrospray source operated in negative ion mode. The collision cross sections of multiply charged H3PO4 cluster anions were determined by stepped-field experiments on an Agilent 6560 drift tube ion mobility Q-TOF instrument using either helium or nitrogen as buffer gas. Two sets of pre-IMS and post-IMS parameters were tested, from soft to harsh conditions in the pre- and post-IMS regions of the DTIMS instrument, and the resulting CCS values monitored. Reduced ion mobilities were obtained in duplicate for each tuning and then used to determine the CCS. Measurements were also performed on a Waters traveling wave ion mobility SYNAPT G2 HDMS to perform calibration and test the resulting accuracy.

Unambiguous assignments of the drift times for phosphoric acid cluster anions were obtained by overlaying the arrival time distributions of clusters with adjacent aggregation numbers. This allows to discriminate the ion mobility peaks of the intact precursor ions from that of the fragment ions.

A comparison of the overlaid ion mobility peak profiles extracted for different tunings highlighted that harsh conditions affected the overall distribution of clusters. Experimental parameters changed the ratio of the abundance of the clusters that reach the detector intact versus the abundance of cluster ions that dissociate during their trajectory through the instrument. The CCS values, noted ^{DT}CCS(He) or ^{DT}CCS(N_2), were not affected by the changes in experimental conditions, showing phosphoric cluster ions dissociate rather than change conformation. A relative variation lower than 2.5% was observed for the ^{DT}CCS determined with different experimental conditions.

The most adequate tuning for the determination of ^{DT}CCS vales was harsh pre-IMS and very soft post-IMS conditions. Under these conditions, we determined 107 ^{DT}CCS(He) values ranging from 96 to 706 Å^2 and 93 ^{DT}CCS(N_2) values from 155 to 818 A^2 with K0 values of 2.6-5.7 cm^{2}V^{-1}s^{-1} in He and 0.7-1.3 cm^{2}V^{-1}s^{-1} in N_2 for clusters ions with charges states 1- to 4-.

The ^{DT}CCS(N_2) values obtained here with the Agilent instrument showed a systematic difference of about 5%, compared with previous ^{DT}CCS(N_2) determined with a Tofwerk DTIMS.

These ^{DT}CCS values were then used to obtain calibration correlations in traveling wave ion mobility. Charge-dependent correlations were found between the drift times measured in the TWIMS device and the ^{DT}CCS(He) and ^{DT}CCS(N_2) values. The resulting accuracy of the CCS determined with TWIM using the calibrations obtained from ^{DT}CCS(He) and ^{DT}CCS(N_2) values showed a relative error for all the tested ions of 1% and 2.5 %, respectively.

O22 - Distribution study of paracetamol and its metabolites in rat whole body after on-tissue chemical derivatization by MALDI Mass Spectrometry Imaging

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Matrix-Assisted Laser Desorption/Ionization (MALDI) Mass Spectrometry Imaging (MSI) is recognized as a promising technique for distribution studies of small exogenous molecules such as drugs and their metabolites. Indeed, MALDI-MSI presents advantages compared to autoradiography, conventionally used for distribution studies: it does not require radiolabelling of targeted molecules and allows their distinction from eventual metabolites. Despite these advantages, the lack of sensitivity encountered in some cases remains a strong limitation of this technique. Therefore, novel procedures could be developed in order to enhance the sensitivity such as adding an on-tissue chemical derivatization (OTCD) step during the sample preparation. OTCD consists in modifying the chemical structure of analytes in order to improve their ionization yields. Thus, we employed this technique to enhance the sensitivity of one of the most used drugs in the world, paracetamol. This drug and some of its metabolites are not detectable in tissues of rats treated with 300 mg/kg of paracetamol by MALDI-MSI. Our strategy consists in employing N-(2-(Bromomethyl)benzyl)-N,N-diethylethanaminium bromide (CAX-B) and 2-fluoro-1-Methylpyridinium p-tolunesolfonate (FMPTS) as derivative reagents in order to increase the ionization yield of paracetamol and its major metabolites thus allowing the study of their distribution in whole body rat tissue sections by MALDI-MSI.

O23 - Electrospray Ionization and co-elution in Meta-metabolomics: a biomarker or a suppressed ion?

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Environmental meta-metabolomics consider studying mixtures containing endogenous and xenobiotic metabolites, issued from the application of anthropogenic compounds to an environmental matrix.

Our main research aim is to develop a Chromatography-Mass Spectrometry-based meta-metabolomics approach as an alternative tool for the evaluation of pesticides' environmental fate and impact. This approach named "Environmental Metabolic Footprinting" consists of comparing meta-metabolomes of control and pesticide-spiked environmental matrix for several defined time points, in order to determine matrix' "resilience time". This considers the recovery of sample's biological system by comparing these meta-metabolomes, using statistical analysis. Moreover, this approach aims to determine endogenous biomarkers, in order to understand the biological impact of the applied pesticide.

Several technical issues may affect conclusions built on statistical analysis of LC-MS data. Ion suppression phenomenon is one of these issues, occurs in the Electrospray Ionization source. This phenomenon consists of suppressing the signal of a compound due to an ionization competition with another co-eluted molecule, which may originates from xenometabolome. It may leads to consider several non-significant molecular features as markers of discrimination.

We have observed this phenomenon in one of our applications. In fact, pesticide-derived xenometabolites suppressed the signal of some co-eluted endometabolites, which could be considered as potential markers of discrimination. Here, we aim to exploit this case by analyzing LC-QToF data and statistical results, in order to notice this potentially recurrent issue in metabolomics, and the importance of the awareness about Mass Spectrometry fundamentals to assure reliable conclusions.

O24 - Analyse d'oxylipines par LC-MRM

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Institut Gustave Roussy, plateforme métabolomique

Les oxylipines ont un rôle important dans le métabolisme, notamment en participant comme médiateurs des acides gras. Ils sont dérivés de plusieurs acides gras polyinsaturés de type omega-3 et omega-6. Les dérivés des omega-3 possèdent un rôle « anti-inflammatoire » alors que ceux dérivés des omega-6 acides gras polyinsaturés « pro-inflammatoire », ce qui les rend intéressants dans le cadre de la recherche contre le cancer (système immunitaire et nerveux).[1]

La plateforme métabolomique de Gustave Roussy a mis en place une méthode d'analyse des oxylipines par LC-MRM afin de l'incorporer dans l'analyse de routine des études précliniques. Ce développement s'est fait au niveau de la chromatographie, du spectromètre de masse et de l'extraction, en tenant compte des impératifs de coût et du temps limité dédié au développement. La plateforme ne possédant pas initialement de standards, le développement a été réalisé avec des échantillons de plasma humain extraits.

Les oxylipines sont des molécules sensibles à l'oxydation, donc l'extraction est une étape importante à développer. Des tests avec une extraction sur phase solide (SPE) ont été mis en place, en comparaison avec une extraction par précipitation protéique, déjà utilisée en routine sur la plateforme. En parallèle, la méthode chromatographique et la méthode d'analyse par MRM ont aussi été développées et optimisées. D'abord sur un couplage UHPLC-Orbitrap q-Exactive puis sur un couplage UHPLC-QTRAP 6500+. Des tests sur la reproductibilité et la répétabilité ont par la suite permis de tester la robustesse de la méthode, qui est aujourd'hui utilisée en routine sur la plateforme avec des échantillons de souris (tissus, plasma).

1 M. Gabbs and al., Advances in Our Understanding of Oxylipins Derived from Dietary PUFAs, American Society for Nutrition, 2015, 6, p513–540

O25 - nanoLC-MS/MS of glycoproteoforms and proteolytic glycopeptides combined with glycan fingerprinting: a powerful strategy for glycoprotein characterization

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It is estimated that more than half of the circulating proteins are glycosylated. In vivo, protein glycosylation is a key factor of ligand-receptor interaction, allowing specific cell signaling pathways. Those post-translational modifications (PTMs) are produced during the protein maturation in the ER and Golgi apparatus and hence one can only assess protein glycosylation by the direct characterization of the mature proteoforms.

Different approaches have been developed to address the heterogeneity of the glycoproteome. The characterization of the glycans released from the glycoprotein provides an overview of the glycan population of a given sample but bypasses the question of their localization. Proteolytic glycopeptides LC-MS/MS analysis overcomes this limitation. However, the glycan molecular heterogeneity can only be studied by analyzing the entire proteoforms without prior digestion. While this might allow to study the structure-function correlation of those glycoproteoforms, the observed number of combinations is very high and involves monosaccharides with closely related structures and similar mass range.

Human Choriogonadotropin (hCG) is a glycohormone produced by the placenta starting from the first week of pregnancy, and plays a role in myometrium quiescence, utero-placental vascularization, trophoblast differentiation and maternal immunotolerance. While hCG concentration is monitored during gestation, its glycosylation is generally overlooked. Some studies have shown that hCG hyper-glycosylation is correlated to cancer or congenital disorders. It is thus of foremost importance to decipher hCG carbohydrates structural complexity. The hCG □□ heterodimer contains 8 glycosylation sites (2 N-glycosylation sites on both α and β subunits, and 4 O-glycosylation sites on the β subunit) and polysaccharides account for around 30% of the total mass of the hCG molecule.

In the present project we aim at characterizing the intact glycoproteoforms of hCG by nanoLC-FT MS/MS to map their heterogeneity and identify those correlated to different biological sources (various populations, pathologies) as a new source of information. This will be compared to complementary bottom-up and glycomics strategies.

O26 - Combining tandem mass spectrometry with ion mobility spectrometry to decrypt information encoded in sequence-defined poly(alkoxyamine phosphodiester)s

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Inspired by DNA and its ability to store genetical information at a molecular level thanks to a set of four bases, sequence-defined synthetic polymers are efficient media to store and deliver information. In such polymers, information are encoded thanks to a set of two different co-monomers arbitrarily defined as the 0- and 1-bit of the ASCII alphabet.[1] When the coding system is based on mass, messages can be readily decoded by tandem mass spectrometry (MS/MS) sequencing[2–4] as long as full sequence coverage is achieved. For this purpose, the structure of synthetic polymers can be optimized to simplify fragmentation pattern. Such an MS/MS-assisted design permitted to produce poly(alkoxyamine phosphodiester)s (PAPs) in which weak alkoxyamine bonds made all coding phosphate groups MS/MS silent.[5] Very simple MS/MS data were obtained upon homolysis of all C-ON bonds, and information could be deciphered in a straightforward manner. The structure of PAPs was further optimized to use the alkoxyamine moiety as a second coding group, hence allowing to increase their storage capacity with no modification of their MS/MS pattern.[6]

However, messages of high MS/MS readability can obviously not be used for secret communications. Accordingly, the design of PAPs was further optimized to include an encrypting key based on slight variation of fragment collision cross section. This was achieved by employing two different nitroxides to build the alkoxyamine moiety, each containing a coding alkyl segment of the same mass but different architecture. As a result, the digital sequence determined from primary fragments observed in MS/MS had to be decrypted according to appropriate rules that depend on the drift times measured by ion mobility spectrometry for repeating units released as secondary product ions.[7]

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O27 - HPTLC (High Performance Thin Layer Chromatography) coupled with LA-ICP-MS (Laser Ablation Inductively Coupled Plasma Mass Spectrometry) and LDI/MALDI-FTICR-MS (Laser Desorption Ionization Fourier Transform Ion Cyclotron Resonance Mass Spectrometry) to study asphaltenes

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Heavy fractions are considered to be the most problematic parts of crude oil. In fact, they contain large amounts of hetero elements (S), metals (V, and Ni) and polyaromatic molecules. These elements are poisoning the catalysts used in refining units. They must be extracted by expensive hydrotreatment processes. Information obtained on these hetero-elements and their chemical environment also referred as speciation, are important to improve treatment steps.

Vanadium and nickel in crude oil are mainly present as small polar molecules called porphyrins. These molecules remain preferentially in asphaltene (part of the crude oil soluble in toluene and insoluble in aliphatic solvent such as C7). This asphaltene part is composed of large polar and hetero-element containing molecules, having a capacity to self-aggregate. They could form aggregates between a few hundred Daltons to several hundred thousand Daltons. Some of these porphyrins could be easily accessible or trapped inside aggregates and become therefore refractory to hydrodemetallation treatment steps.

HPTLC is used for the separation of petroleum and heavy petroleum, so called SARA separation. In this study, HPTLC was used to separate asphaltenes in two fractions among which V, Ni and S containing molecules were detected by LA-ICP-MS. Moreover, LDI/MALDI-FTICR-MS was used for the identification of the molecules containing these elements.

Samples of asphaltene extracted with pentane (A C5) or heptane (A C7), asphaltene 2017 (A 2017, reference asphaltene produce for the Petrophase 2017 conference) and V and Ni reference porphyrins were separated by HPTLC. The HPTLC plates used are cellulose plates (HPTLC cellulose plate, MERCK, thickness: 0.15-0.2mm). Cellulose as stationary phase gives better signal than classically used silica in LA-ICP-MS and LDI FTICR-MS. A Dichloromethane 99.5%/ Methanol 0.5% mixture was used as mobile phase for the migration.

After migration, UV analysis was performed with a CAMAG TLC Scanner 4. A Laser ablation system (NWR 213 from electro scientific industry) was coupled to an ICP MS instrument (7700 series from Agilent) to determine the quantity of metal and sulfur. Moreover a FT ICR Bruker solarix (12 Tesla) instrument equipped with a MALDI source was used for the identification of molecule.

After the migration step, almost all the reference porphyrins migrated to the solvent front. The asphaltene sample split into two parts. One part remained at the application point and one migrated to the solvent front. It seems to appear that the point at the solvent front corresponds to the free porphyrins, and the other one could correspond to porphyrins trapped into asphaltene aggregates. FT ICR analysis will confirm this hypothesis.

O28 - Characterization of polar lipids in Brewer’s spent grains

Ali ZAITER, Vincent CARRE, François Dupire, Patrick CHAIMBAULT

Université de Lorraine, LABORATOIRE DE CHIMIE ET PHYSIQUE - APPROCHE MULTI-ÉCHELLES DES MILIEUX COMPLEXES (LCP A2MC)

Brewer’s spent grains (BSGs) are the major by-products produced by brewing companies and the large amount of this waste represents an environmental problem. Except their basically use as animal feed or as land fill, their valorization by finding new industrial applications is a key challenge. Interestingly, BSGs have wide-ranging composition such as carbohydrates, lignin, proteins, and lipids. Several studies have been performed to identify the contents of lipid extracts. Even though their significant activities, polar lipids have not been intensively investigated, in contrast to fatty acids and sterols which withdraw more attention in BSGs. Our research conducts the characterization of lipids in BSGs extracts especially phospholipids as they may have important biological activities. For example cyclic phosphatidic acid is known to be a specific inhibitor of DNA alpha polymerase. It has a considerable effect on the inhibition of cancer cell invasion and metastasis. The purpose of this study is to characterize some of the phospholipids by FT-ICR-MS and MS in Tandem. Results demonstrate the presence of new cyclic phosphatidic acids in different lipidic extracts of BSGs.

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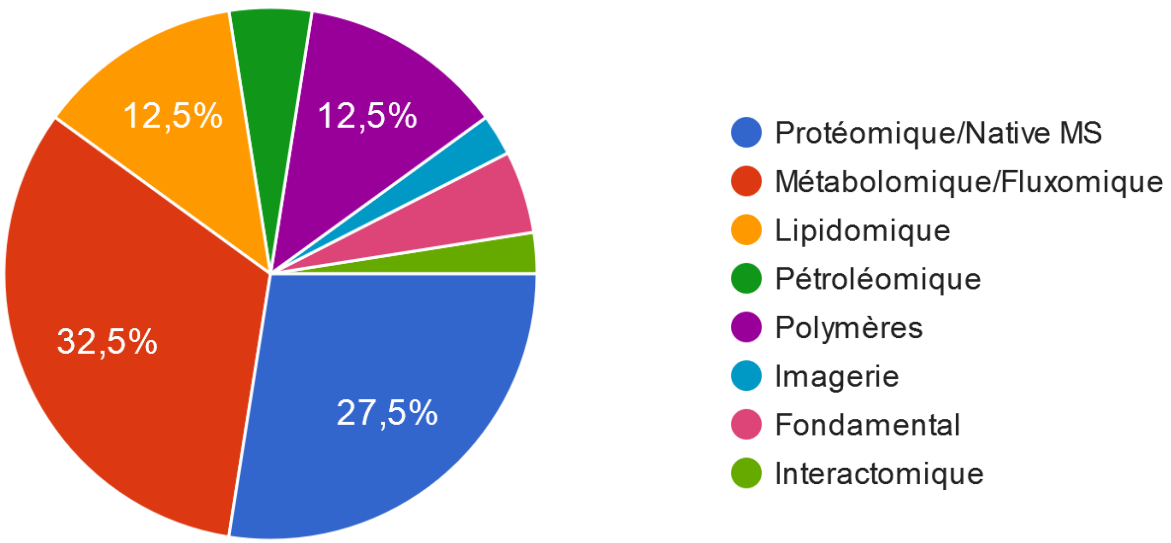
Domaines de recherche



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