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The routine application of Ion Mobility in Metabolomics

Combining separation strategies for maximum depth of coverage and information content

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The Omics

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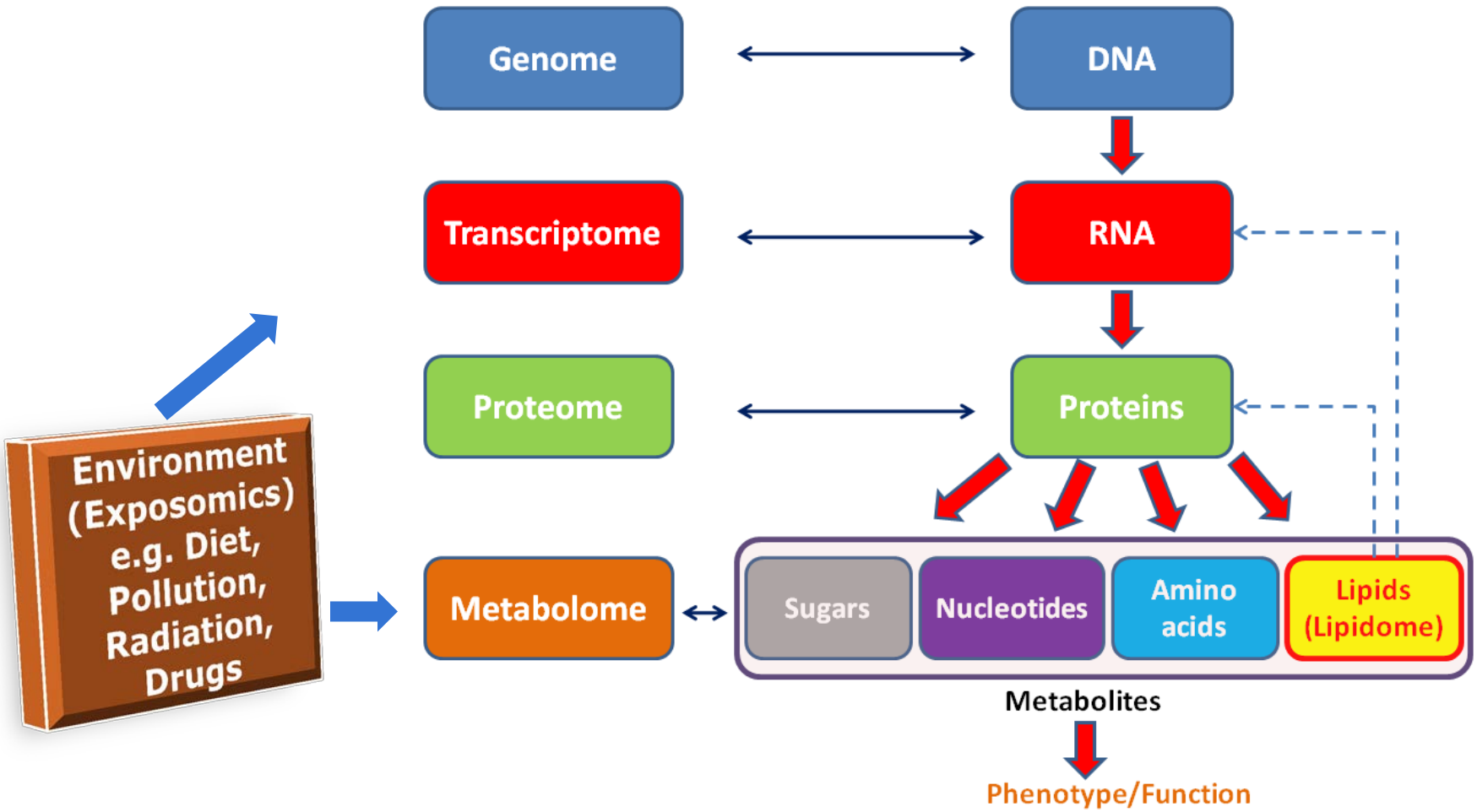

Metabolomics Applications

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- Biomedical Sciences
  - Biomarker discovery
  - Drug Discovery and Development
  - Microbiology
  - Personalized medicine
- Environmental Sciences
  - Strain fingerprinting and ID
  - Genetic modifications to improve phenotypes
  - Pesticide Residue
- Food Sciences
  - Nutrients composition
  - Purity
- Metabolic engineering
  - Improvement of metabolic pathways for the production of fuels and chemicals
- Natural Products
  - Traditional medicines

Reasons for failure in biomarker translation

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- Small number of samples that are analysed
- Lack of information on the history of the samples
- Case and control specimens which are not matched with age and sex
- Limited metabolic and proteomic coverage
- The need to follow clear standard operating procedures for sample selection, collection, storage, handling, analysis and data interpretation

Experimental Design	Sample Handling	Analytical Approach

Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine
*Druker and Krapfenbauer The EPMA Journal 2013, **4**:7*

Controlling Variance

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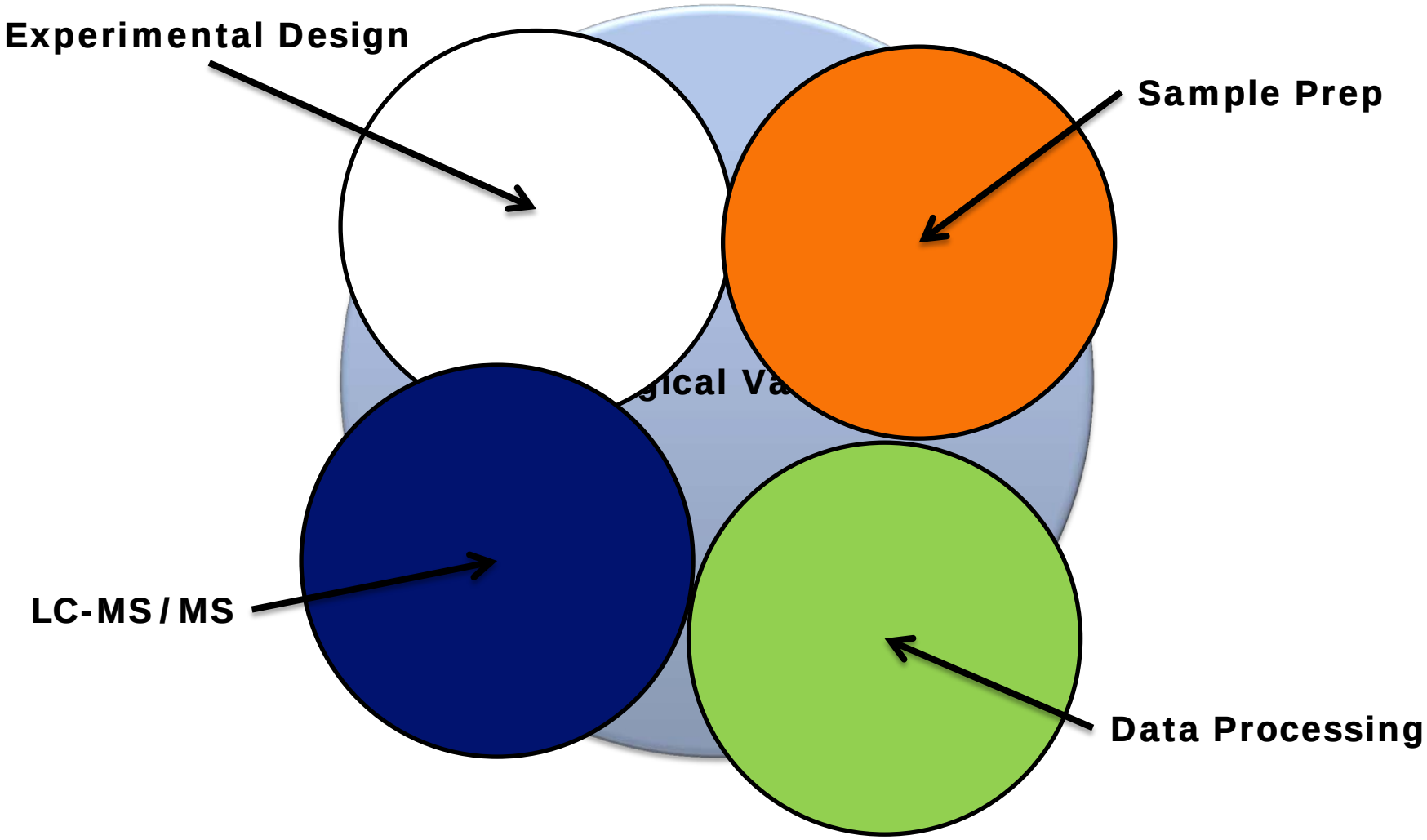

Non-Targeted Metabolomics/Lipidomics

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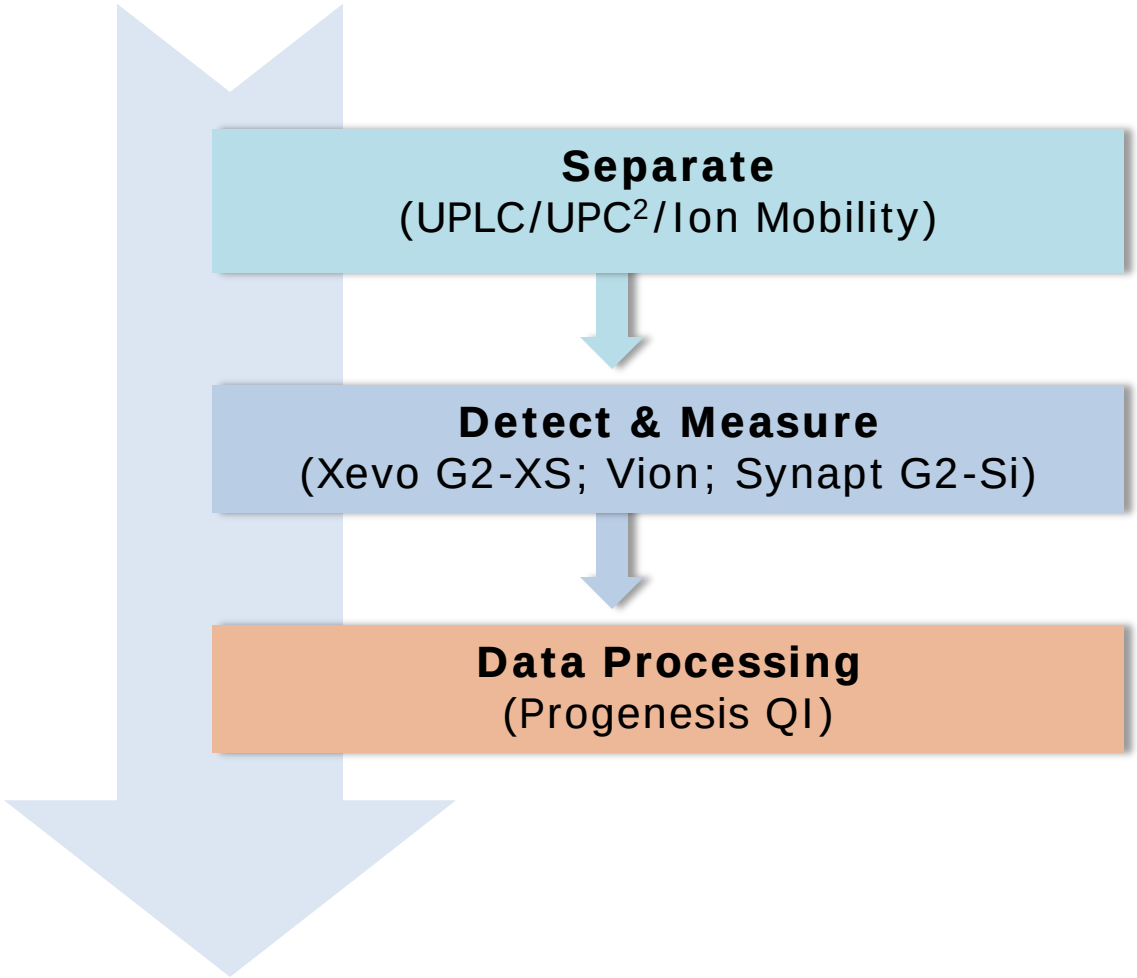

Why Chromatographic Separation?

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- Reduces ion suppression
- Separates many isobaric interferences
- Often separates isomers
- Better detection limits
  - Concentration effects
  - Reduced background noise
- Records a physiochemical property

Untargeted Metabolomics: Separate Polar Metabolites - HILIC

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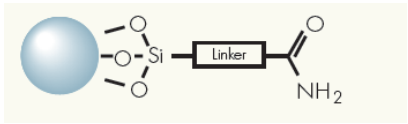
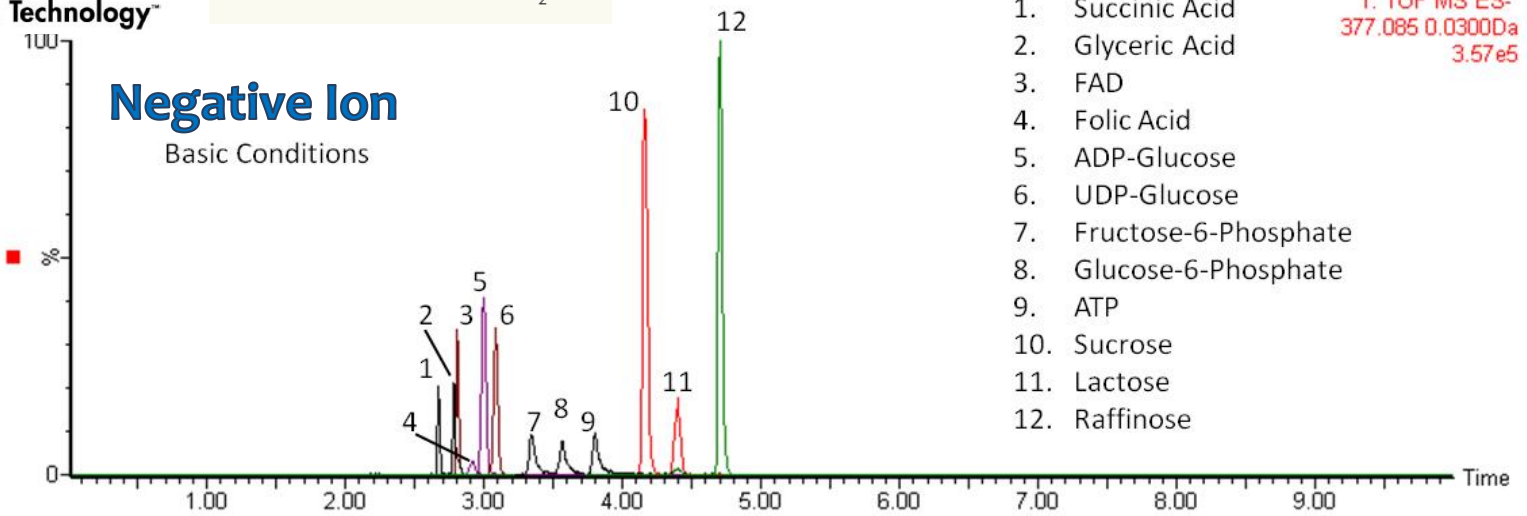
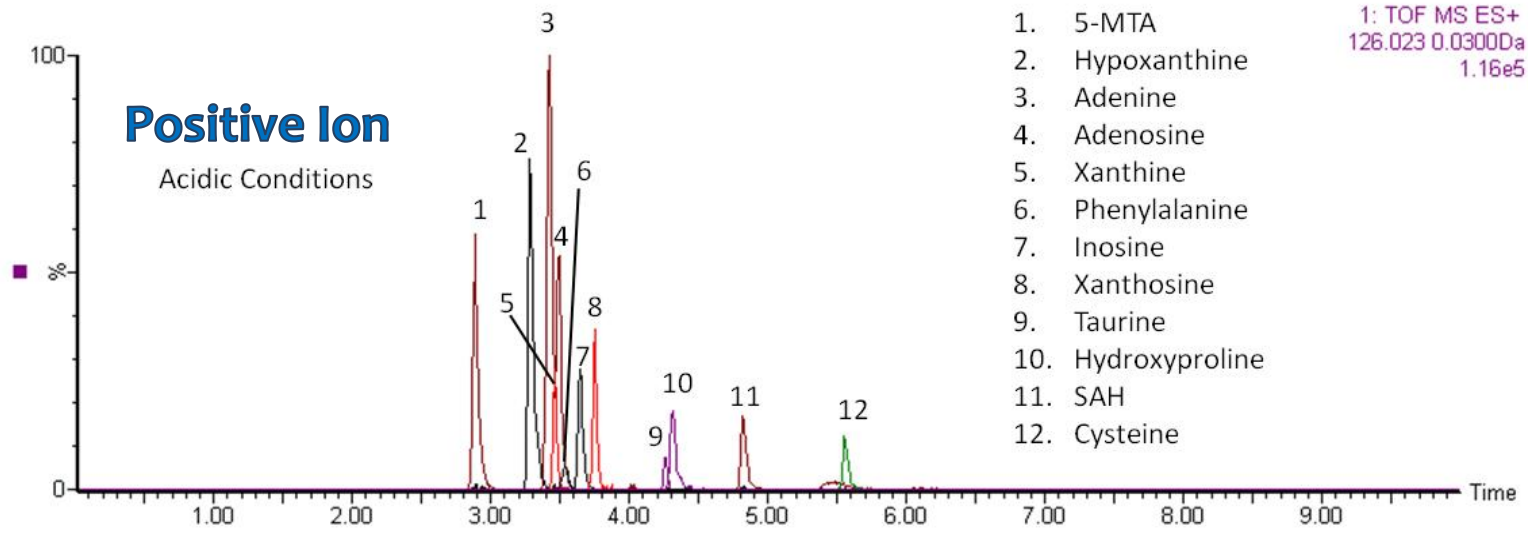




1. Succinic Acid
2. Glyceric Acid
3. FAD
4. Folic Acid
5. ADP-Glucose
6. UDP-Glucose
7. Fructose-6-Phosphate
8. Glucose-6-Phosphate
9. ATP
10. Sucrose
11. Lactose
12. Raffinose



1. 5-MTA
2. Hypoxanthine
3. Adenine
4. Adenosine
5. Xanthine
6. Phenylalanine
7. Inosine
8. Xanthosine
9. Taurine
10. Hydroxyproline
11. SAH
12. Cysteine

Retention Mechanisms for Lipids

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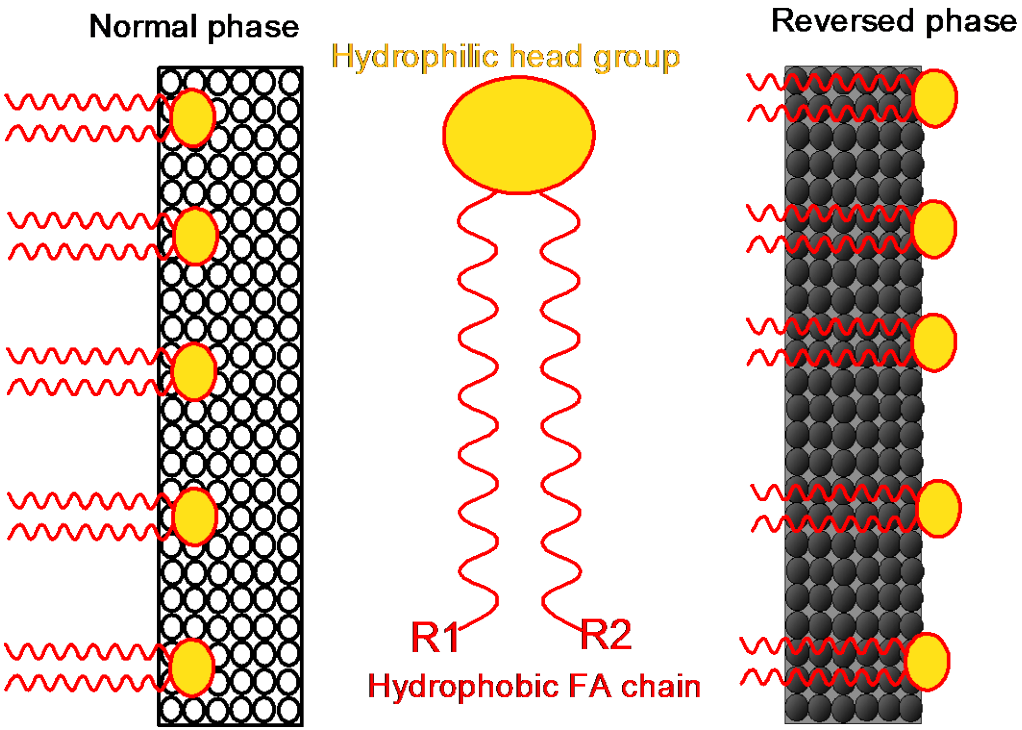

- Bare silica or silica bonded to polar group such as cyano, amino, PVA
- Non polar MP Hex, chloroform
- Separation based on **adsorption of the head group to the NP material** for lipid class separation.

- Silica bonded to nonpolar group such as C18, C8, C4
- Polar MP water, MeOH, ACN
- Separation based on hydrophobic **interaction of the FA chain and RP material** for lipid molecular species separation.

Online-separation MS: LC/MS

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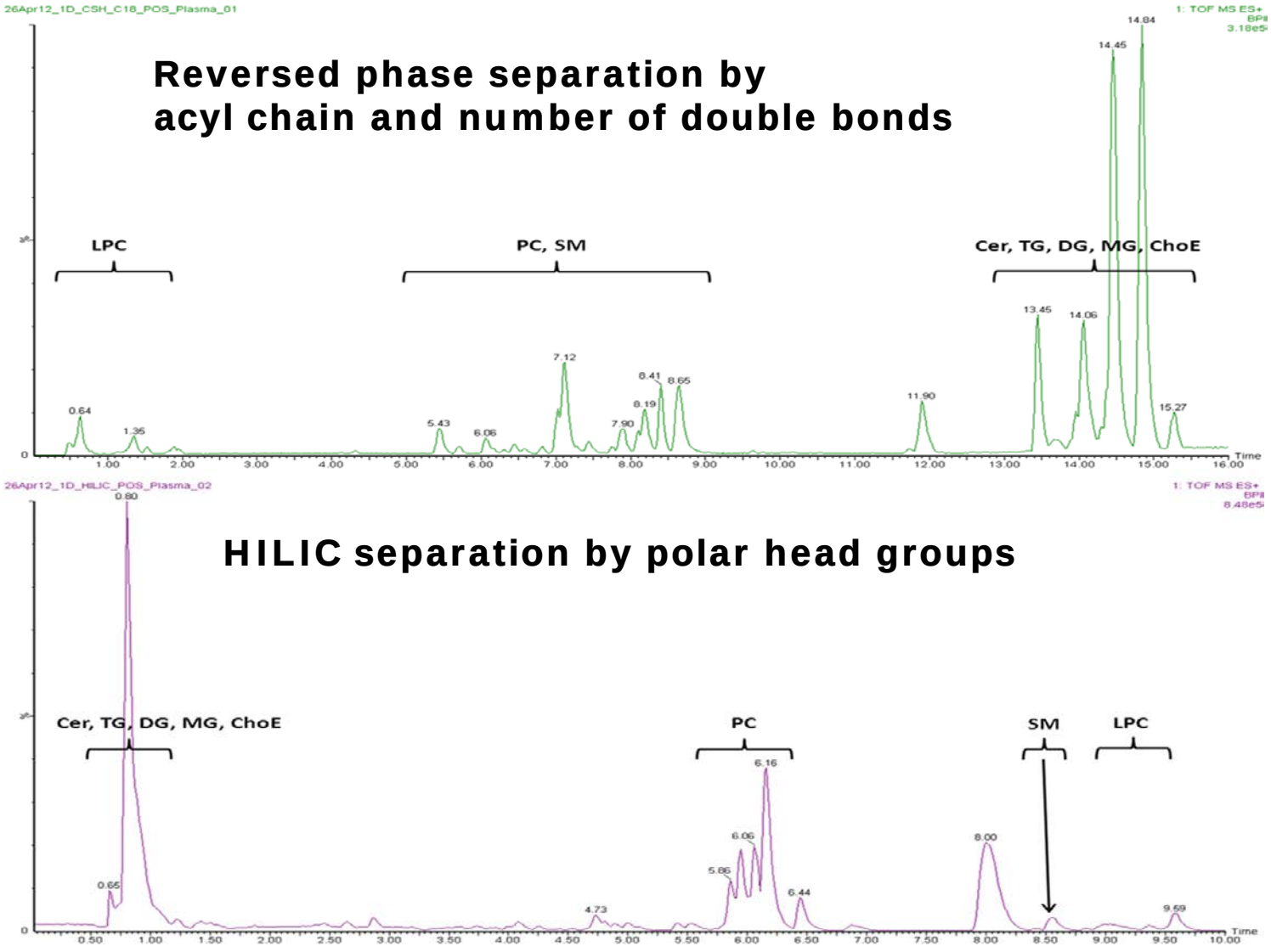

ACQUITY UPLC with *CSH C_{18}*
liver extract

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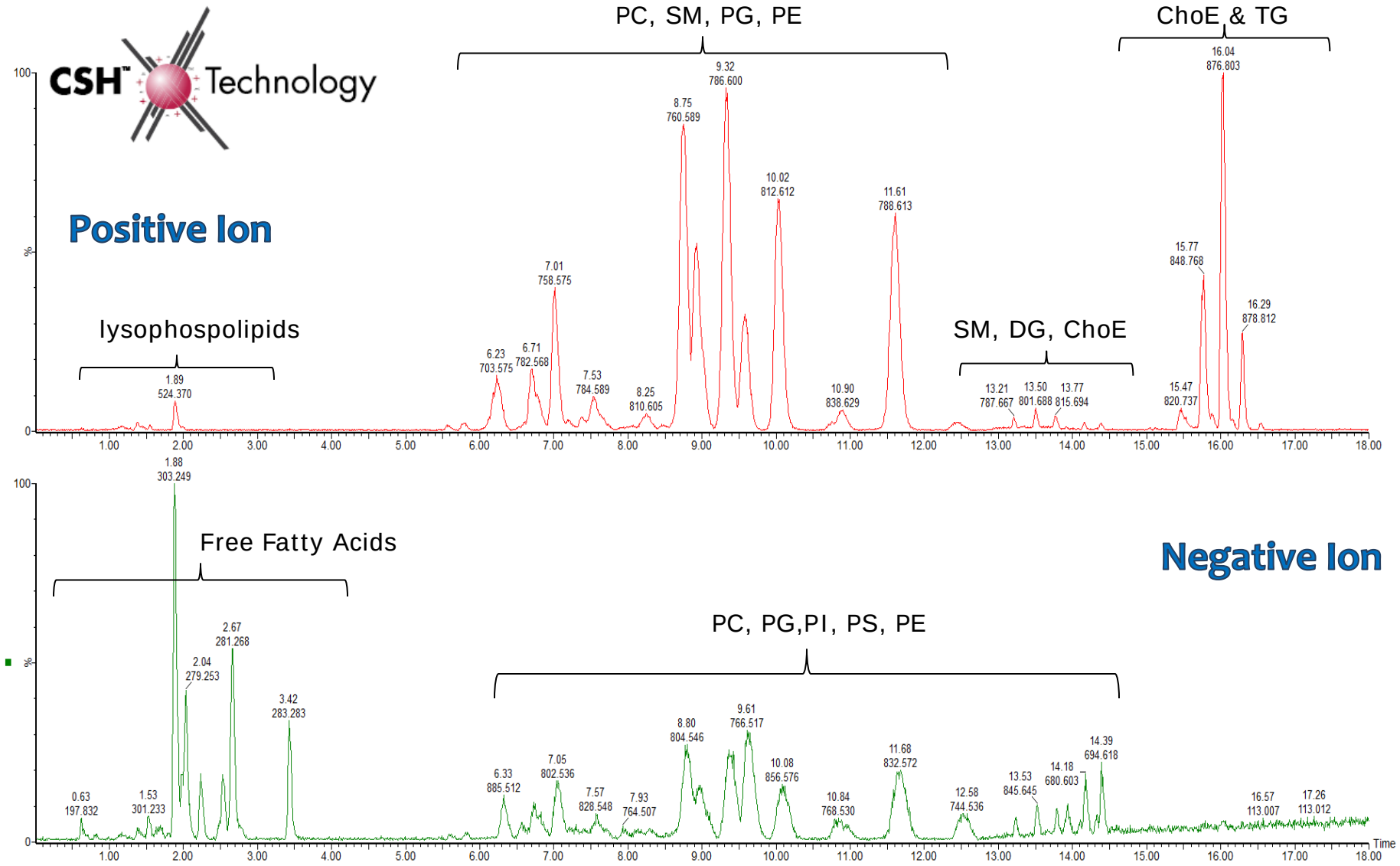

Isomers Separation: *CSH C_{18}*

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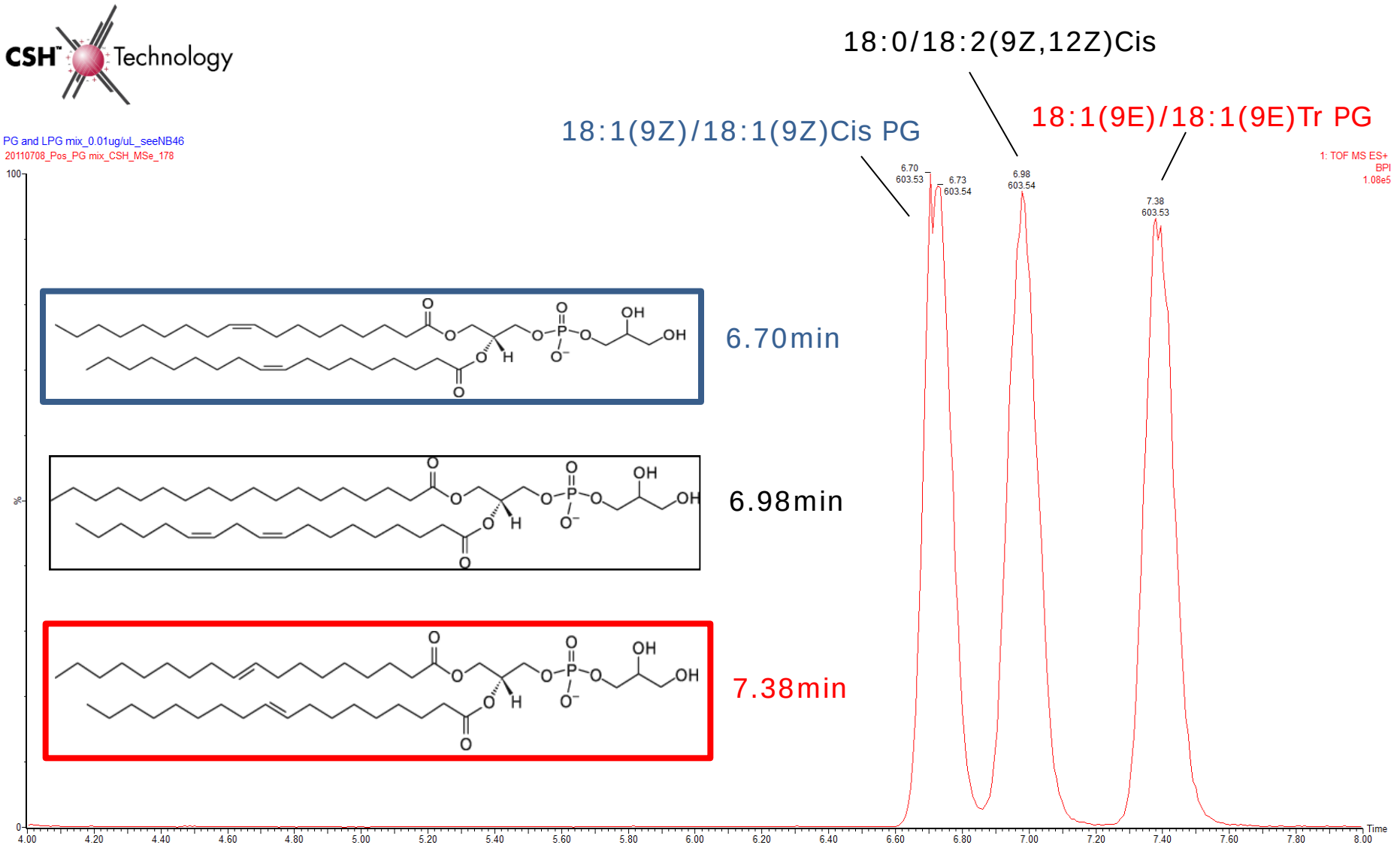
CSH™ Technology



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Convergence Chromatography

What is a Supercritical Fluid?

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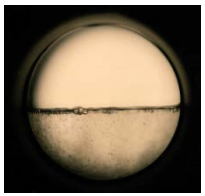
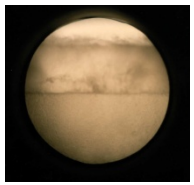
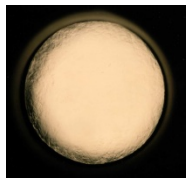


Increase temp and pressure



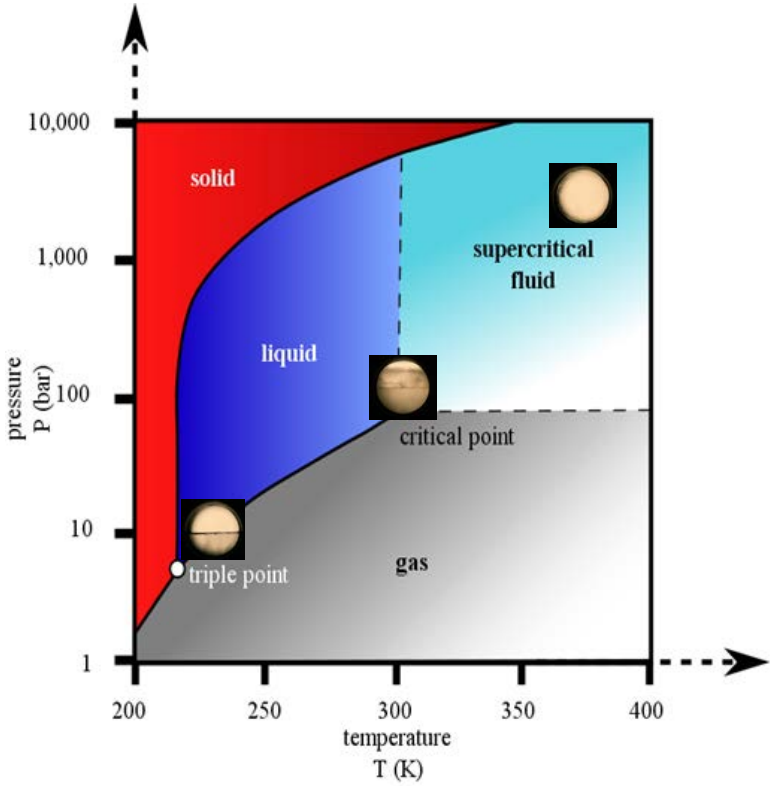
Increase temp and pressure



Liquid / gas | **Critical point** | **Supercritical fluid**

	Diffusivity (cm^2/s)	Viscosity (g/cm x s)
Gas	10^{-1}	10^{-4}
Supercritical Fluid	10^{-4} - 10^{-3} Liquid Like	10^{-4} - 10^{-3} Gas Like
Liquid	< 10^{-5}	10^{-2}

High diffusivity, and low viscosity result in **fast, efficient chromatography**



What is UPC²?

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- Same as SFC but uses sub-2µm particle to increase chromatographic performance such as
  - Speed of separation
  - Peak capacity
  - Complements to MS due to its low solvent load
- Uses CO_2 as a major solvent and
- Uses co-solvents such as methanol to vary the mobile phase strength

Convergence Chromatography:
Applied to Neutral and Polar Lipids

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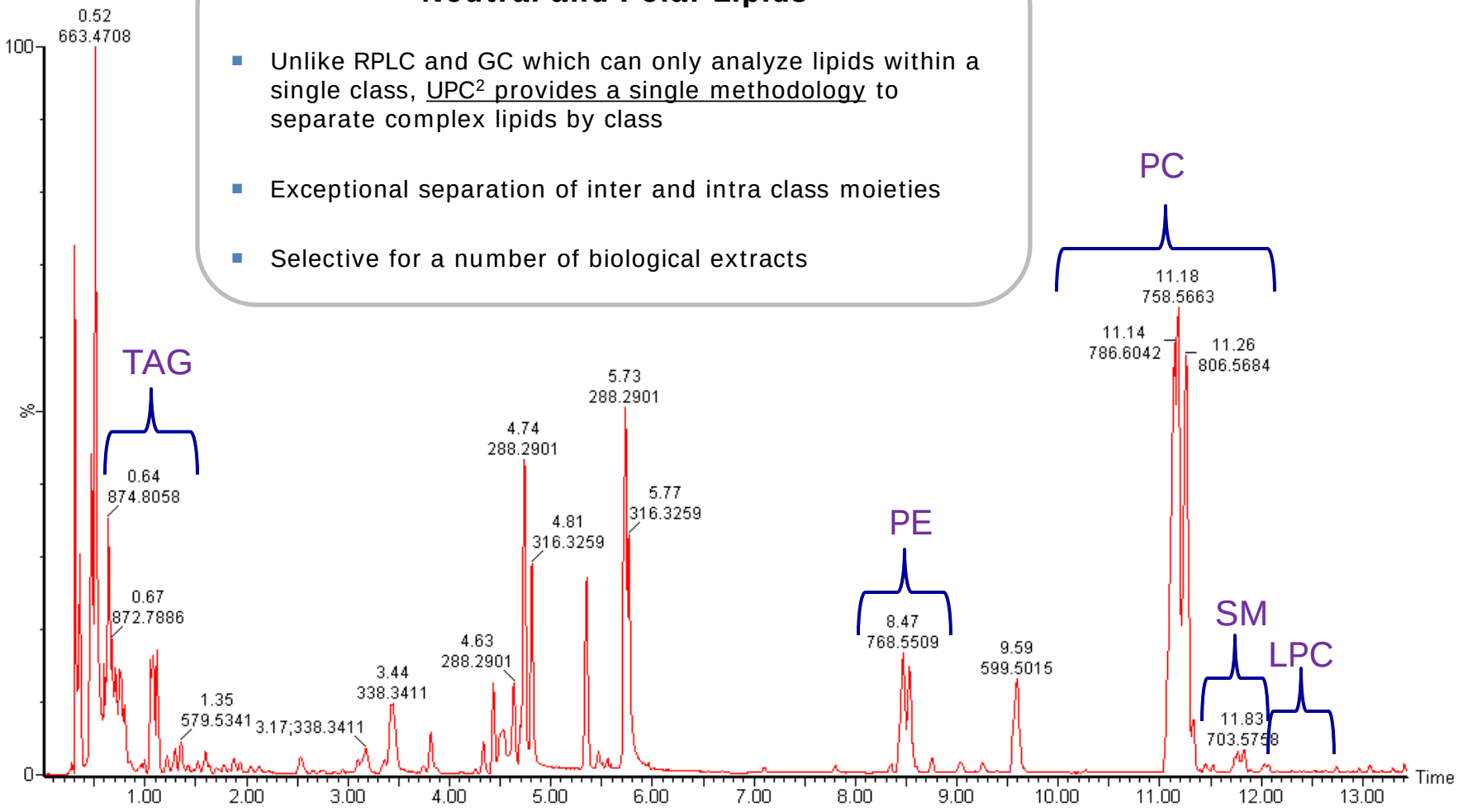
Neutral and Polar Lipids

- Unlike RPLC and GC which can only analyze lipids within a single class, UPC² provides a single methodology to separate complex lipids by class
- Exceptional separation of inter and intra class moieties
- Selective for a number of biological extracts



TAG: Triacylglycerides
SM: Sphynogomyelin

PE: Phosphotidylethanolamine
LPC: Lysophosphotidylcholine

PC: Phosphotidylcholine

Fatty Acid Standard Mixture

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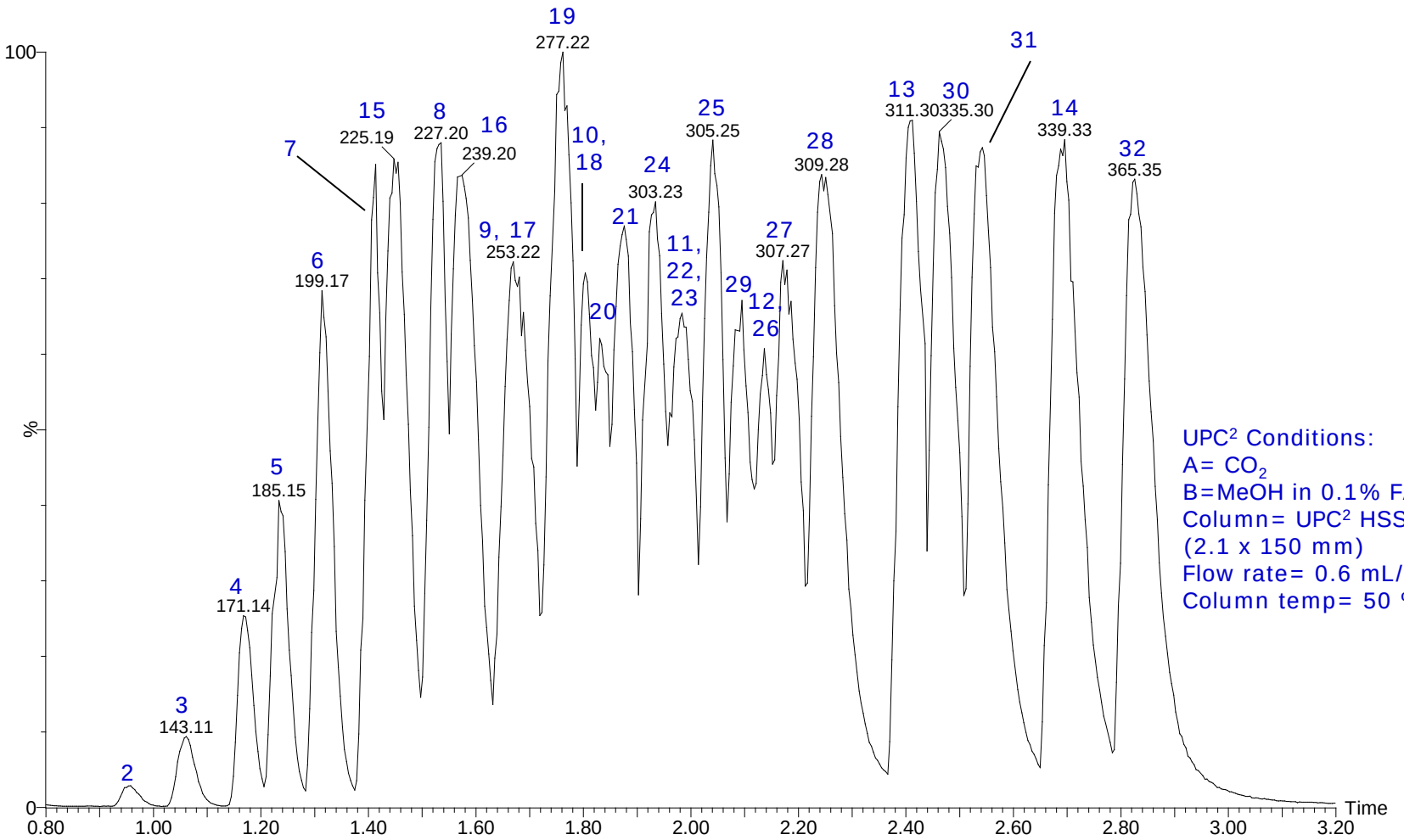

The separation of complex standard mixture that contain saturated, unsaturated, short and long chain FFA (32 different species).

Improving Workflow with Convergence Chromatography

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	Gas Chromatography	Convergence Chromatography	Reversed-phase LC
STEP 1	SPE Extraction (Florisil)		SPE Extraction (Oasis HLB)
STEP 2	Elution in hexane/ethyl acetate	**Direct Analysis on UPC²**	Elution in methanol
STEP 3	Evaporate to dryness		Evaporate to dryness
STEP 4	Reconstitute in cyclohexane		Reconstitute in water
STEP 5	Derivatize sample		Ready for analysis
STEP 6	Ready for analysis		

Convergence Chromatography

Eliminate lengthy evaporation and reconstitution steps

No need for derivatization

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Mass Spectrometry

Synpat G2-Si

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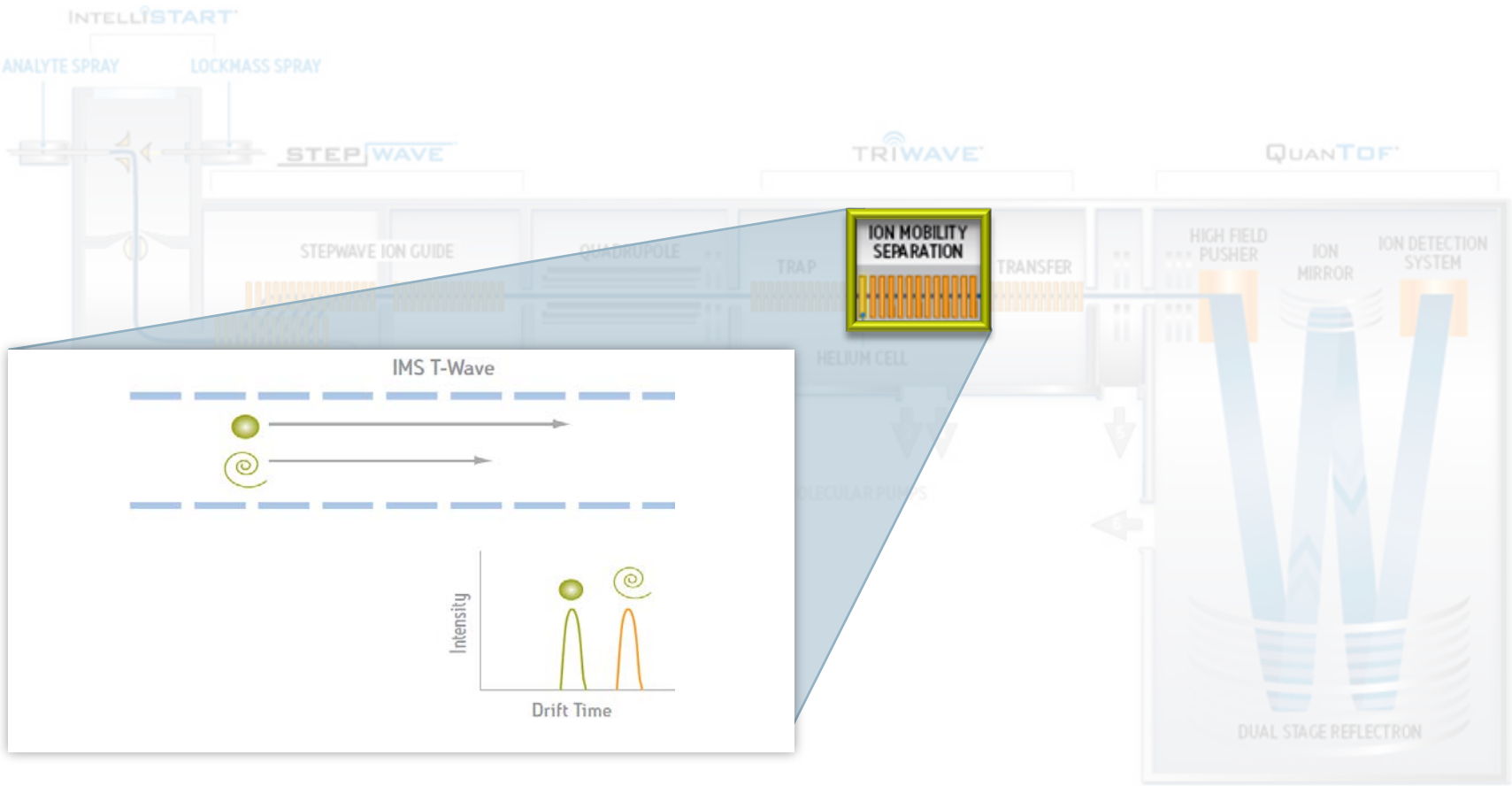

Vion™ IMS QTof

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What is Ion Mobility?

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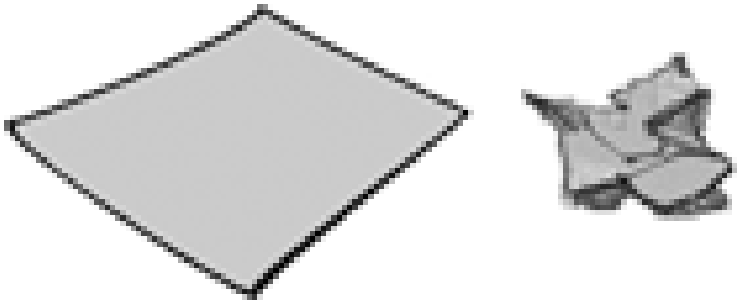
- Measuring the ion mobility of an ion;
  - Can yield information about its structure as small, compact, ions drift quicker than large extended ions
  - Introduce an additional dimension of sample separation to complex mixtures

- Similar to the effect that causes an extended paper towel to drift to the ground much more slowly under the influence of gravity and air resistance than a crushed towel of the same mass



Different types of Ion Mobility (integrated with MS)

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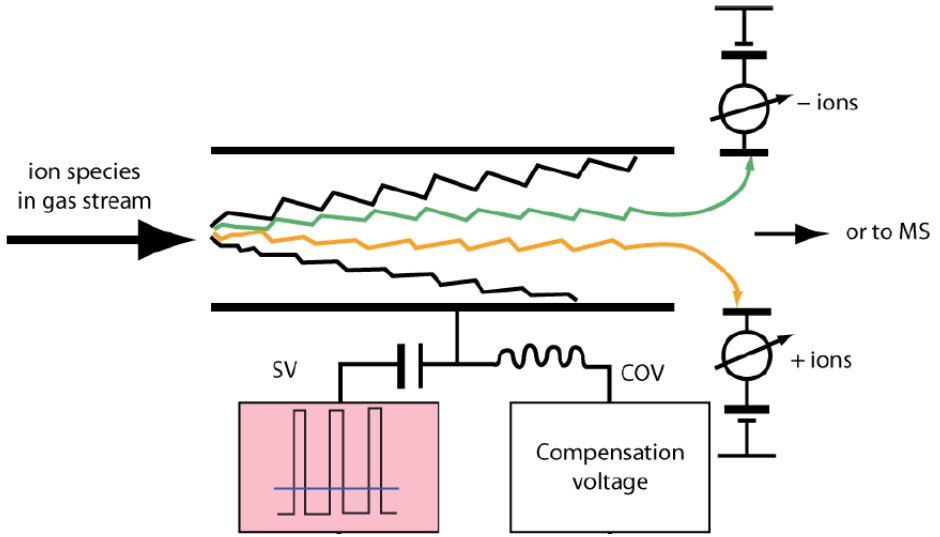
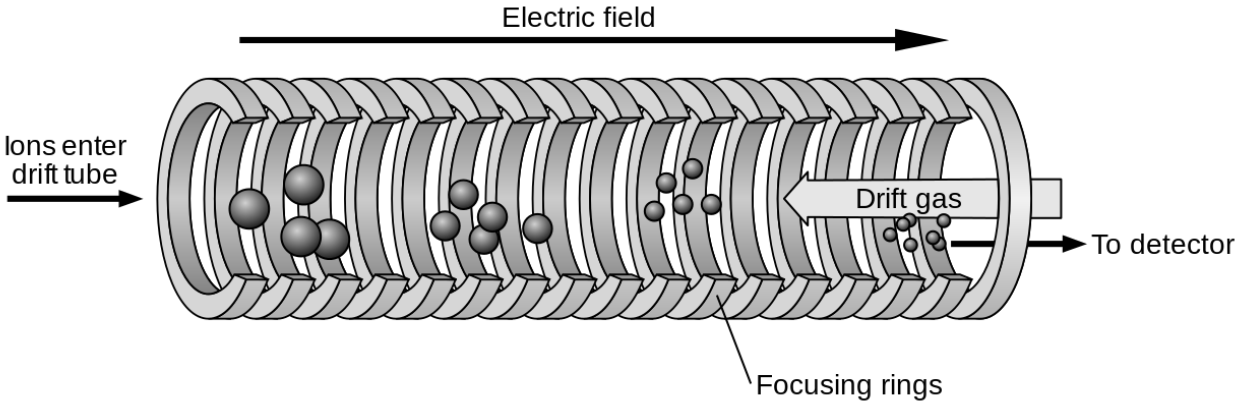
- Filtering devices
  - Differential Ion Mobility
  - SelexIon (SCIEX)
  - FAIMS (Thermo)
  - Front end



- Sorting devices
  - Drift Tube Ion Mobility (Agilent, Bruker)
  - Traveling Wave Ion Mobility (Waters)
  - Integrated



Different types of Ion Mobility

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- Filtering devices
  - Good for target analysis where a method (CV & modifier) can be selected.
  - Good separation but only for specific compounds
  - Not suitable for untargeted analysis of unknowns
  - Sensitivity increases only through selectivity
  - Duty cycle suited to low numbers of target compounds
  - No CCS values

- Sorting devices
  - Good for untargeted analysis of unknowns
  - Increases overall system peak capacity
  - Duty cycle suited to full scan analysis
  - Measures CCS

An RF-Only Stacked Ring Device

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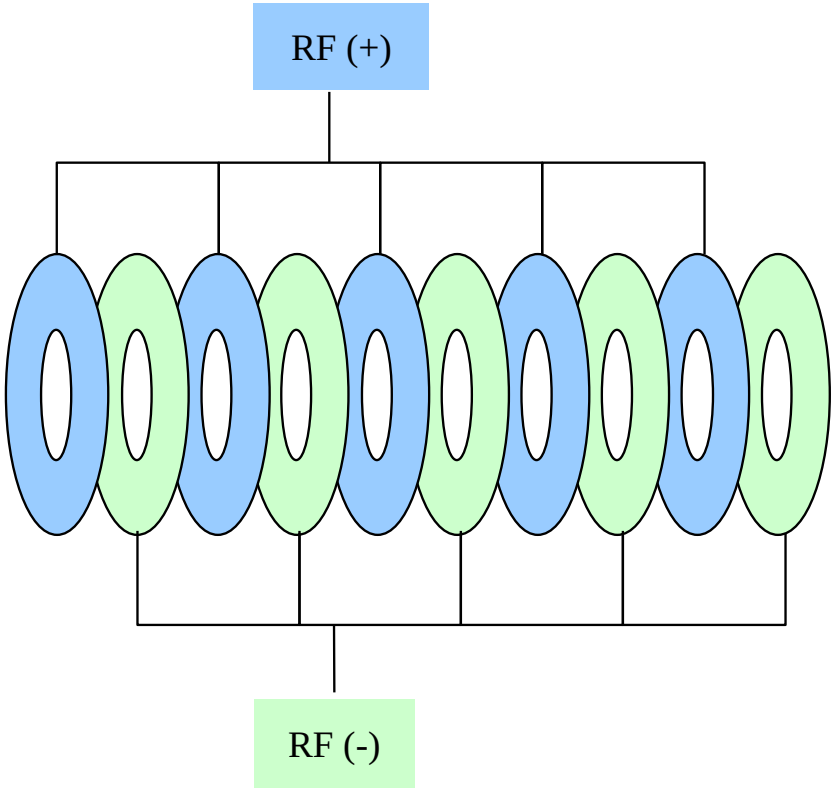
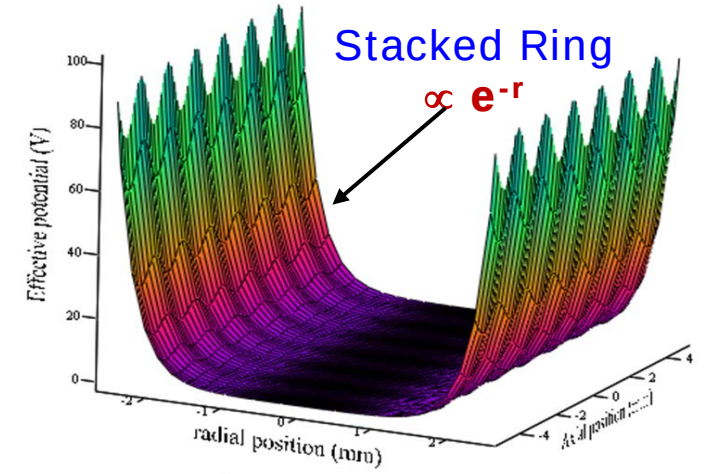
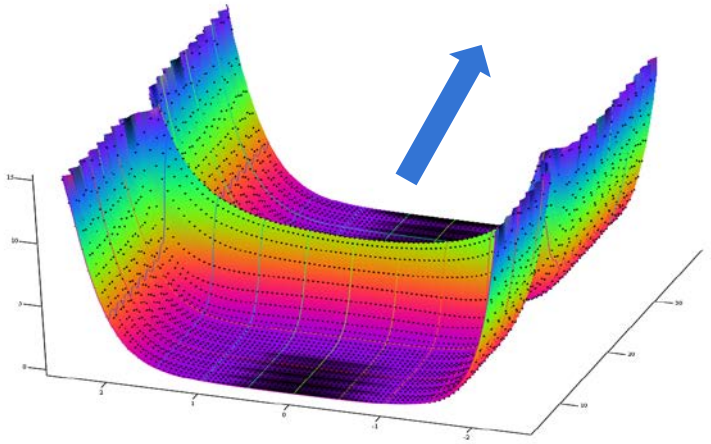
- Bahr, Gerlich and Teloy in 1969[1] and onward[2]
  - ion trapping device for studying ion-molecule reactions







T-WAVE

1. Bahr R, Gerlich D, Teloy E. *Verhandl. DPG (VI)* 1969; **5**: 131
2. Gerlich D. *in* State-Selected and State-to-State Ion-Molecule Reaction Dynamics, Part 1: Experiment, Wiley: 1992

T-wave technology in SYNAPT mass spectrometer

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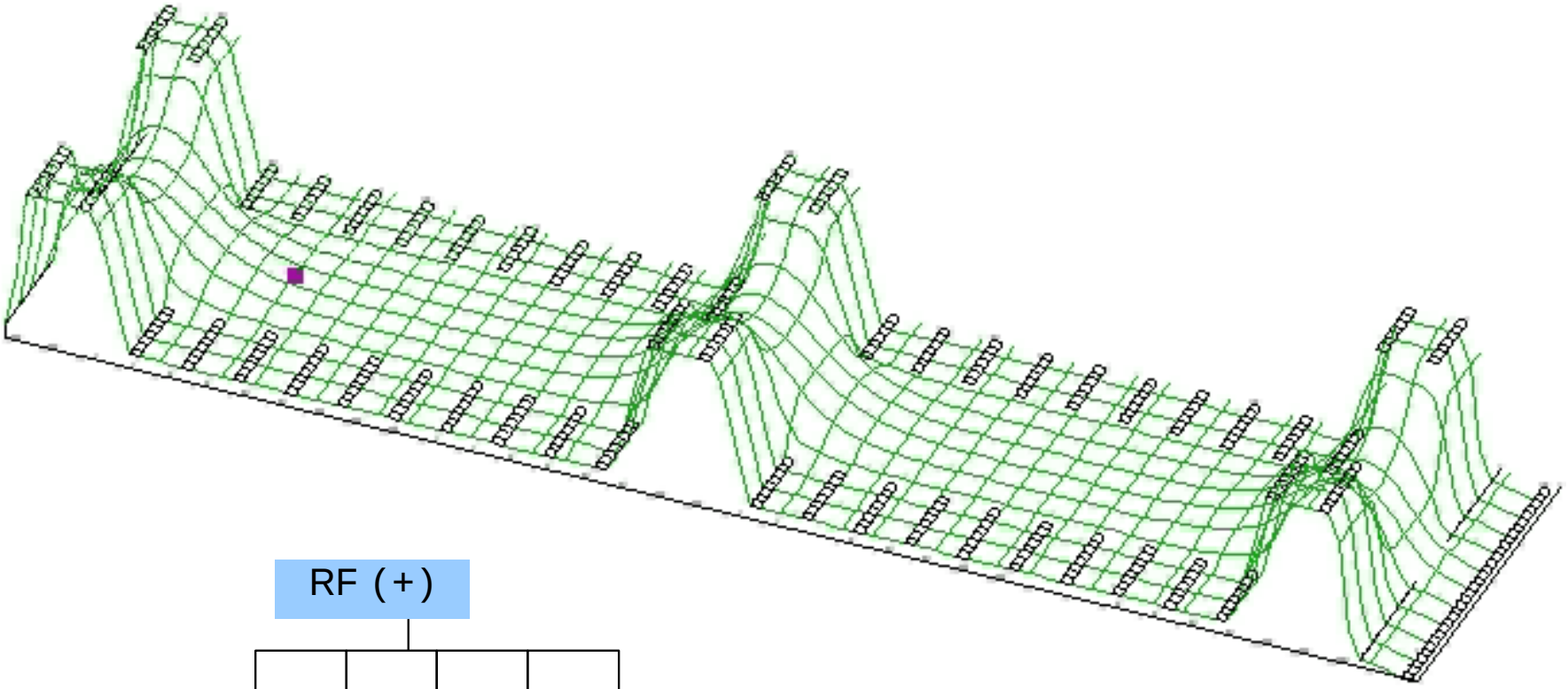

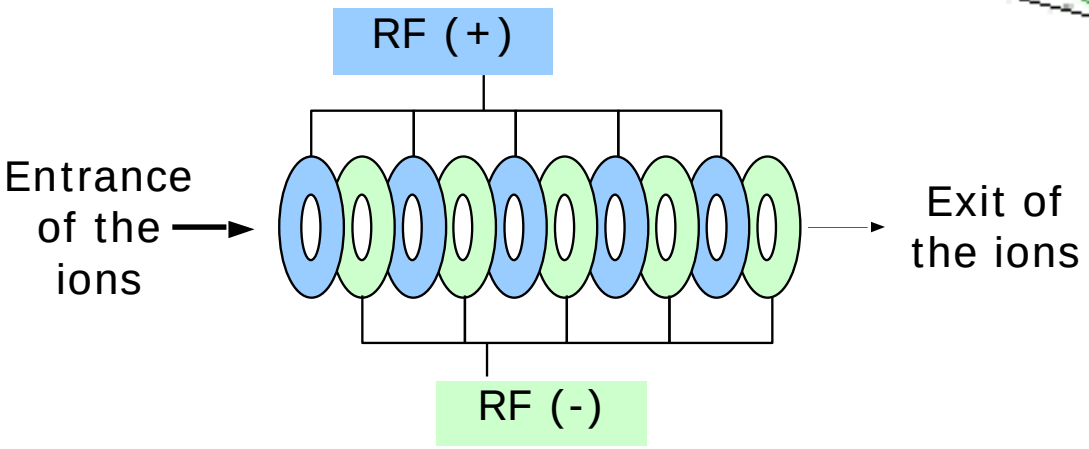

Ion Mobility approaches in Metabolomics

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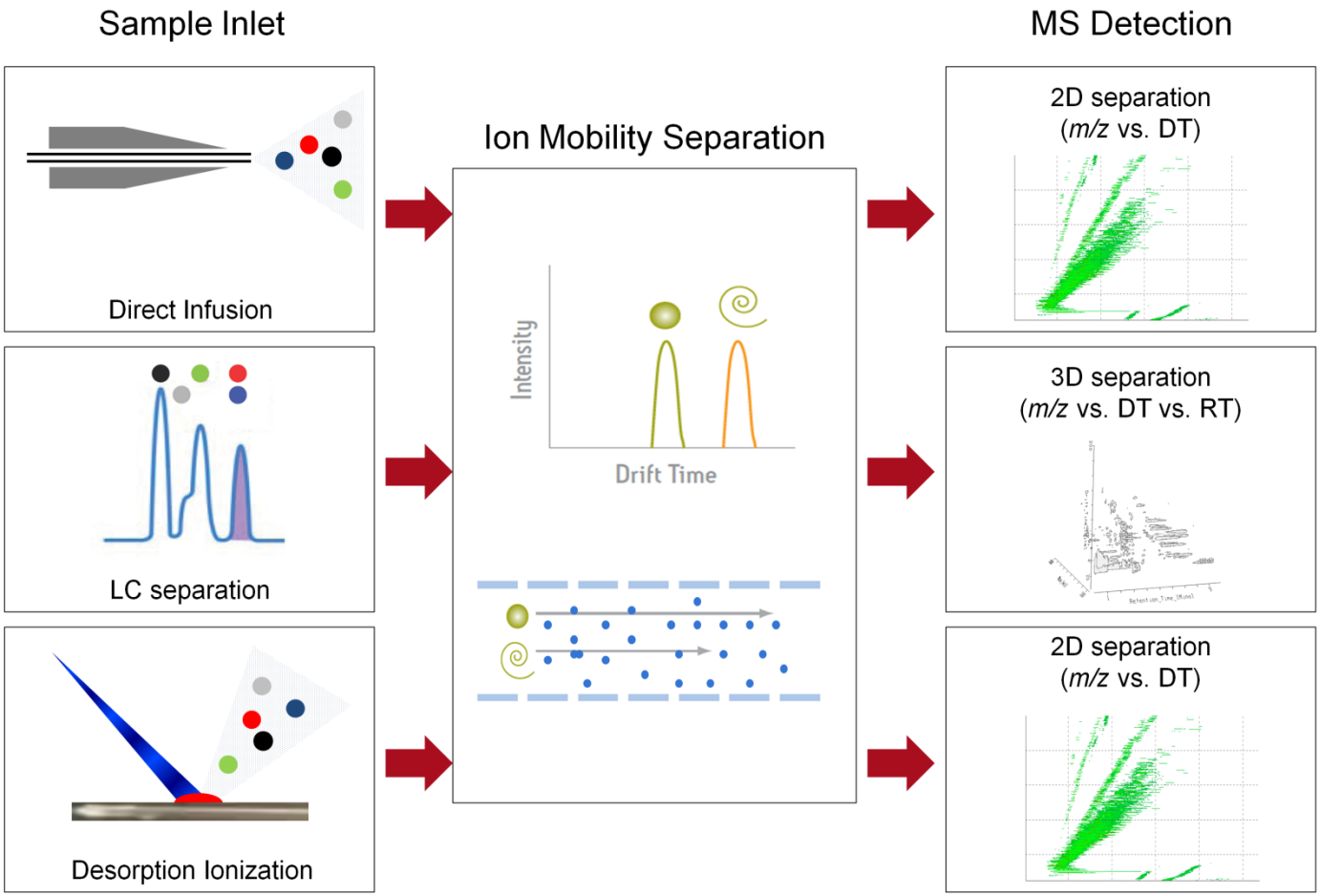

Astarita and Paglia 2013

System Peak Capacity

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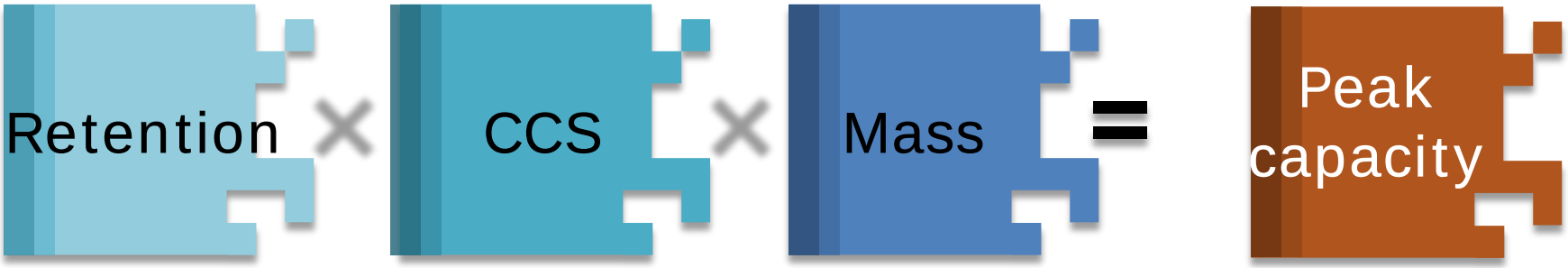

Acquity UPLC®

T-WAVE™ ION MOBILITY POWERED

QuanTof

UPLC/HDMS

Separation Power

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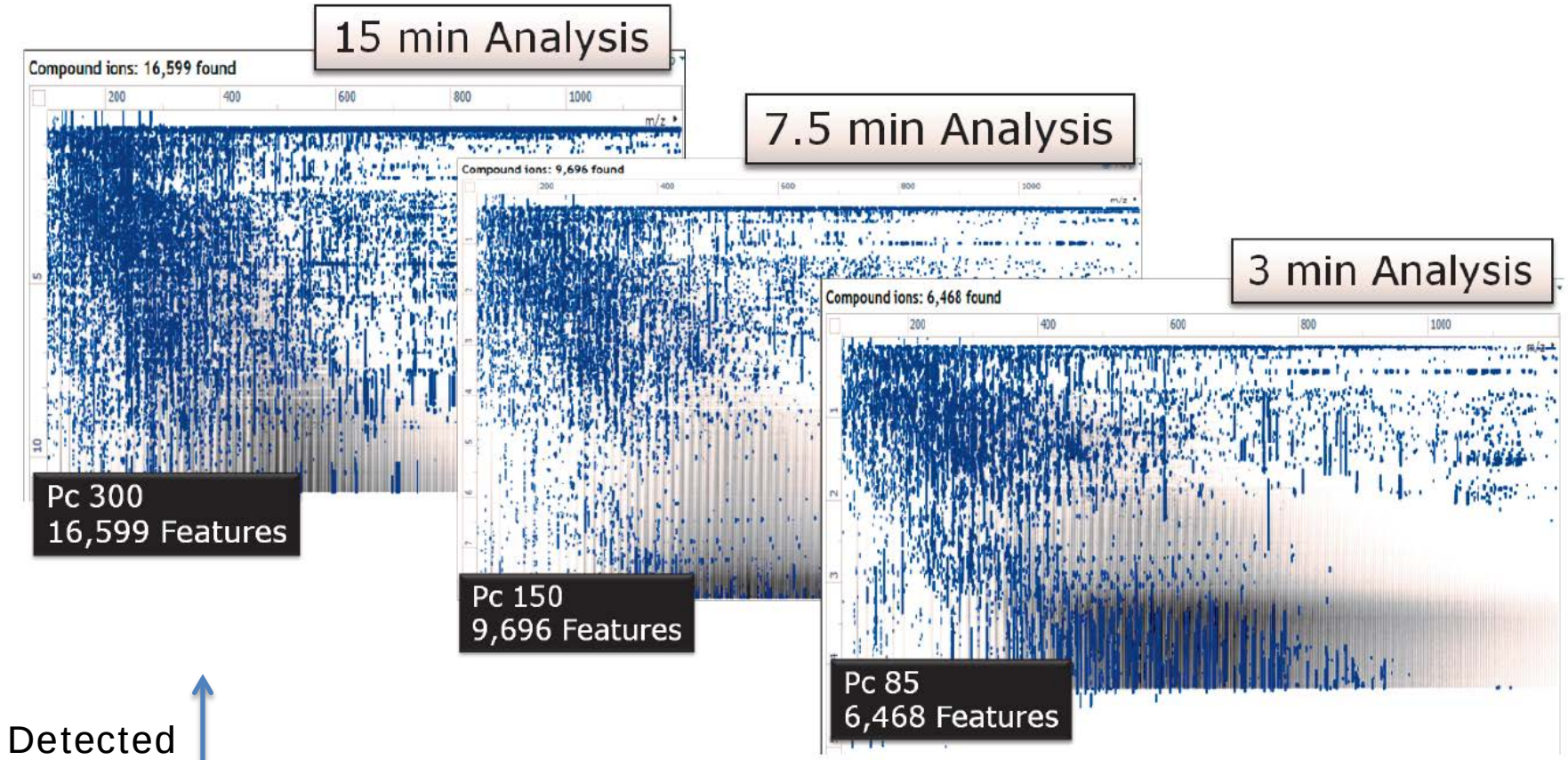

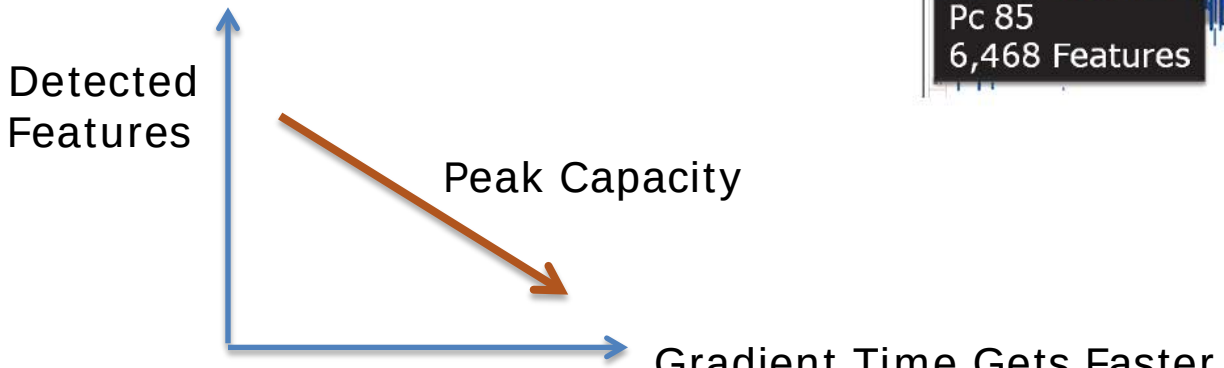

Separation Power

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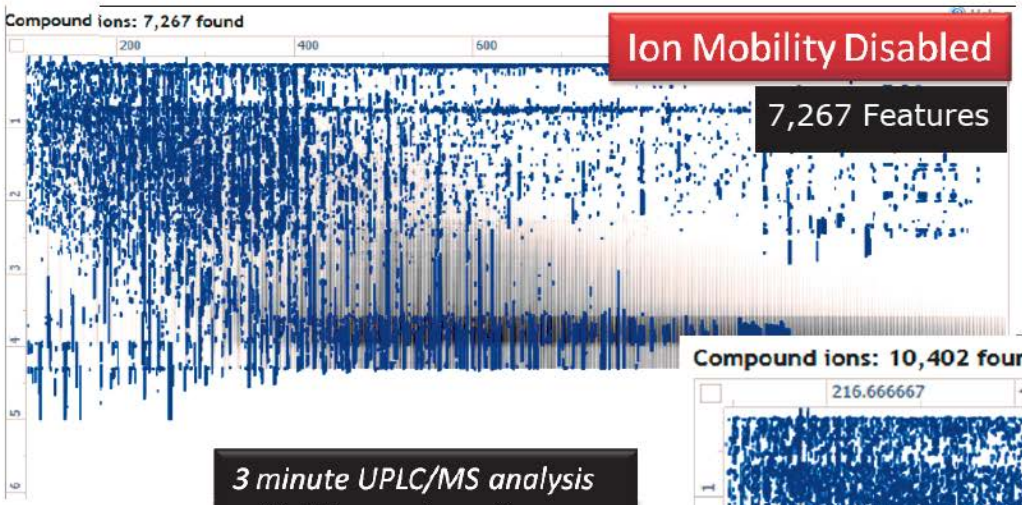

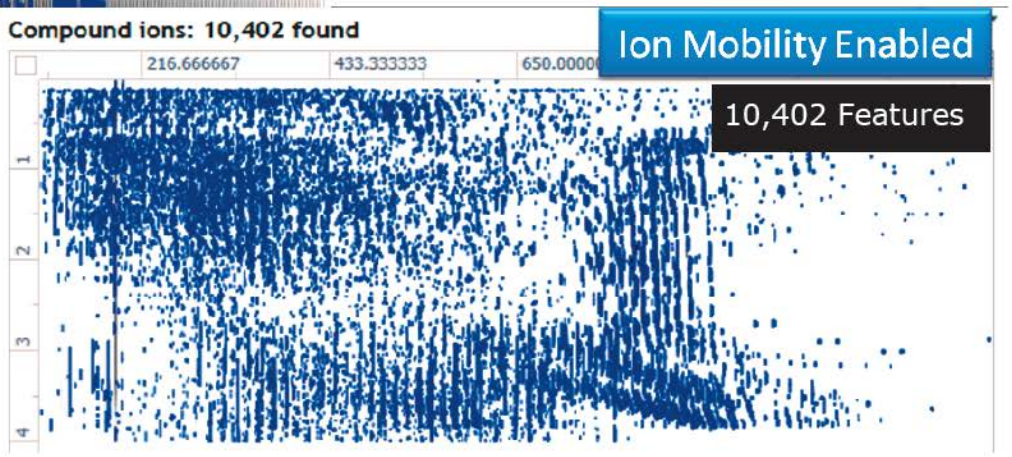

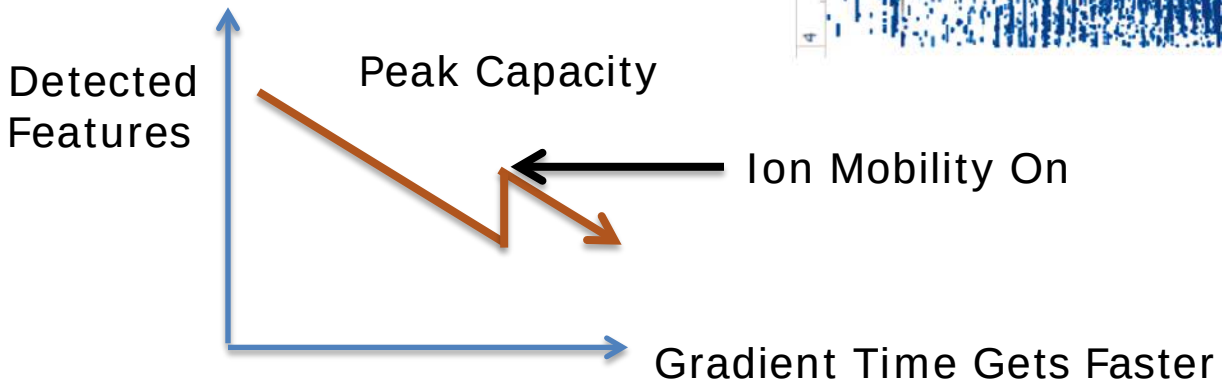

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Ion Mobility Enhanced DIA Increases Information Content

Spectra for closely co-eluting lipids from Liver Extract

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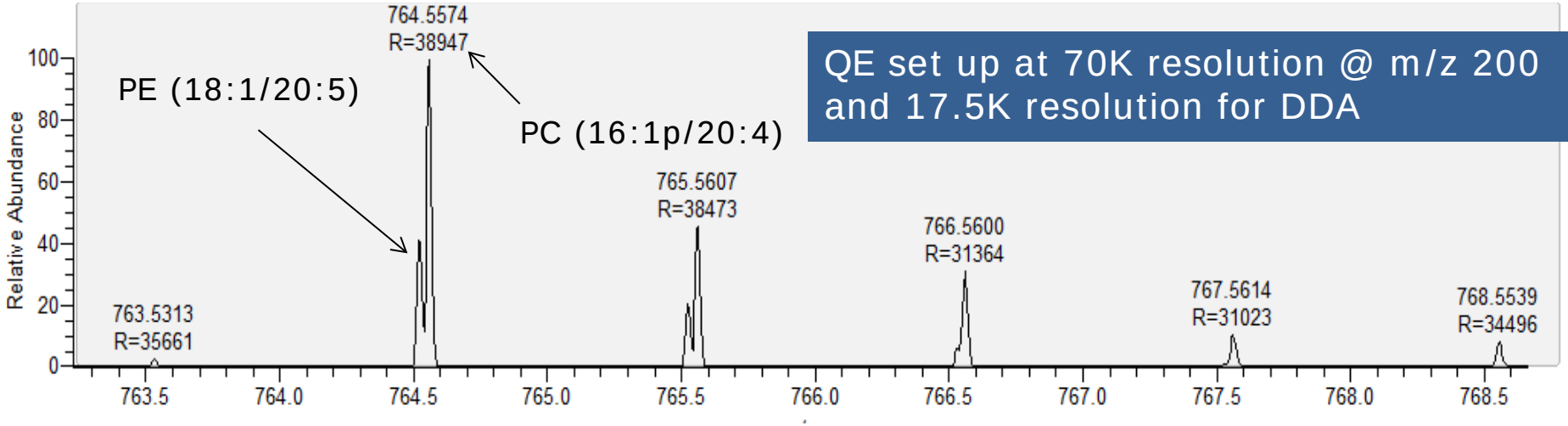
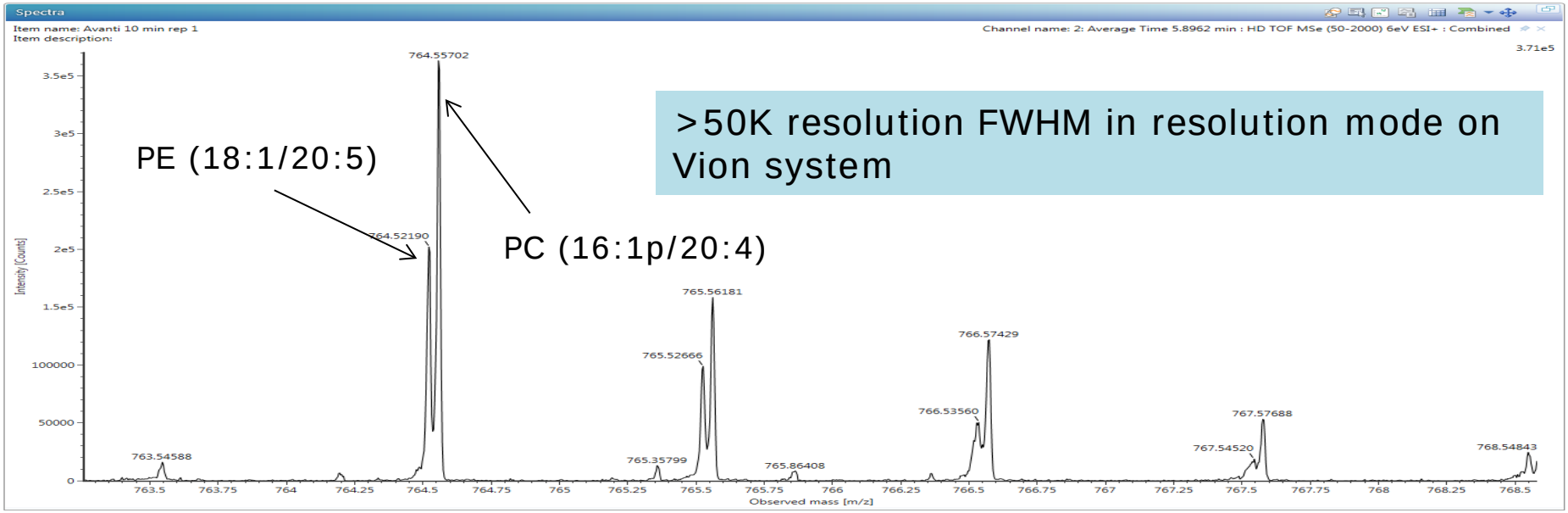


QE set up at 70K resolution @ m/z 200 and 17.5K resolution for DDA



>50K resolution FWHM in resolution mode on Vion system

Separation Power - HDMS^E Maximizing MS/MS content

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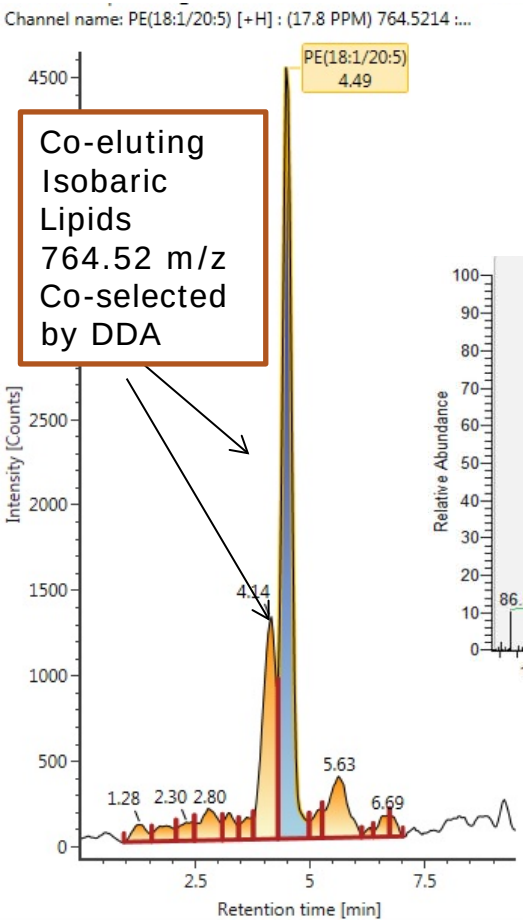
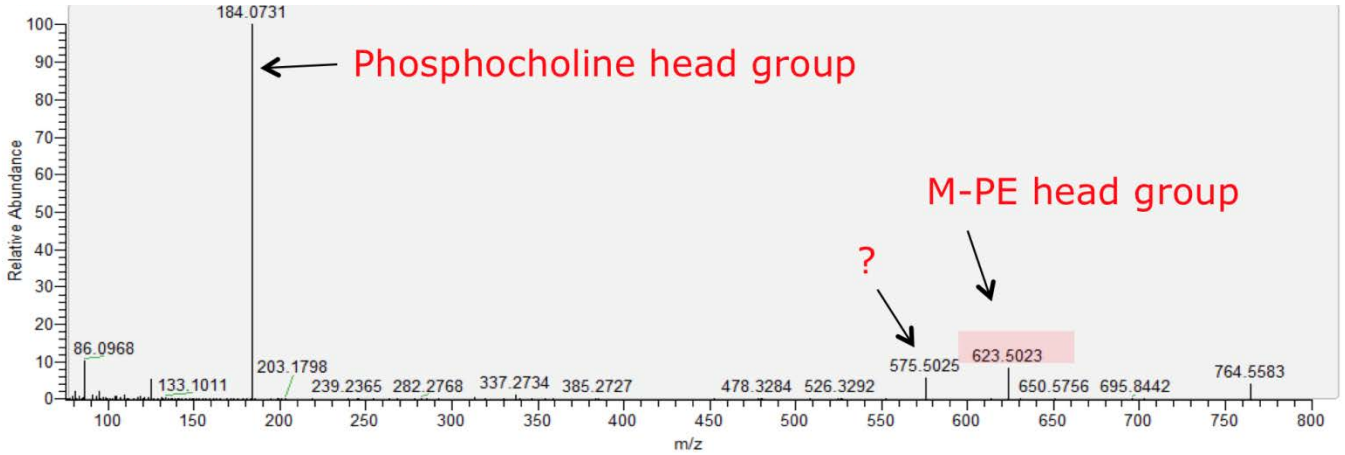


Q-Exactive DDA Data – One MS/MS Spectrum



Retention and drift time separation … LC-DIA-IM-MS (HDMS^E)

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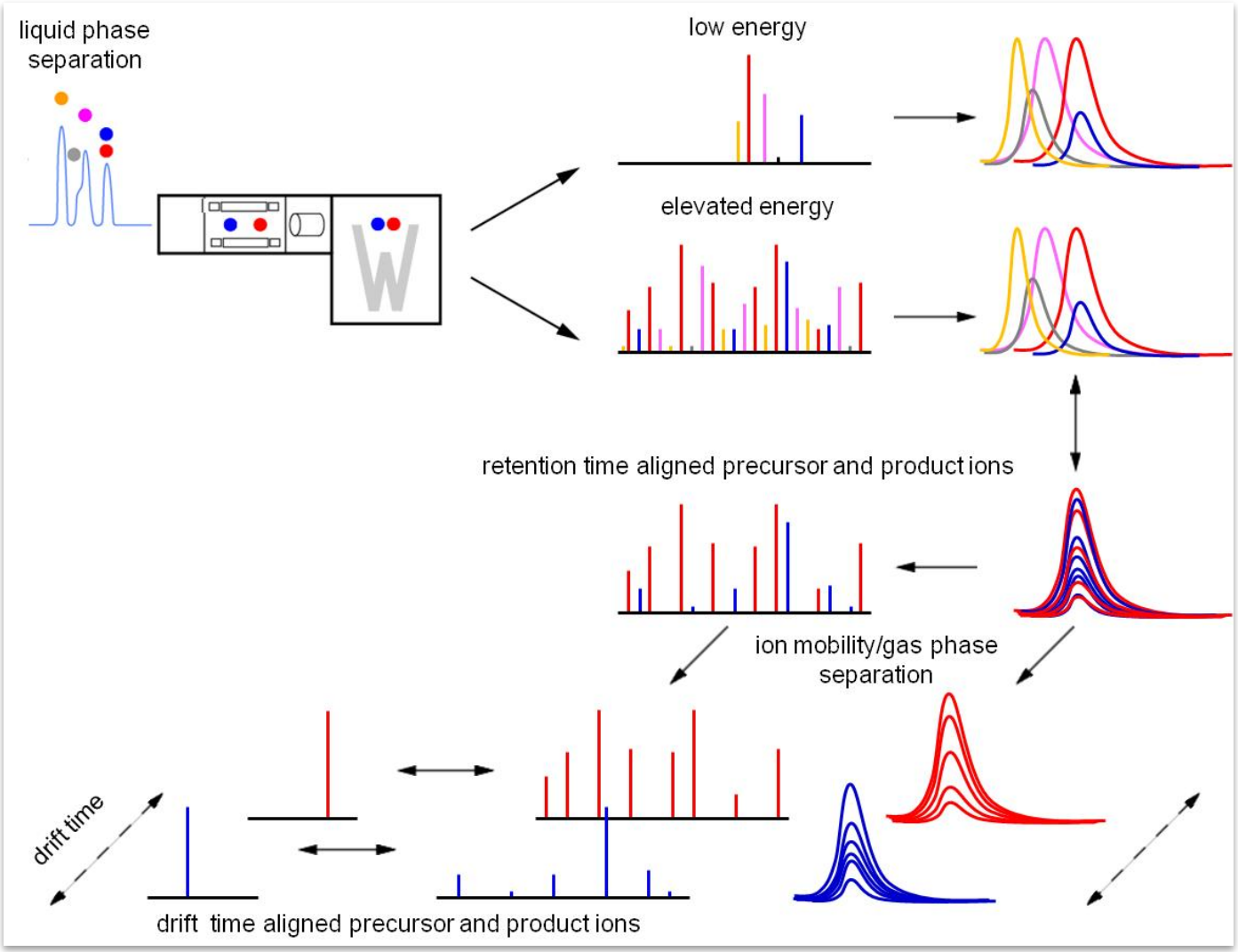

Separation Power - HDMS^E Maximizing MS/MS content

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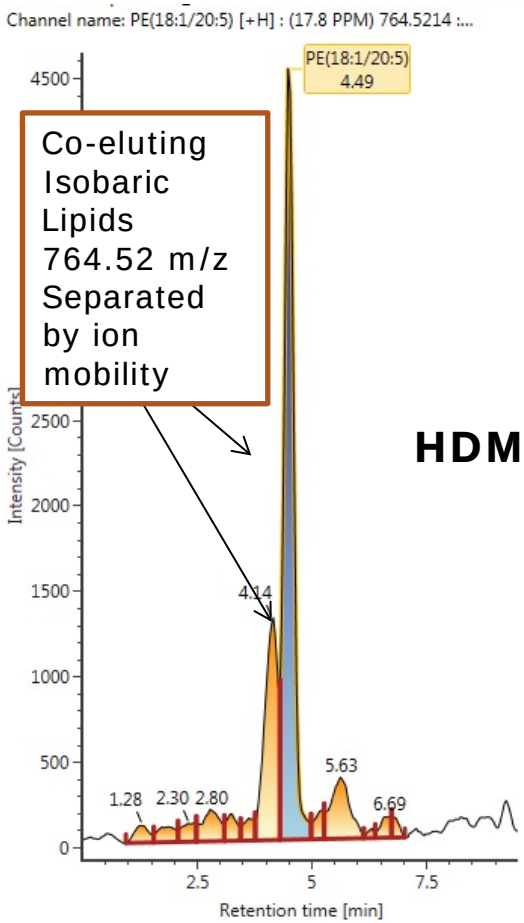
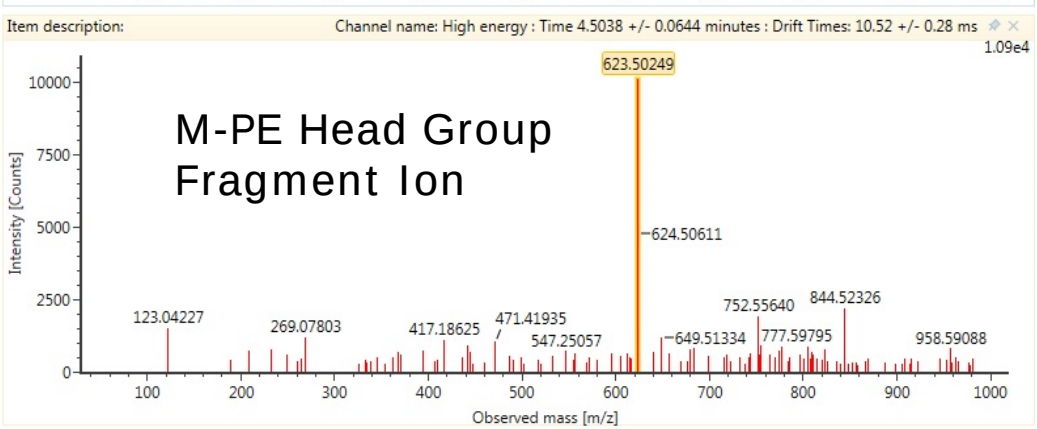
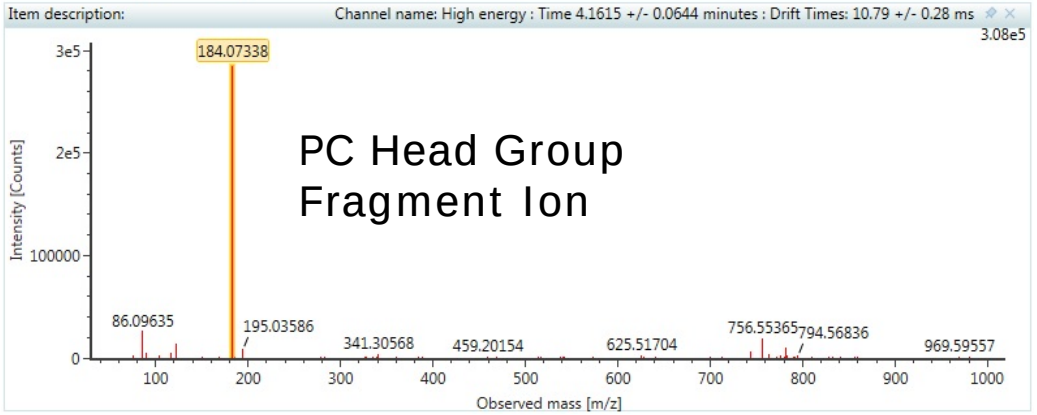
Combination of Ion Mobility and HDMS^E extracts more discrete spectra than traditional MS/MS

More interpretable data helps identification and quantitation



HDMS^E





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Collision Cross Section

Increasing analytical perspective

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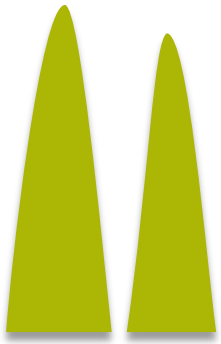
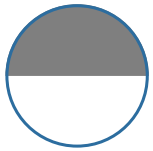
Representative analytical measurement		Property of molecule
	rt	K_D
	m / z	mass
	dt	CCS 

What is CCS?

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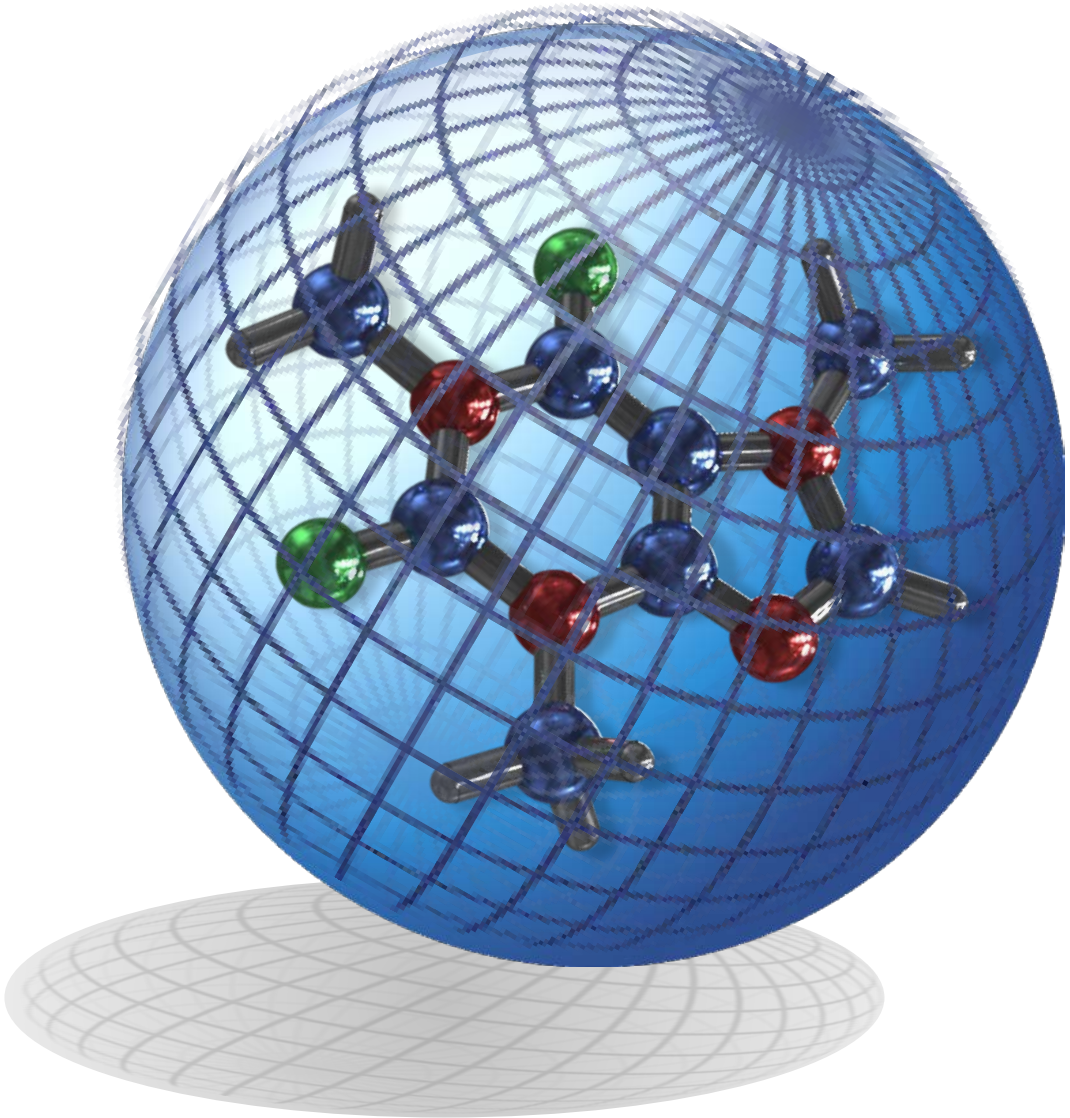
Important differentiating characteristic of an ion

- Chemical Structure (mass, size)
- 3-dimensional Conformation (shape)

Precise Physicochemical Property of an ion



What are the Benefits of Ion Mobility in Metabolomics?

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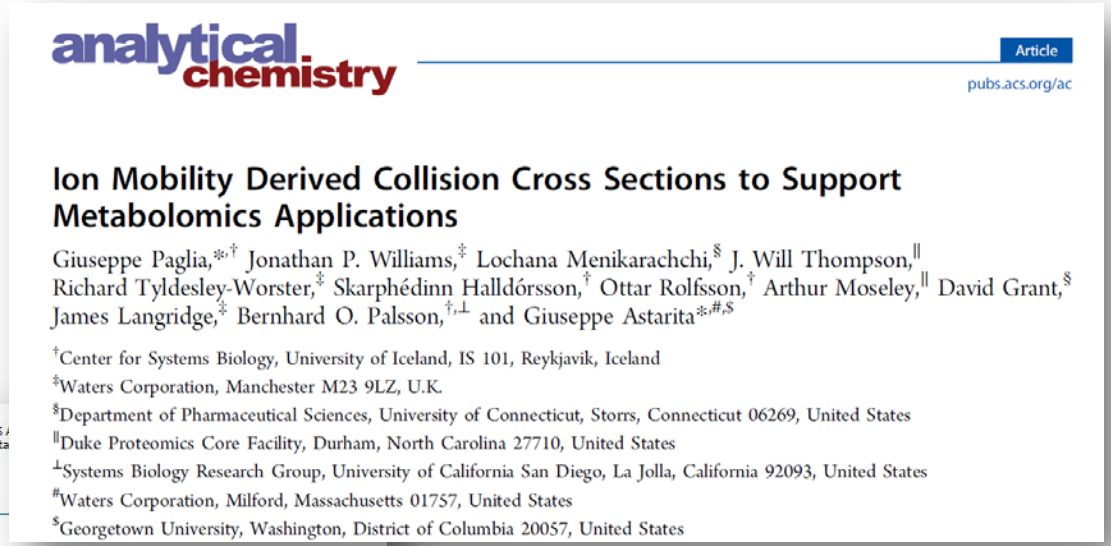

analytical chemistry

Article

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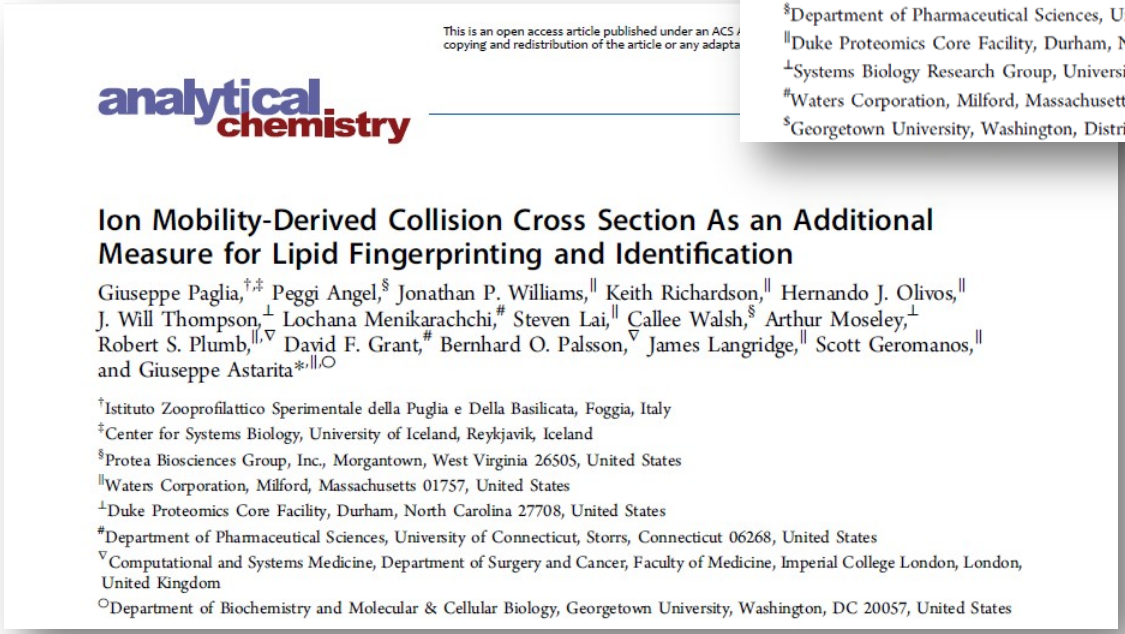
Ion Mobility Derived Collision Cross Sections to Support Metabolomics Applications

Giuseppe Paglia,[*,†] Jonathan P. Williams,[‡] Lochana Menikarachchi,[§] J. Will Thompson,[∥] Richard Tyldesley-Worster,[‡] Skarphédinn Halldórsson,[†] Ottar Rolfsson,[†] Arthur Moseley,[∥] David Grant,[§] James Langridge,[‡] Bernhard O. Palsson,[†,⊥] and Giuseppe Astarita[*,#,$]

[†]Center for Systems Biology, University of Iceland, IS 101, Reykjavik, Iceland
[‡]Waters Corporation, Manchester M23 9LZ, U.K.
[$]Department of Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut 06269, United States
[∥]Duke Proteomics Core Facility, Durham, North Carolina 27710, United States
[⊥]Systems Biology Research Group, University of California San Diego, La Jolla, California 92093, United States
[#]Waters Corporation, Milford, Massachusetts 01757, United States
[$]Georgetown University, Washington, District of Columbia 20057, United States



analytical chemistry

Ion Mobility-Derived Collision Cross Section As an Additional Measure for Lipid Fingerprinting and Identification

Giuseppe Paglia,[†,‡] Peggi Angel,[§] Jonathan P. Williams,[∥] Keith Richardson,[∥] Hernando J. Olivos,[∥] J. Will Thompson,[⊥] Lochana Menikarachchi,[#] Steven Lai,[∥] Callee Walsh,[§] Arthur Moseley,[⊥] Robert S. Plumb,[∥,▽] David F. Grant,[#] Bernhard O. Palsson,[▽] James Langridge,[∥] Scott Geromanos,[∥] and Giuseppe Astarita[*,∥,○]

[†]Istituto Zooprofilattico Sperimentale della Puglia e Della Basilicata, Foggia, Italy
[‡]Center for Systems Biology, University of Iceland, Reykjavik, Iceland
[§]Protea Biosciences Group, Inc., Morgantown, West Virginia 26505, United States
[∥]Waters Corporation, Milford, Massachusetts 01757, United States
[⊥]Duke Proteomics Core Facility, Durham, North Carolina 27708, United States
[#]Department of Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut 06268, United States
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[○]Department of Biochemistry and Molecular & Cellular Biology, Georgetown University, Washington, DC 20057, United States

CCS Measurements for Common Metabolites

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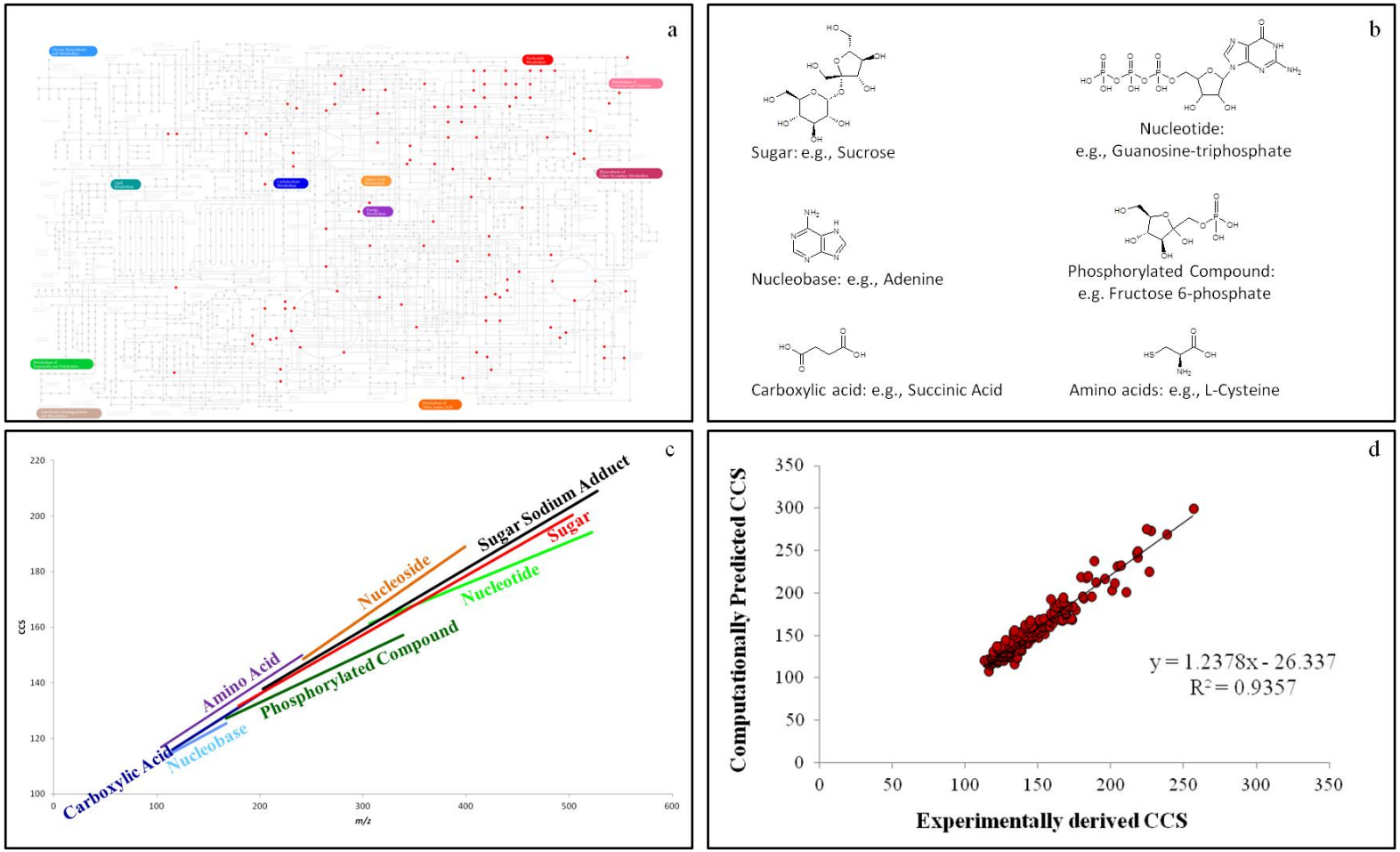

Inter-Lab Reproducibility of CCS Measurements

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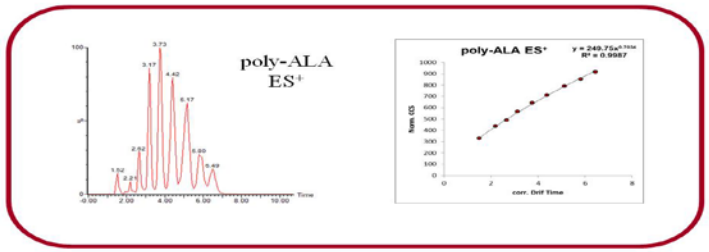
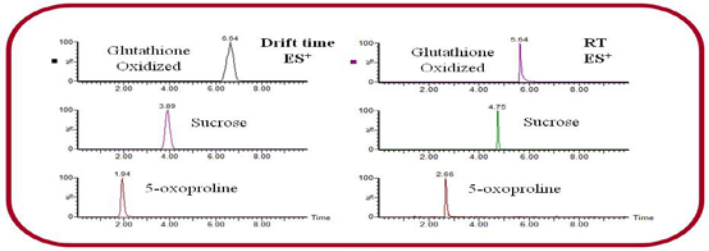
- Drift time calibration with known CCSs for polyAla

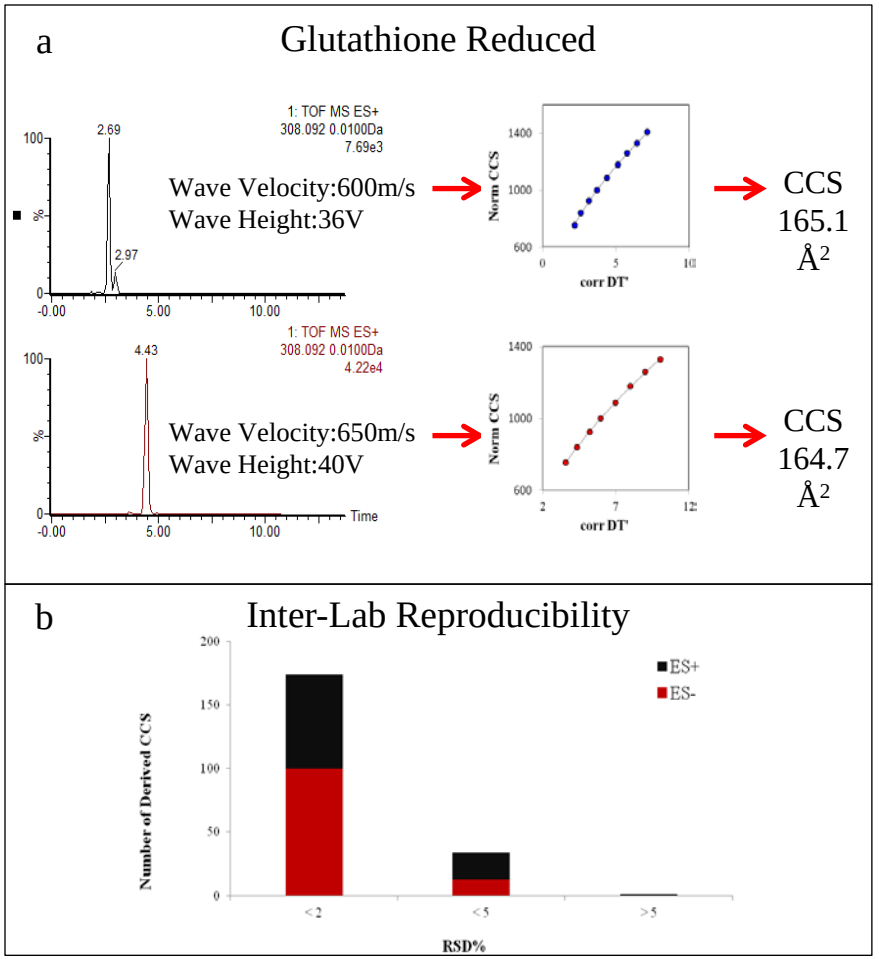


- Annotation of drift times and retention times (RT) of standard metabolites



- Drift time to CCS conversion with polyAla calibration
- Database generation for m/z, CCS and RT

Metabolite	ES+			
	Ion	*m/z*	CCS (Å²)	RT (min)
5-Oxoproline	$[M+H]^+$	130.0504	121	2.68
Sucrose	$[M+Na]^+$	365.1060	170	4.75
Glutathione Oxidized	$[M+H]^+$	613.1598	227	5.70



Matrix effect: Retention Times vs. CCS

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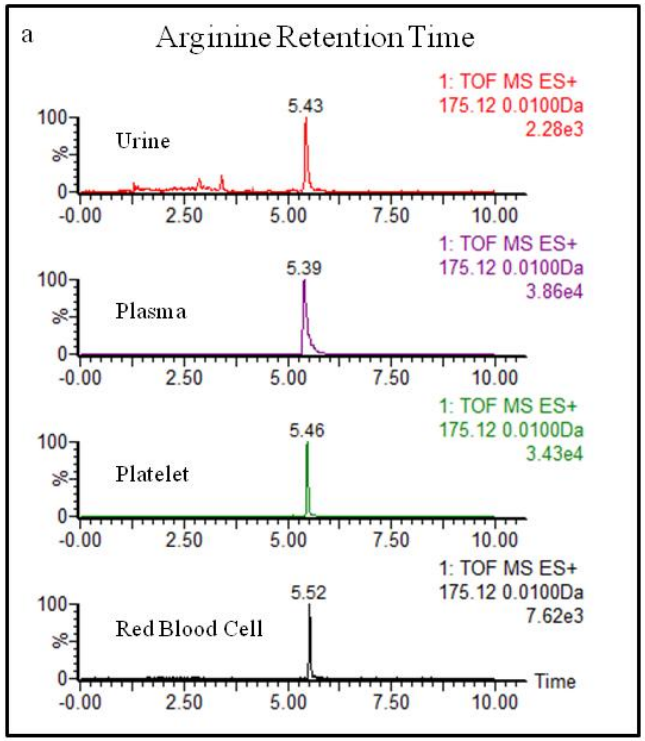

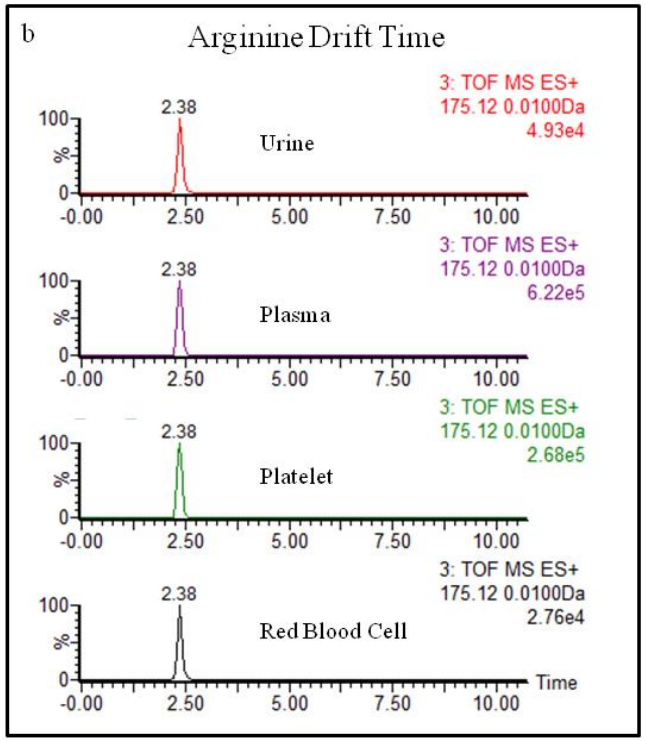

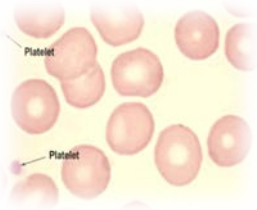

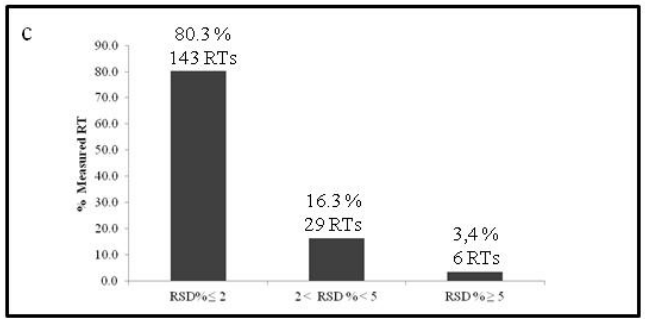

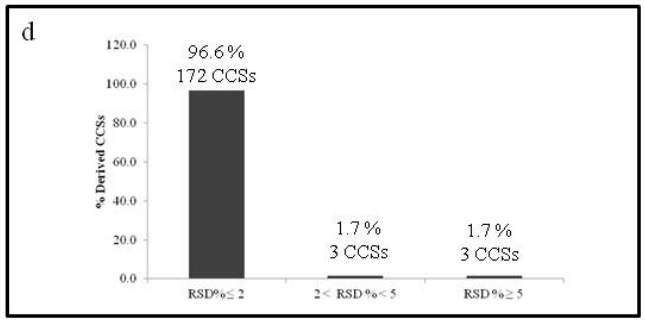

CCS correlation between gradients

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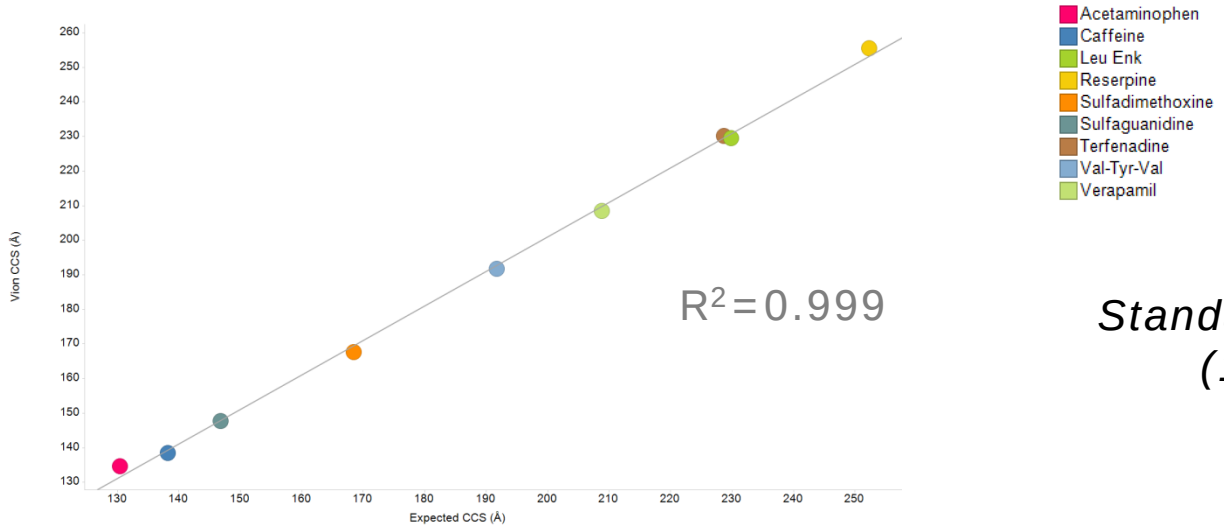
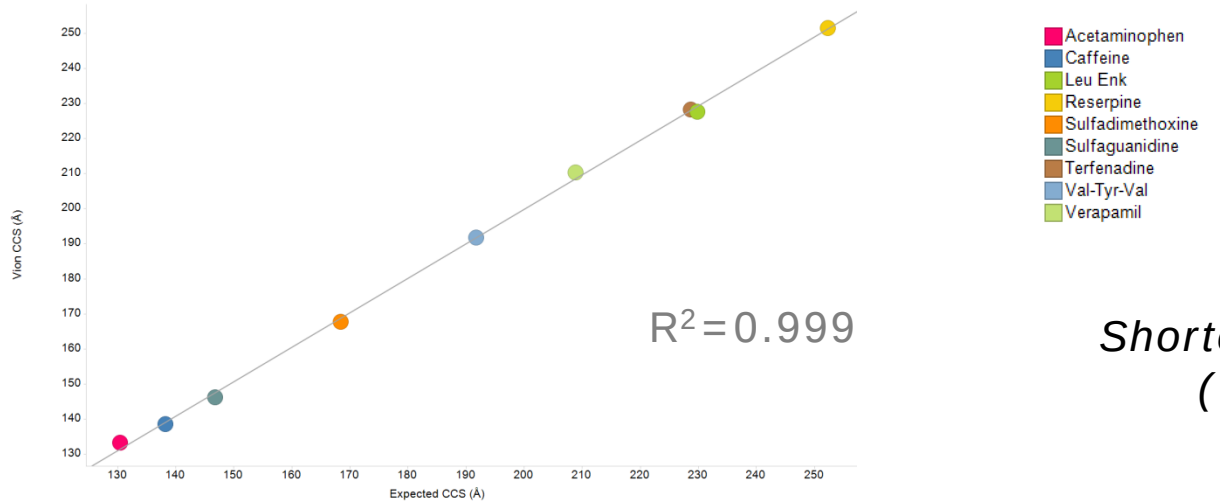


Standard gradient (12 min)



Shorter gradient (7 min)

Inter-Lab Reproducibility of Lipids CCS

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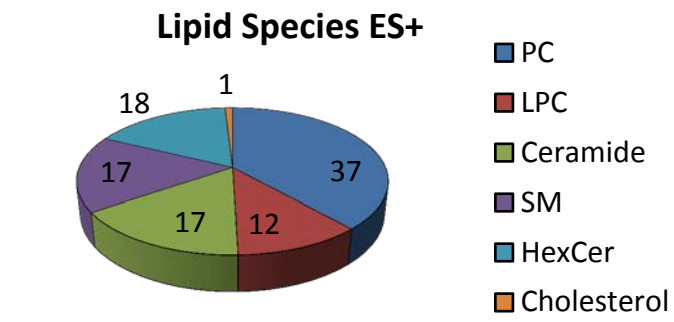

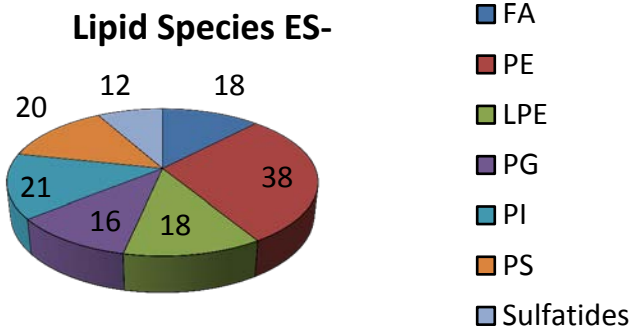

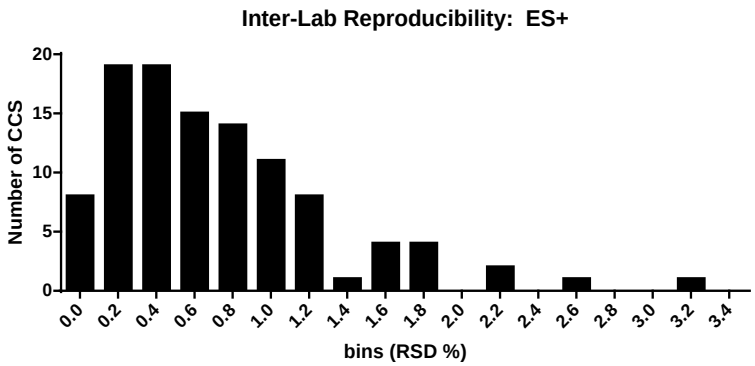

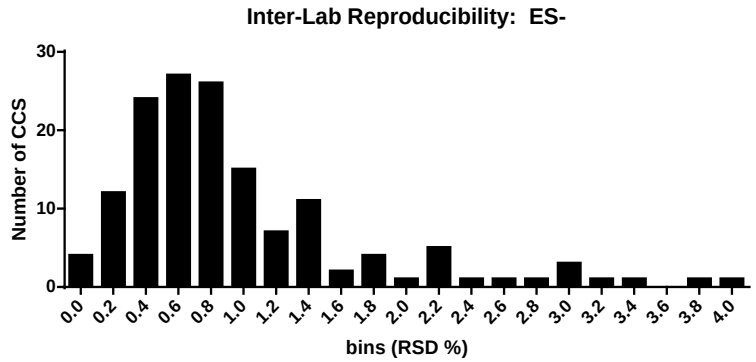

Paglia G.et al. Submitted

Mobility-Mass Correlations

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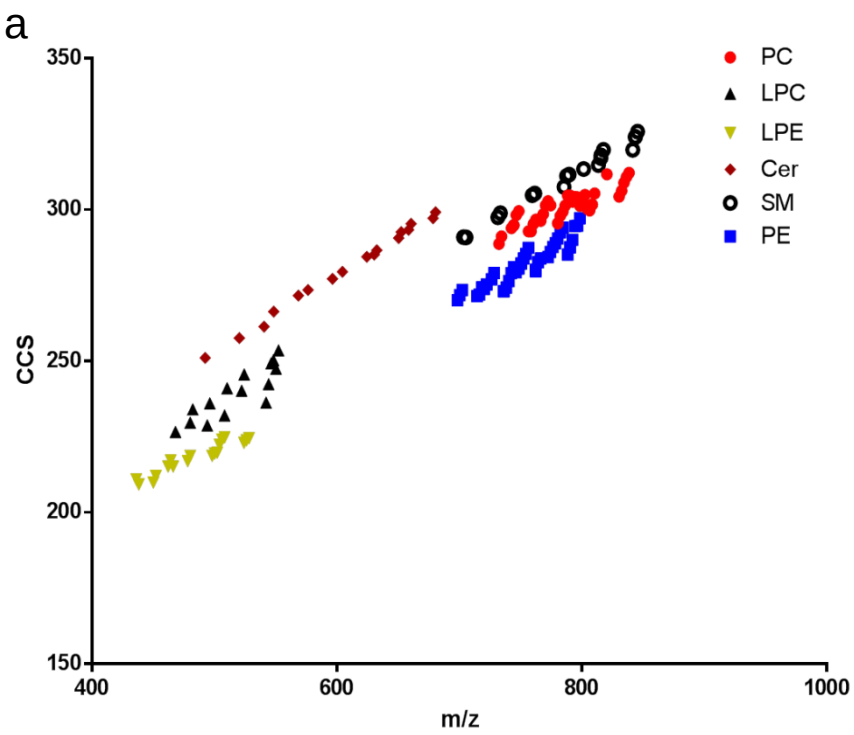

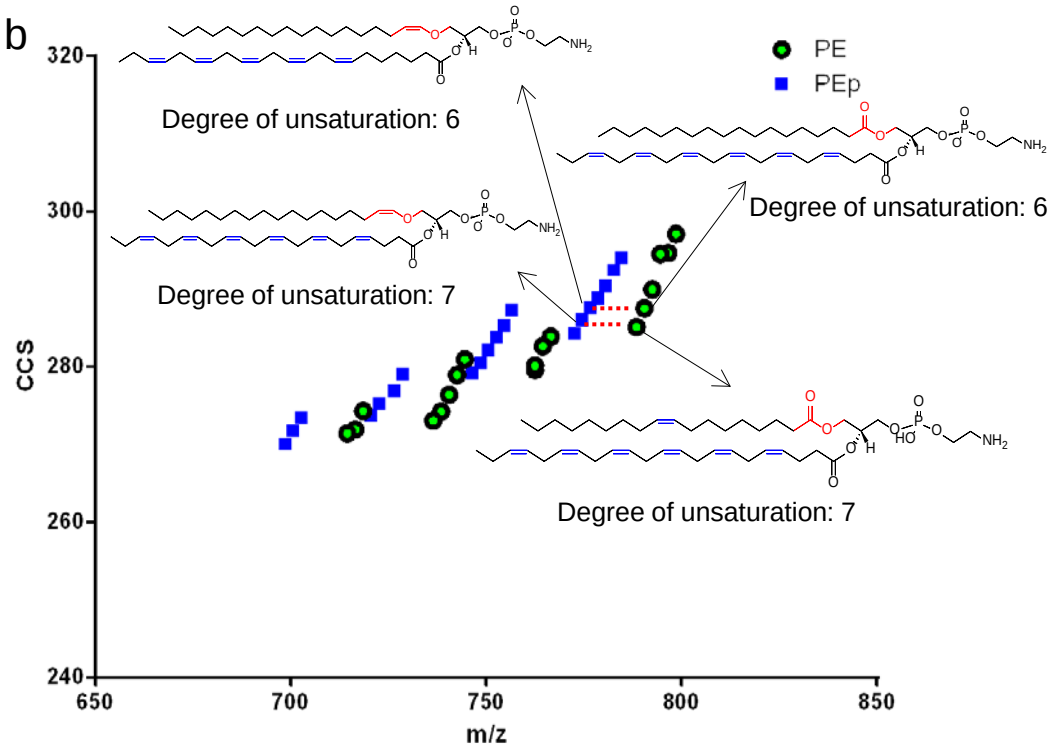

Phosphatidylethanolamine (PE, green dots)
Plasmalogen PE (PEp, blue squares)

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Search Criteria for Maximum Confidence

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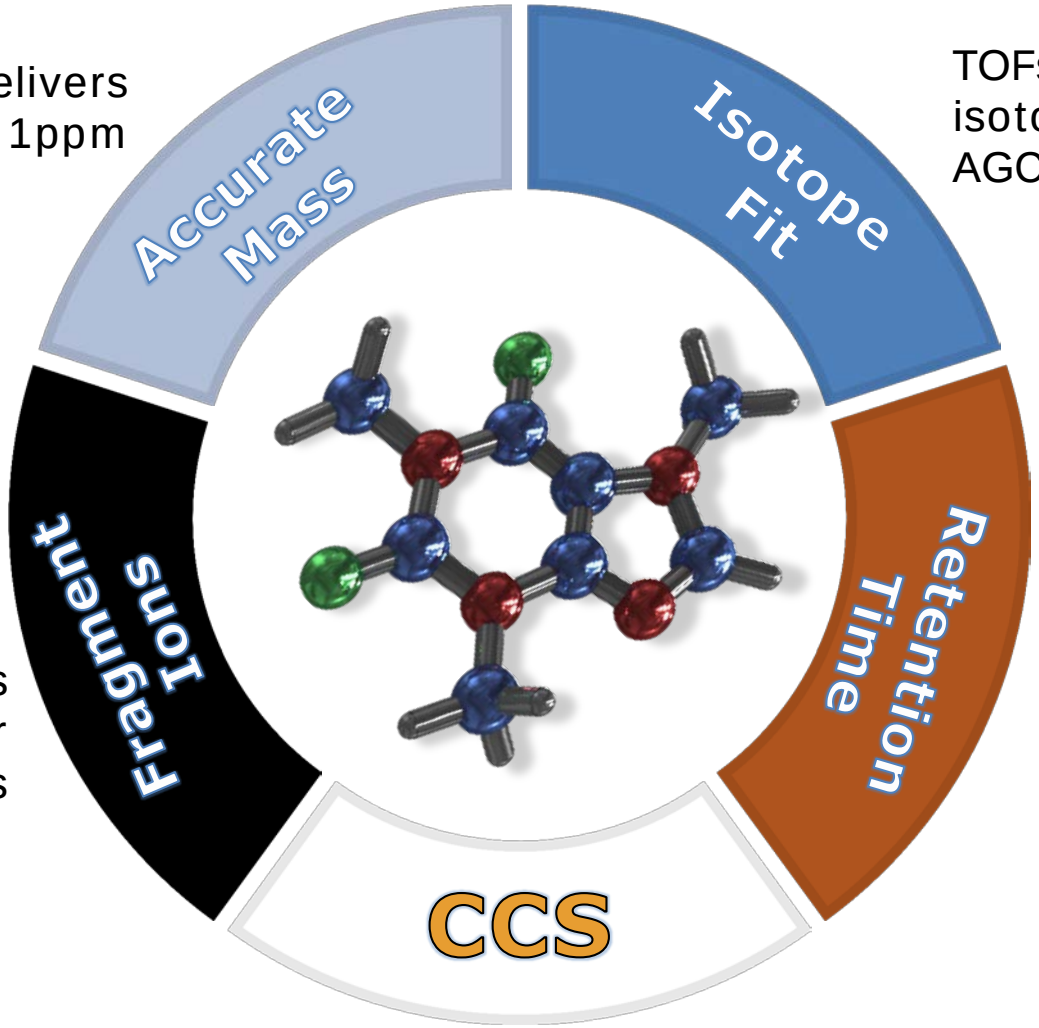
Vion delivers routinely <1ppm

TOFs measure <2% isotope accuracy (no AGC effects)



HDMS^E generates fragments for all ions

ACQUITY offers retention time precision

Vion measures CCS
Routine, Reproducible, Matrix Independent

MS/MS Library Search

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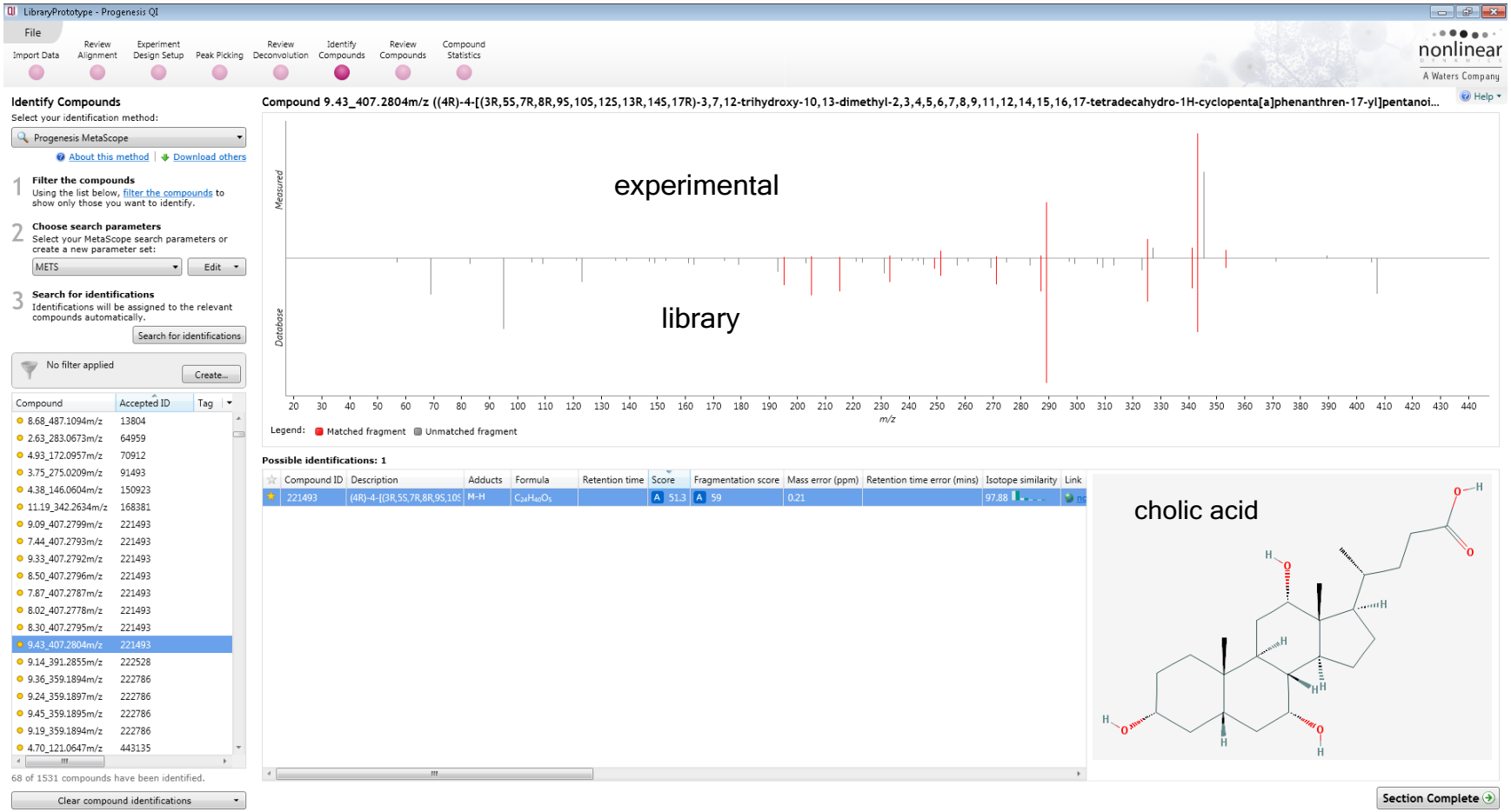

Automatic CCS measurement and search integration

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1.

CCS Measured on all components

Compound	Neutral mass	m/z	z	Retention time	CCS	Peak Width	Tag	Accepted ID	Identifications	Anova (p)	Max fold change
11.35_905.6611m/z	<unknown>	905.6611	1	11.35	331.94	0.09			0	0.364	1.7
11.35_1019.7836m/z	<unknown>	1019.7836	1	11.35	354.11	0.15			0	0.0564	2.1
11.35_1370.3534n	1370.3534	1353.3501	1	11.35	379.21	0.11			0	9.89E-09	Infinity
11.35_1401.2646m/z	<unknown>	1401.2646	1	11.35	359.79	0.04			0	0.00058	Infinity
11.36_563.4414m/z	<unknown>	563.4414	1	11.36	280.81	0.07			0	0.715	1.98
11.36_660.6633m/z	<unknown>	660.6633	1	11.36	298.70	0.08			3	0.00865	2.24
11.36_714.6024m/z	<unknown>	714.6024	1	11.36	306.23	0.11			0	0.755	1.22
11.36_756.6448m/z	<unknown>	756.6448	1	11.36	317.19	0.09			0	0.739	1.98
11.36_908.7803m/z	<unknown>	908.7803	1	11.36	341.04	0.04			0	0.382	1.17
11.36_928.7398m/z	<unknown>	928.7398	1	11.36	337.55	0.07			0	0.912	10.3
11.36_1054.2973m/z	<unknown>	1054.2973	1	11.36	310.90	0.15			0	0.377	15.9
11.36_1054.5987m/z	<unknown>	1054.5987	1	11.36	310.89	0.08			0	0.327	Infinity
11.36_1081.3066m/z	<unknown>	1081.3066	1	11.36	319.41	0.11			0	0.194	Infinity
11.36_1095.3230m/z	<unknown>	1095.3230	1	11.36	319.15	0.09			0	0.261	Infinity
11.36_1440.1966m/z	<unknown>	1440.1966	1	11.36	484.10	0.03			0	0.066	1.44
11.38_467.4076m/z	<unknown>	467.4076	1	11.38	302.07	0.09			0	0.111	1.71
11.38_828.7054m/z	<unknown>	828.7054	1	11.38	327.58	0.14			0	0.296	1.23
11.38_947.7099m/z	<unknown>	947.7099	1	11.38	340.21	0.38			0	0.191	1.14

Progenesis QI

2.

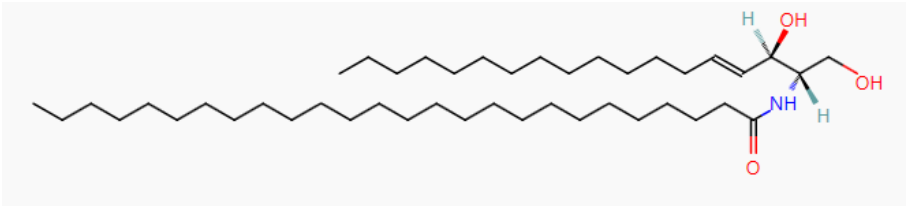
Expected CCS

Difference in CCS (1.2%)

Possible identifications: 3

	Compound ID	Description	Adducts	Formula	Retention time	CCS	Score	Fragmentation score	Mass error (ppm)	Retention time error (mins)	ΔCCS (Å²)	Isotope similarity
★	7850629	Cer(d18:1/26:0)	M+H-H...	$C_{44}H_{87}NO_3$	11.36	295.00	41	6.53	-2.90	1.33e-004	3.70	77.12
☆	173737523	Cer(m18:1(4E)/26:1(17Z))	M+H	$C_{44}H_{85}NO_2$			36.1	6.59	-2.98			77.33
☆	7850637	Cer(d18:0/26:1(17Z))	M+H-H...	$C_{44}H_{87}NO_3$			36	6.53	-2.90			77.12

3.



Cer(d18:1/26:0)

Metabolic Profiling CCS & MS/MS Library

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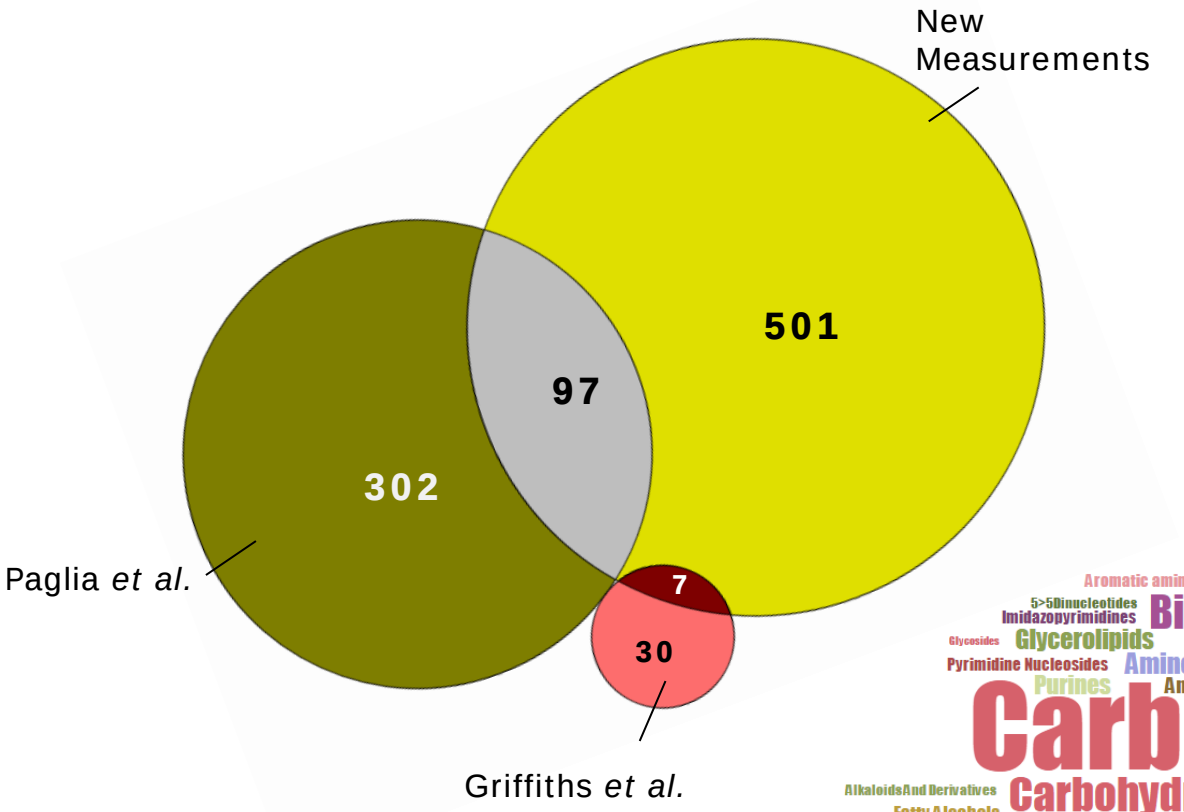
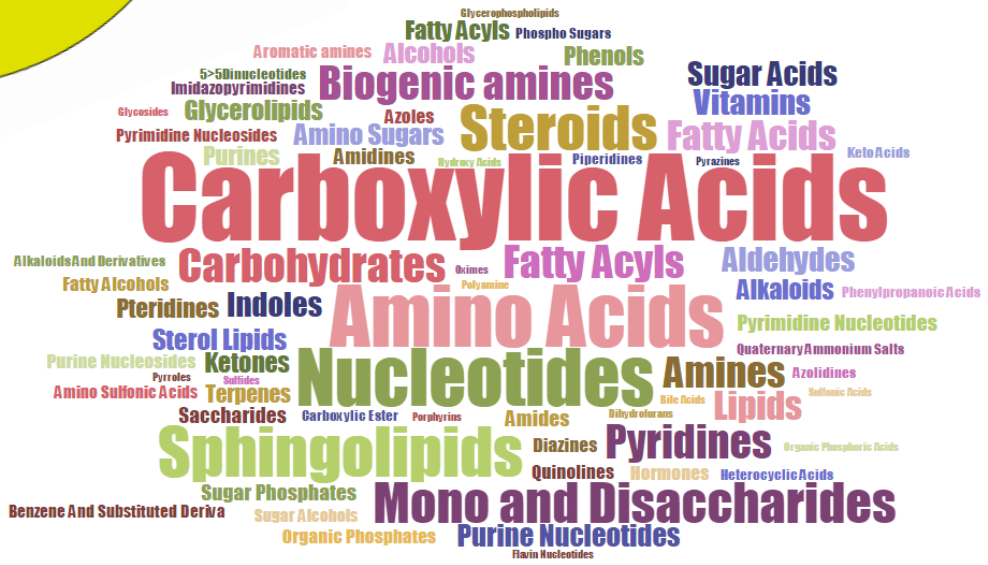


>900 CCS Measurements
>600 MS/MS Spectra



CCS & MS/MS Coverage by ionisation mode

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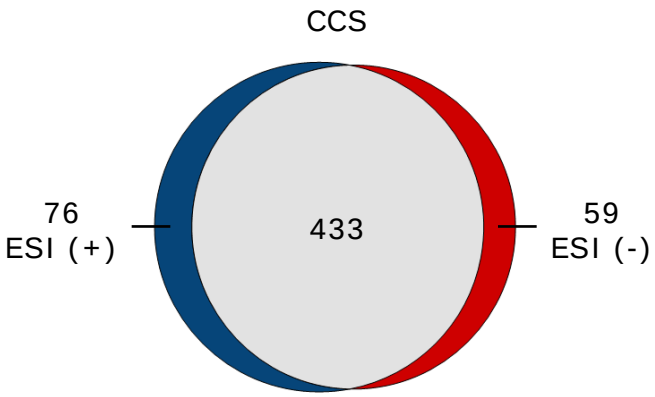

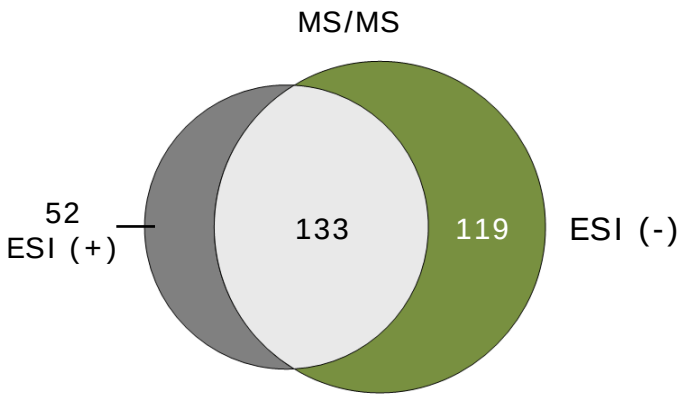

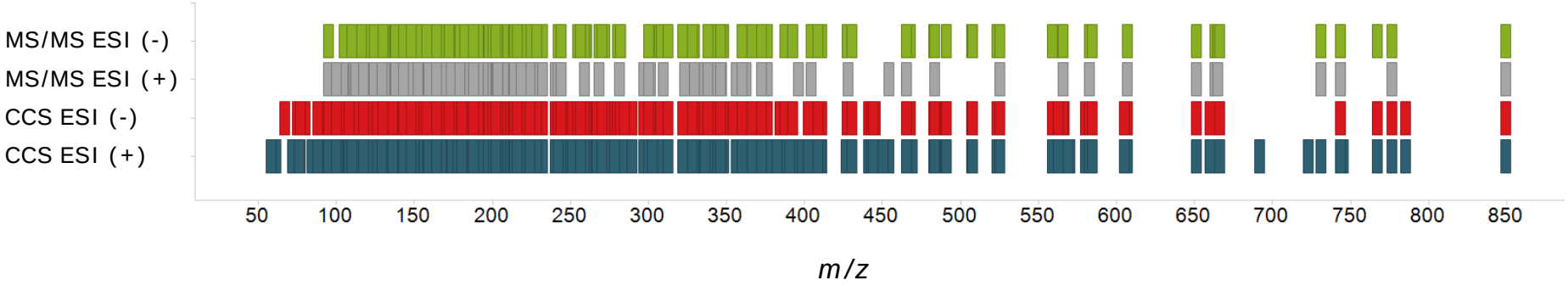

Molecule class relationship to m/z & CCS

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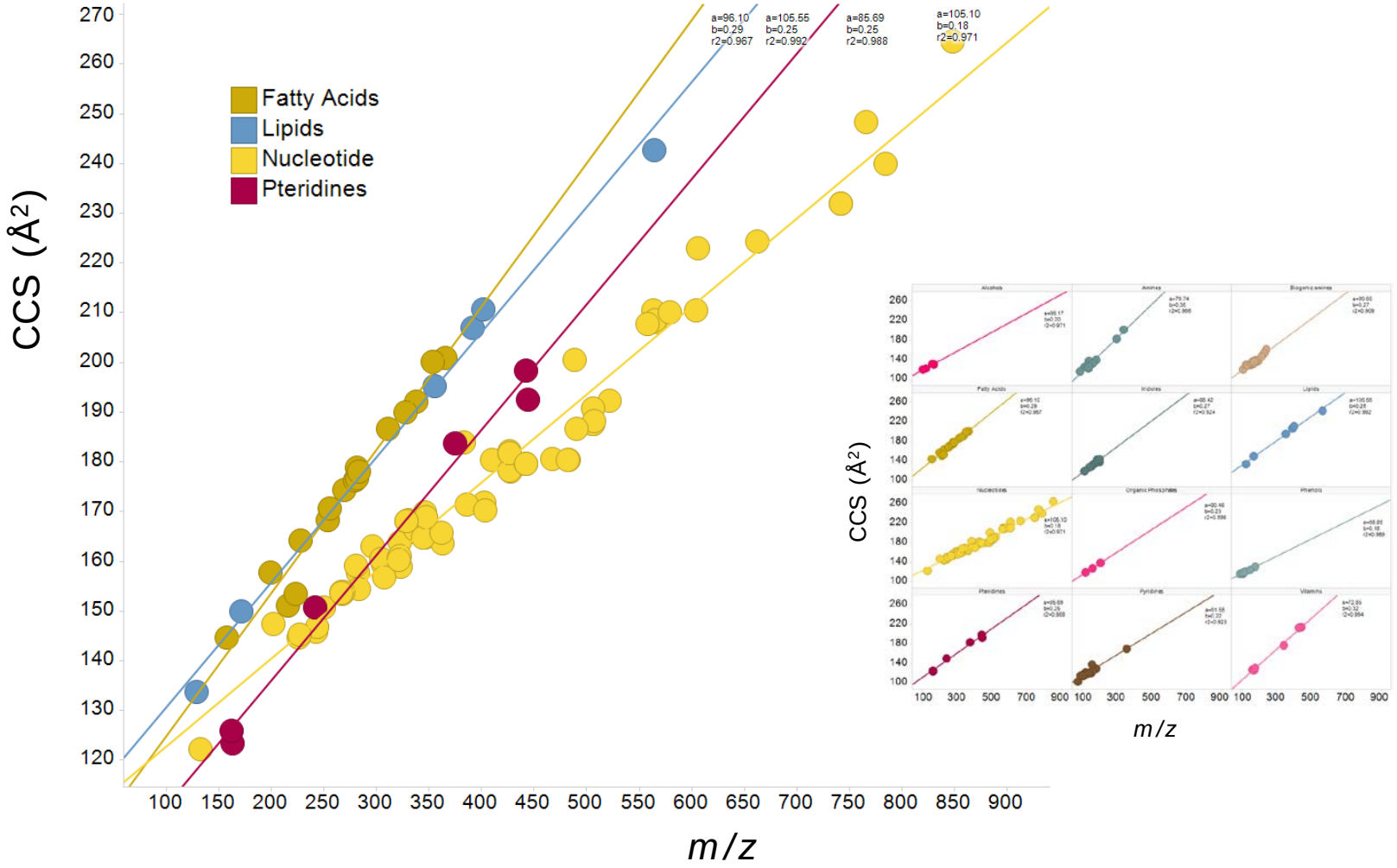

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Data Processing

Metabolomics

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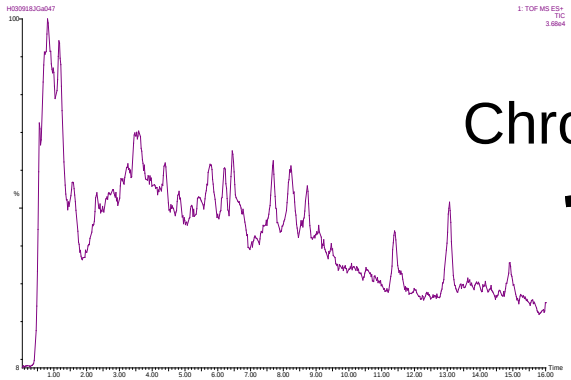


Urine From Group 1

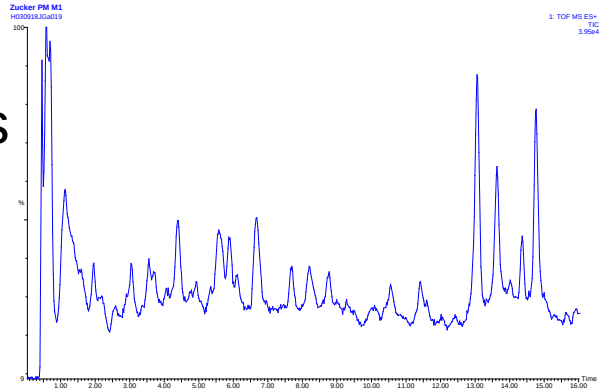
Exact Mass
Chromatographic Peaks

Extract variables

Normalize

Align like variables

Populate Markers Table



Urine From Group 2

Multivariate Data Array

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Retention Time_m/z_Drift Time →

Samples ↓

	2.24_318.0634_12.3	5.46_317.1806_11.7	6.05_317.1722_11.1	2.97_317.1714_10.9
RAT 1	0	0	0	2.15351
RAT 2	0	0	0	2.10822
RAT 3	1.63034	0	0	0
RAT 4	1.62986	0	0	0
RAT 5	4.70965	0	0	0.730389
RAT 6	0	1.03318	0	1.83726
RAT 7	0	0	0	0
RAT 8	2.83714	0.947788	0	0.919644
RAT 9	5.23023	0	0	0.956396
RAT 10	0	0.843124	0	0

Understanding PCA Results

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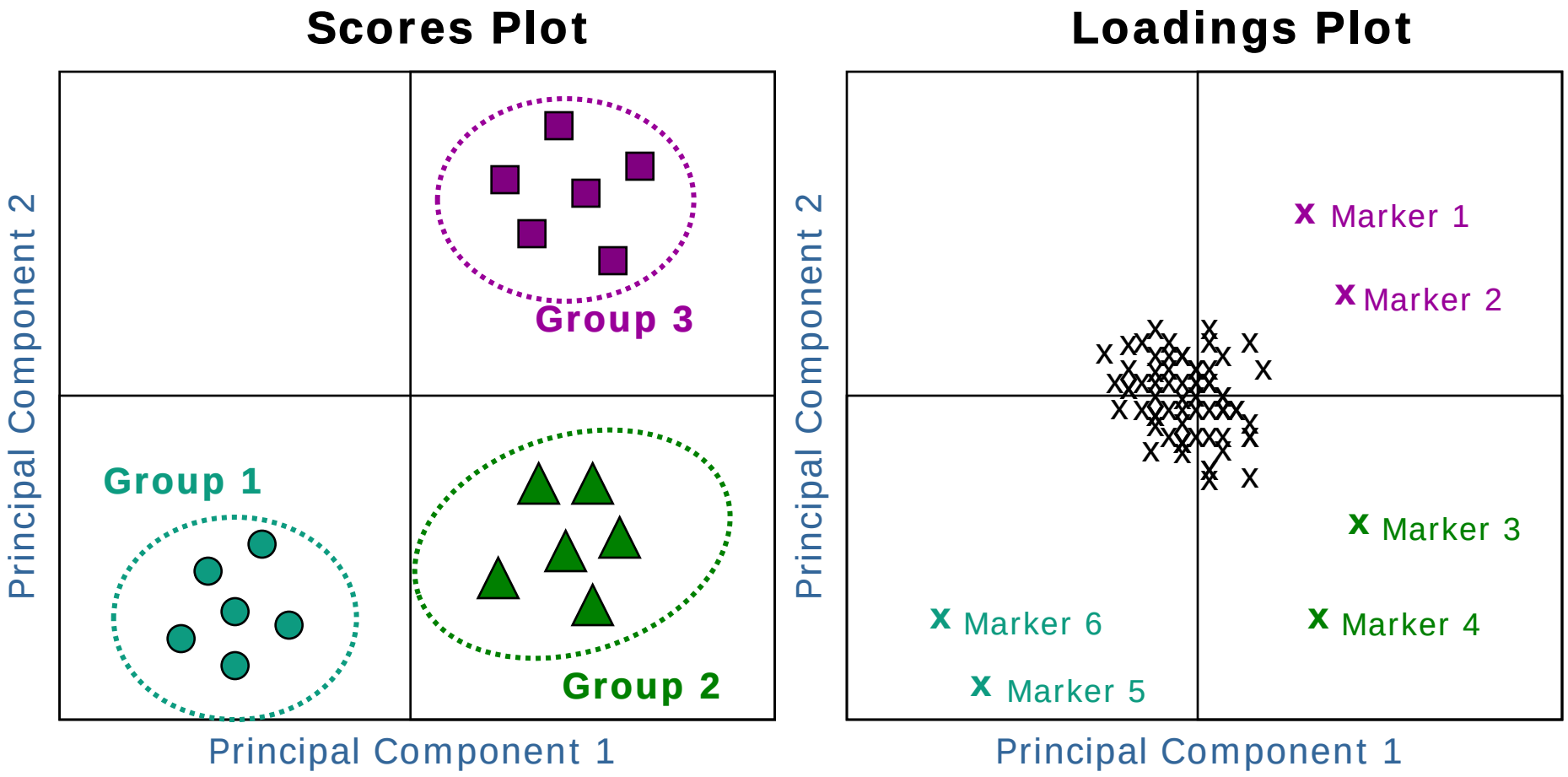

Progenesis QI

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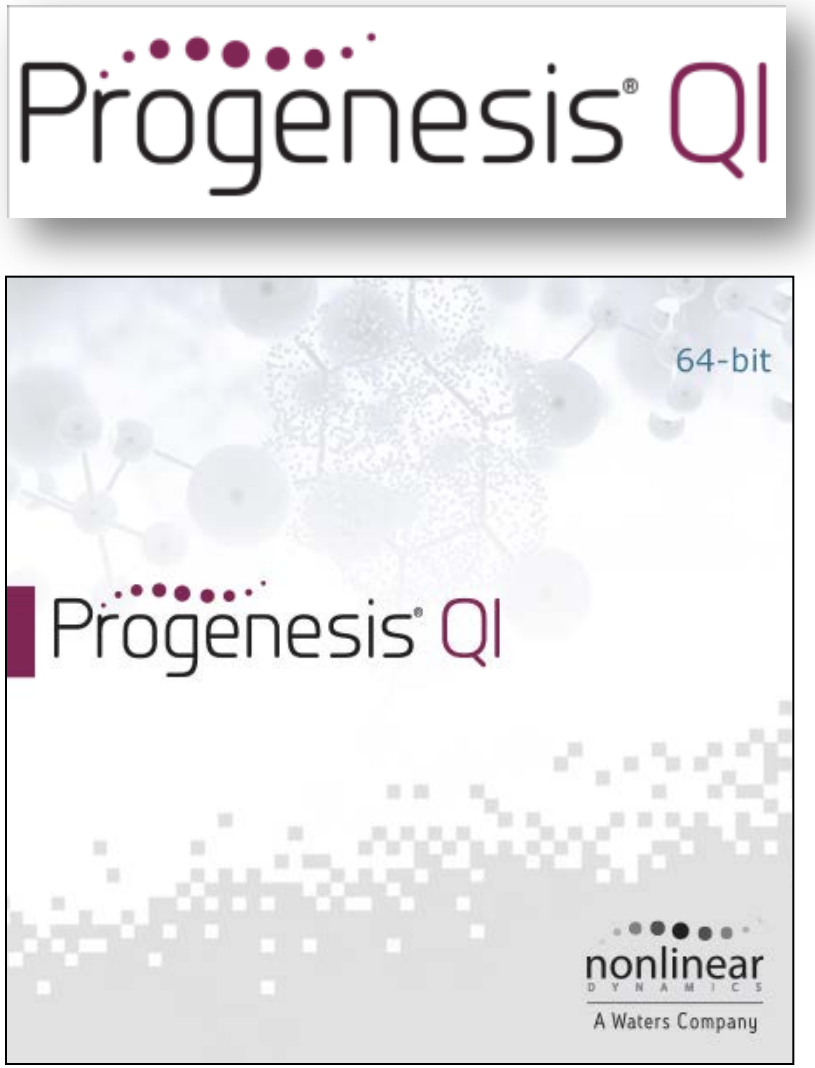

Quantify
Identify

- For 'small molecules'
- Wide applicability
- Metabolomics
- Biomarkers
- Food
- Wine
- Toxicology
- Environmental
- Pesticides
- Etc

Data Import
Multi-vendor support

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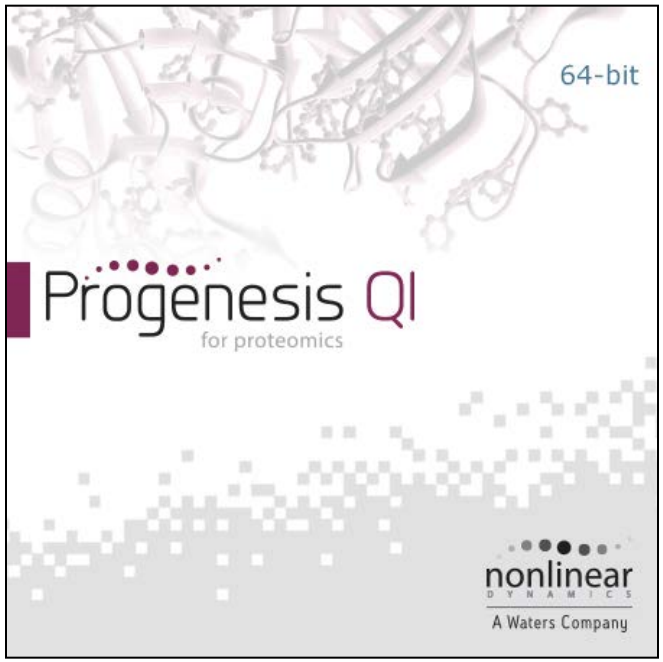

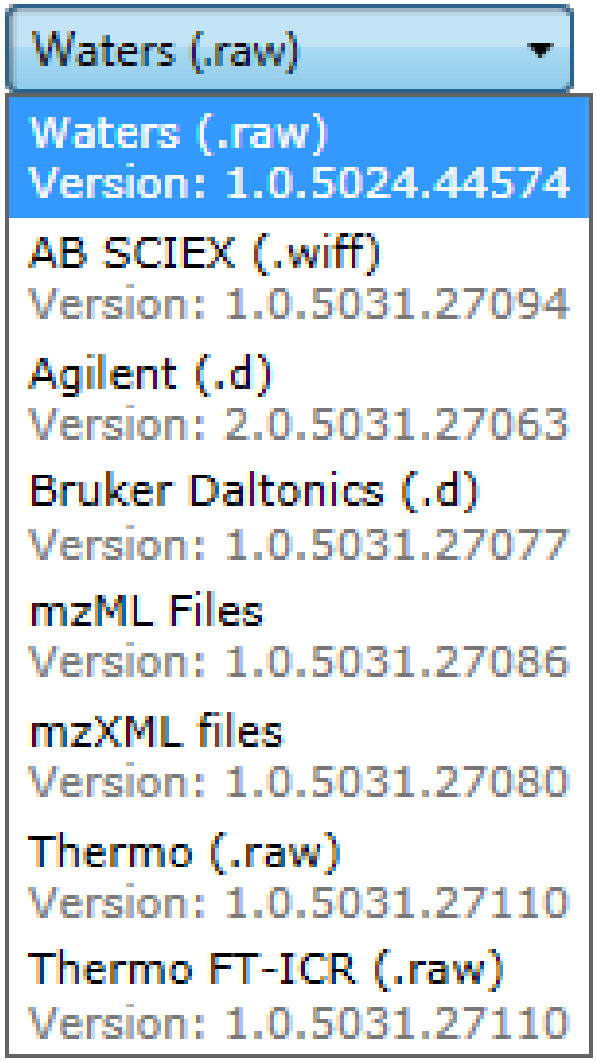

Progenesis QI guided workflow and data import / adduct selection

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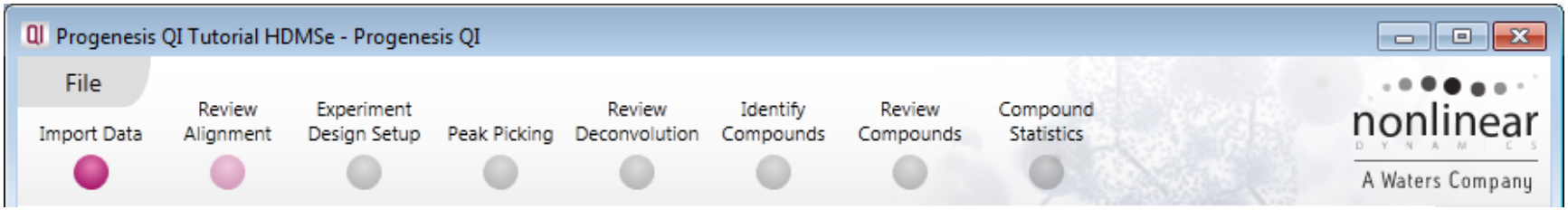
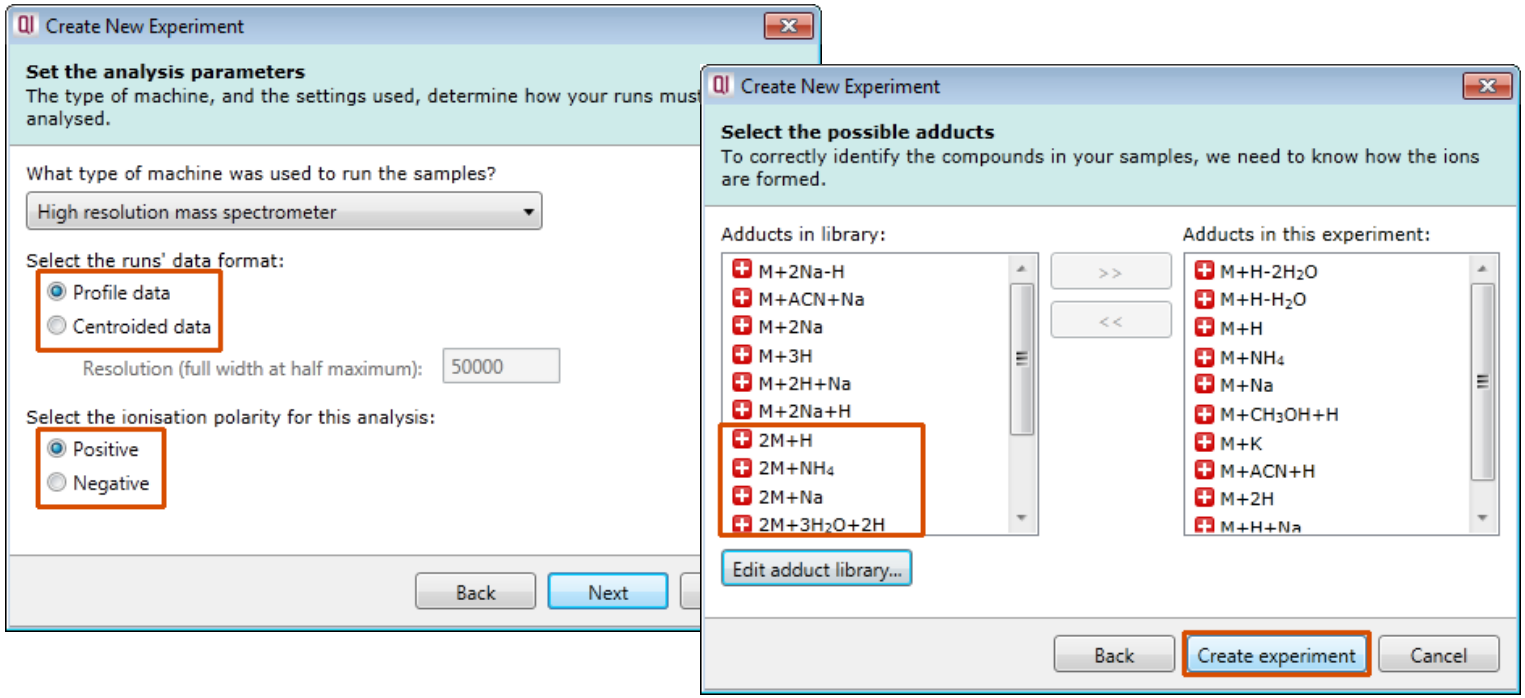


Details of data file format and a list of 'expected' adducts are entered to facilitate the handling of data import



Data Import
Low and High energy views

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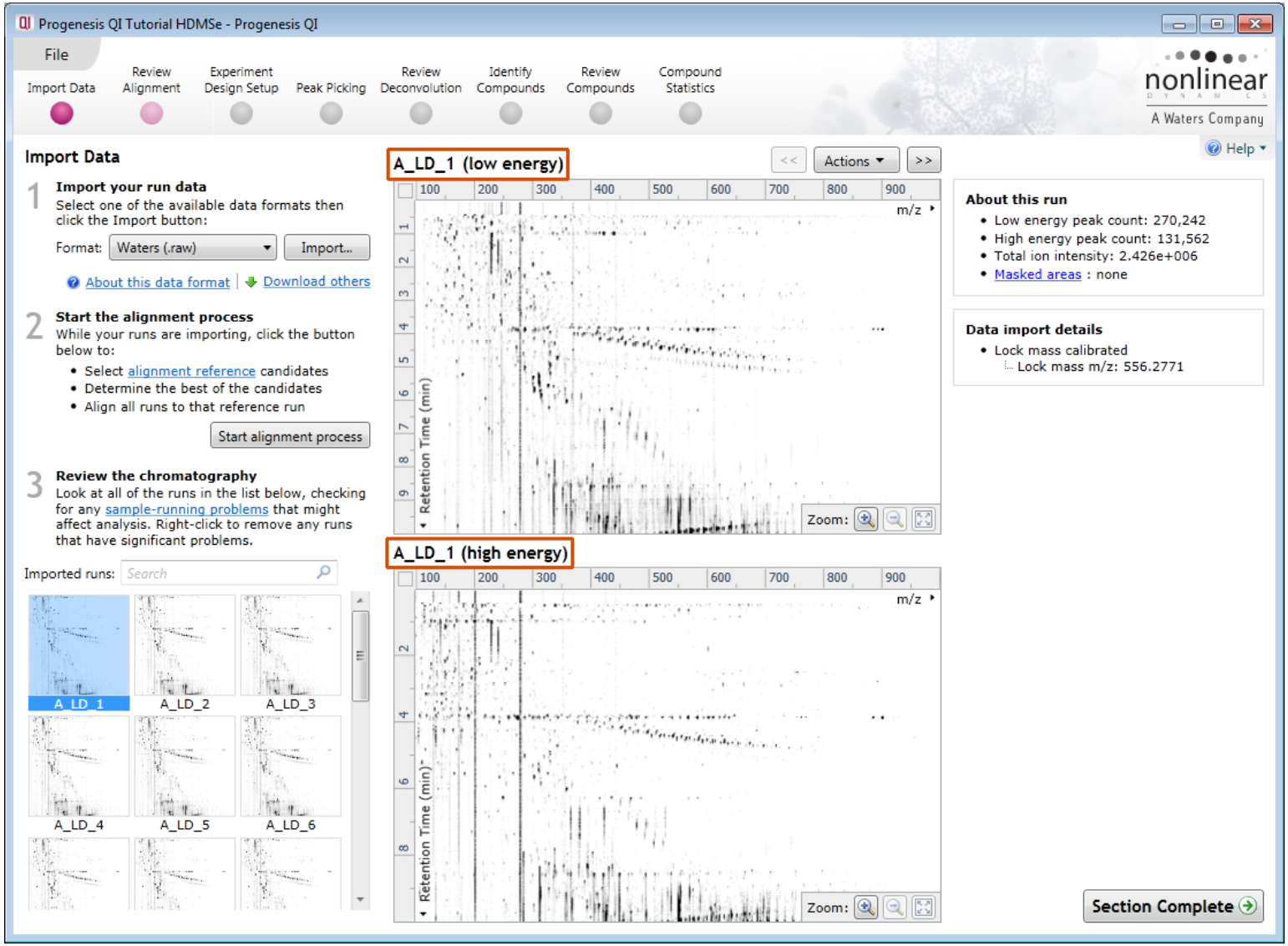

Review alignment (zoom)
Un-aligned

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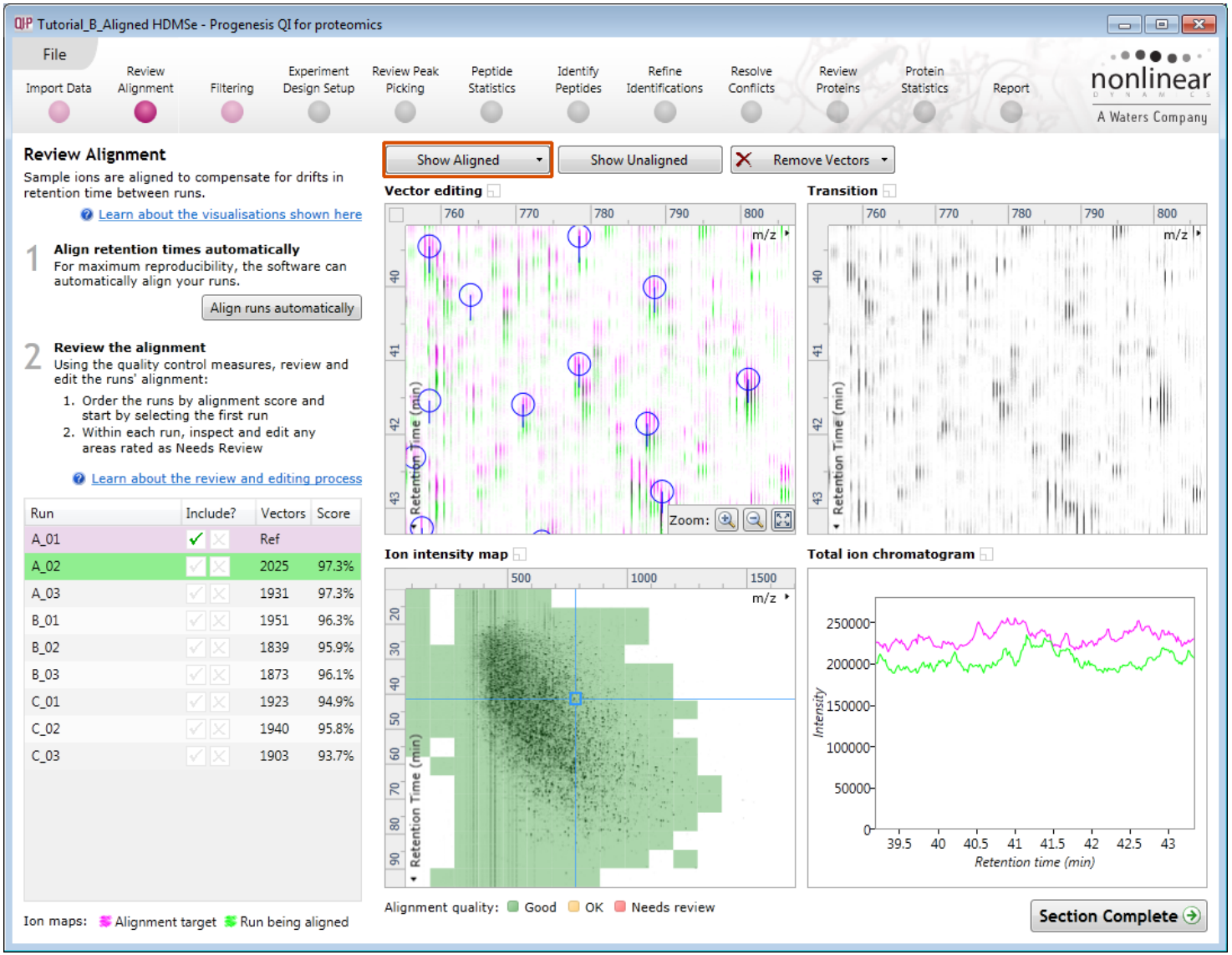

Review alignment (zoom) Aligned

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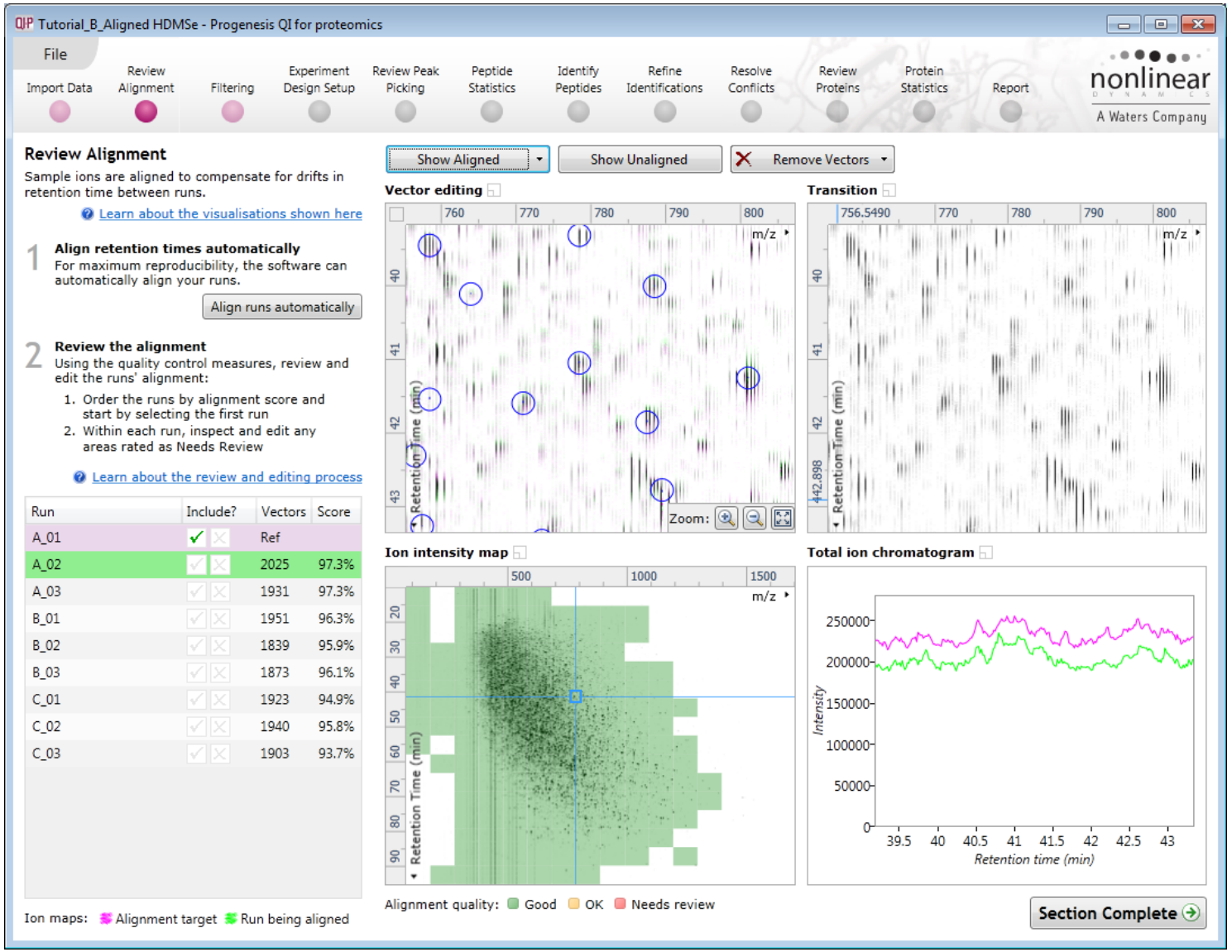

Peak picking and co-detection

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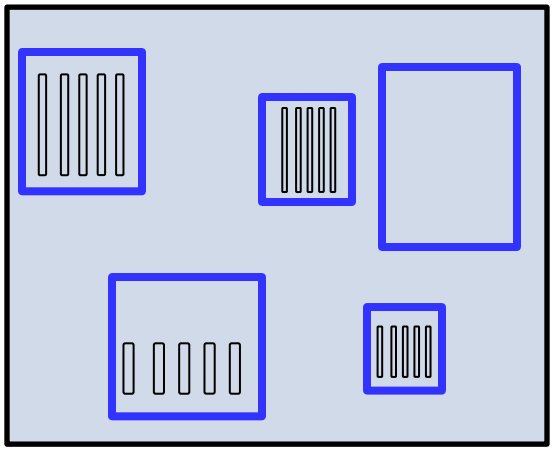
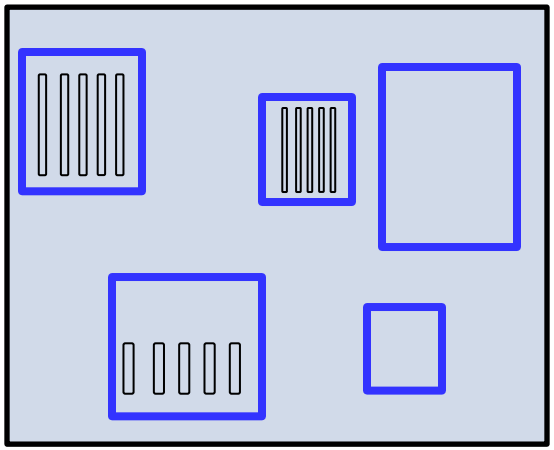
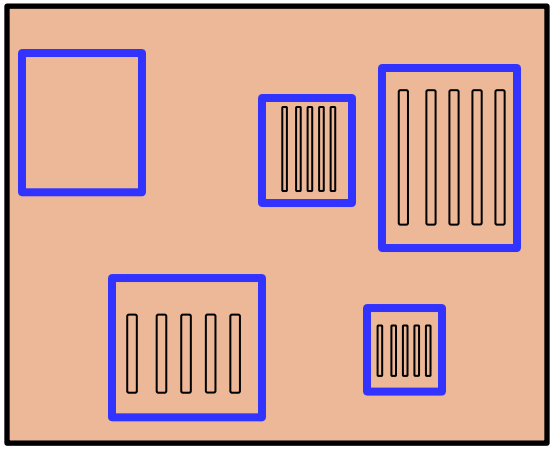
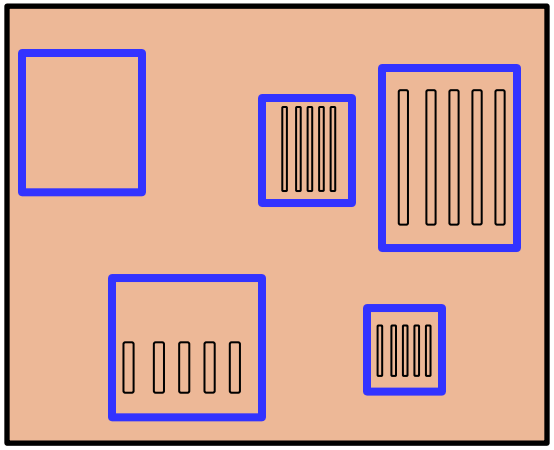
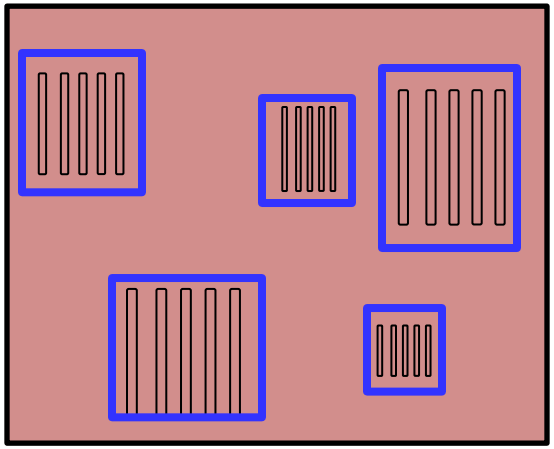




Mapping the detection to all runs avoiding missing data







Aggregate co-detection

Review adduct deconvolution

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Example of the deconvoluted detection for a compound's adducts. Deconvolution is performed during Peak Detection

Tagging – simple filtering tool

Eg. Use to limit number of compounds searched

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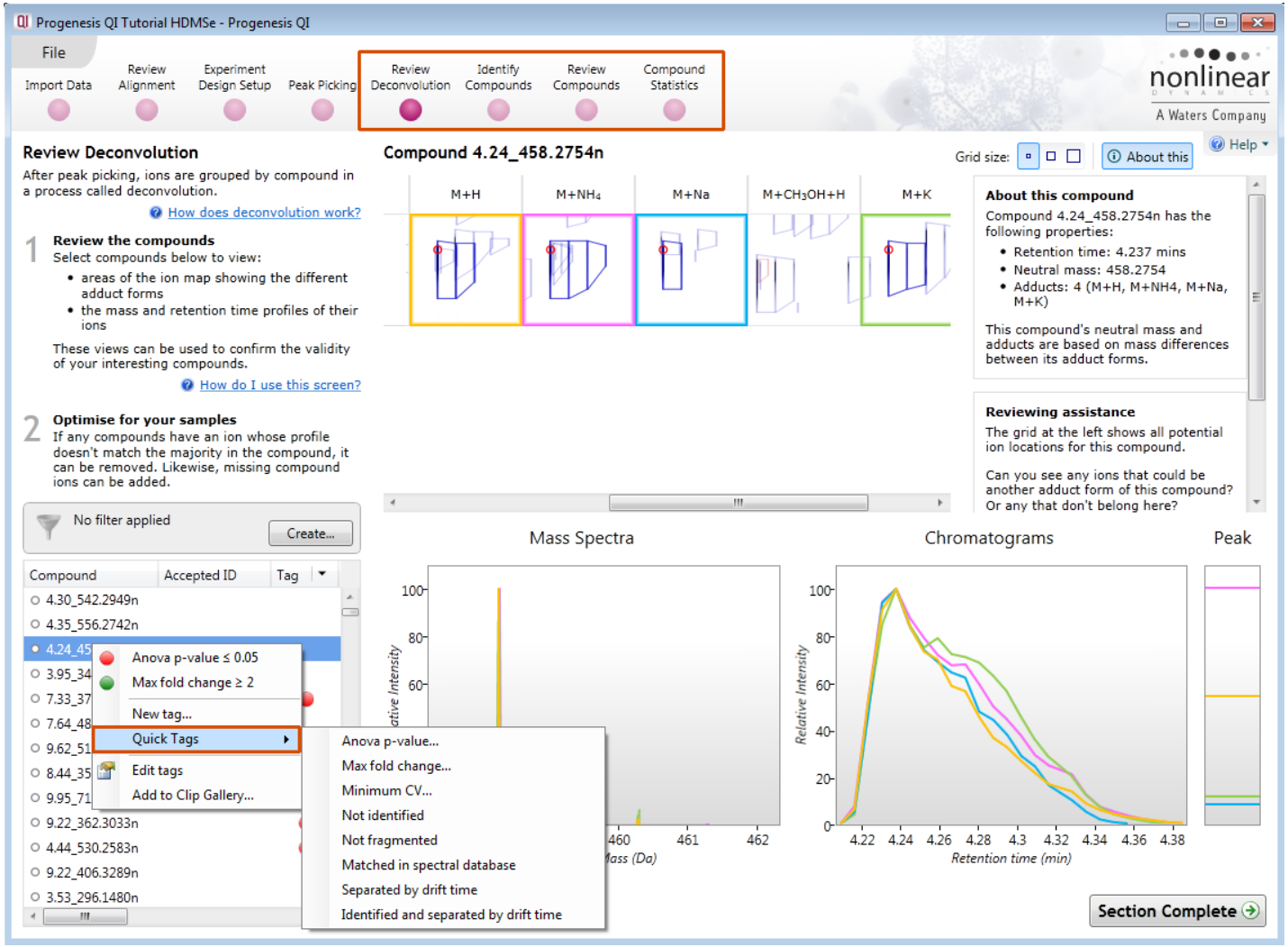

Tagging groups of Compounds based on Statistical attributes is available from Review Deconvolution onwards in the workflow

Compound Statistics
PCA and Export to EZinfo

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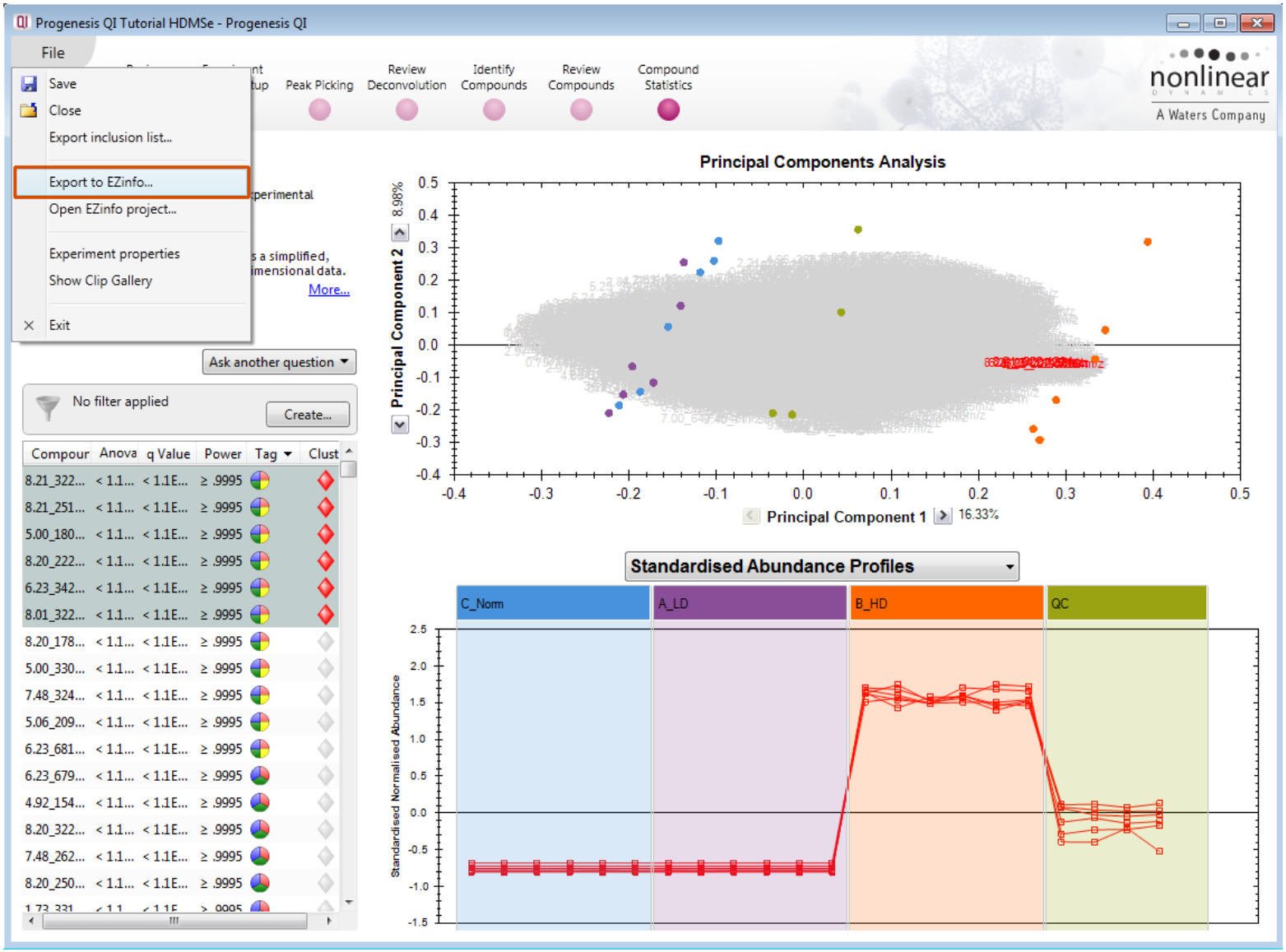

Compound Statistics
EZinfo

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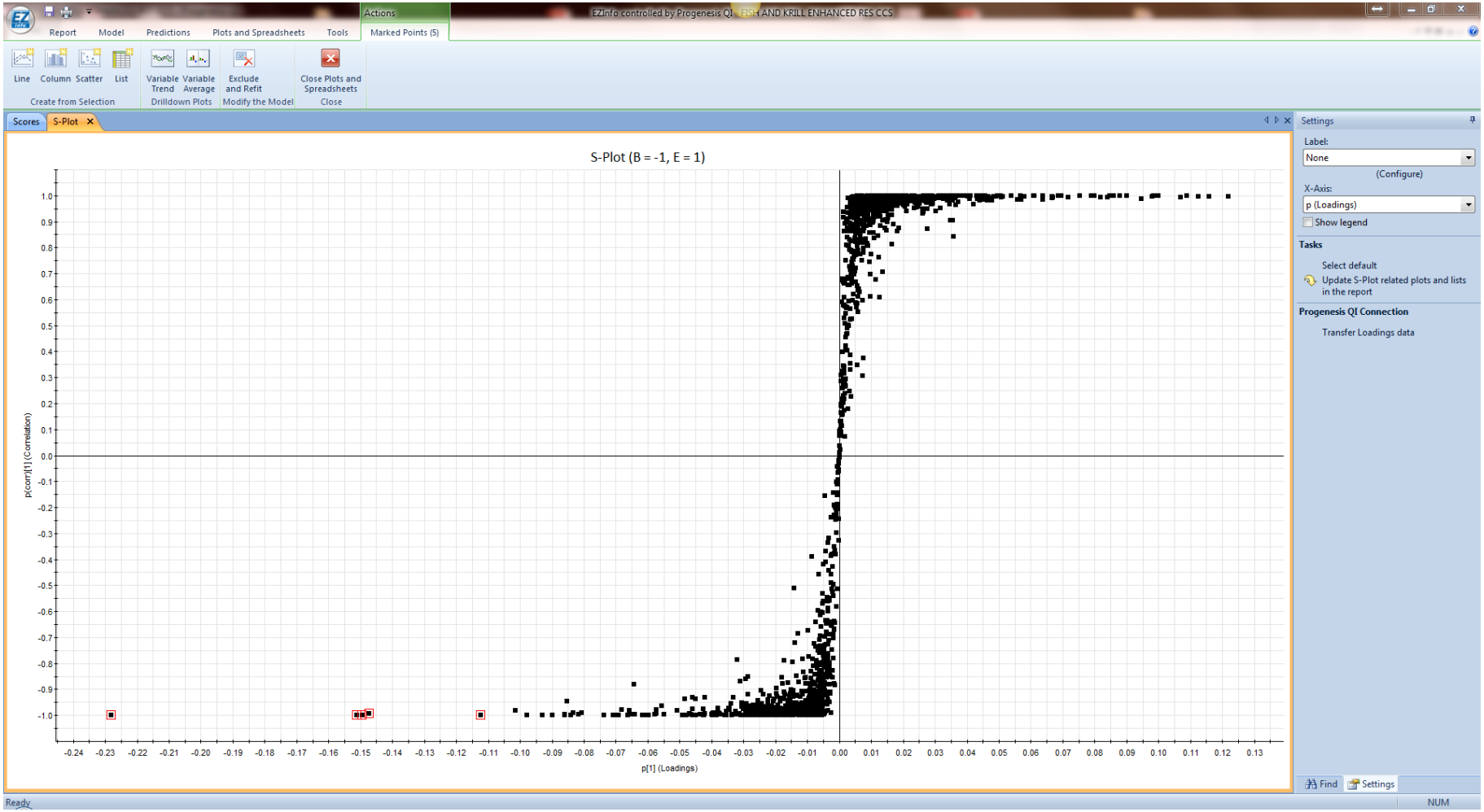

Multivariate Statistical Models: PCA, PLS, OPLS, OPLS-DA

Compound Statistics
Tag-set Back from EZInfo

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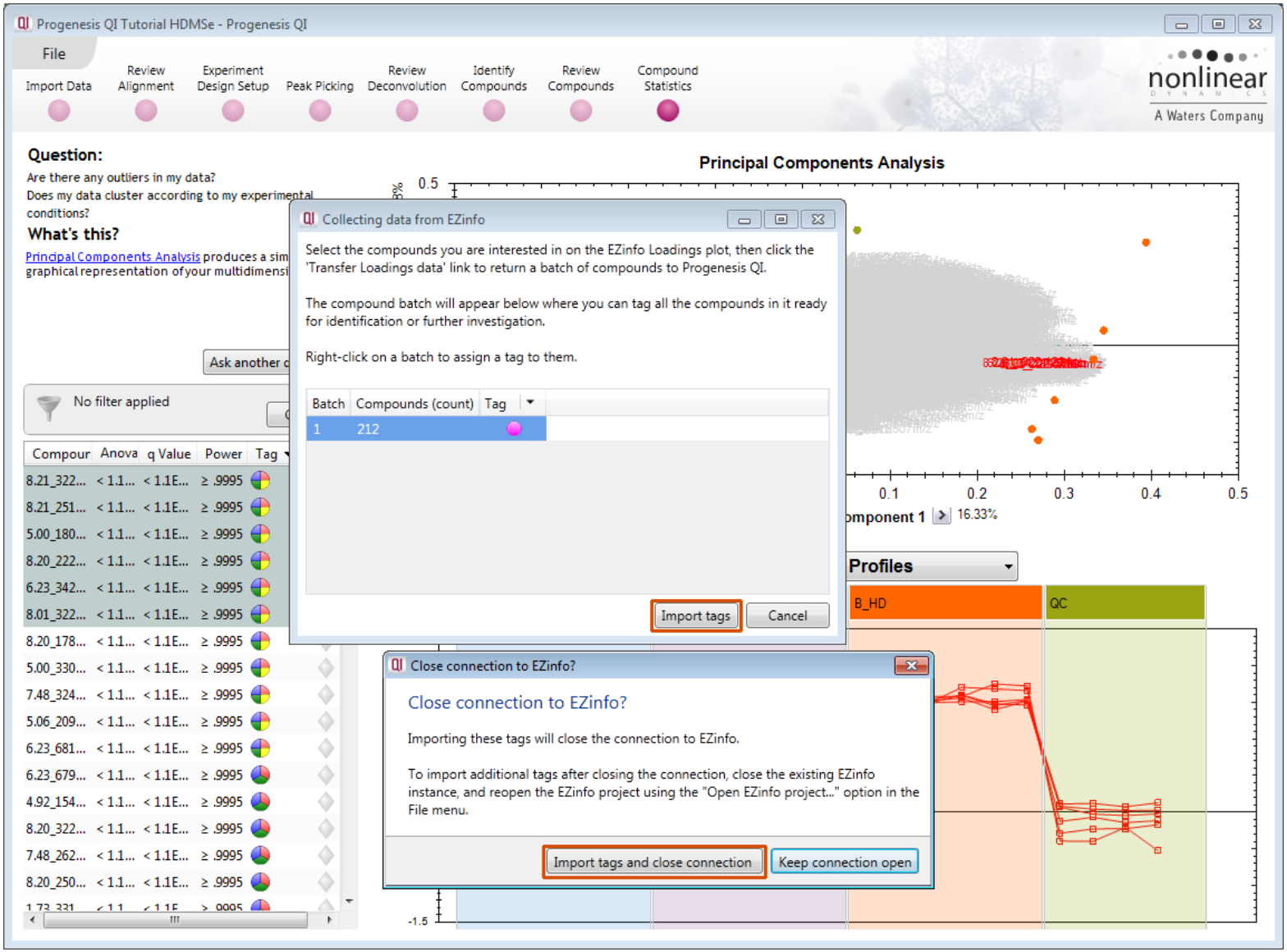

Compound identification
MetaScope search, new features

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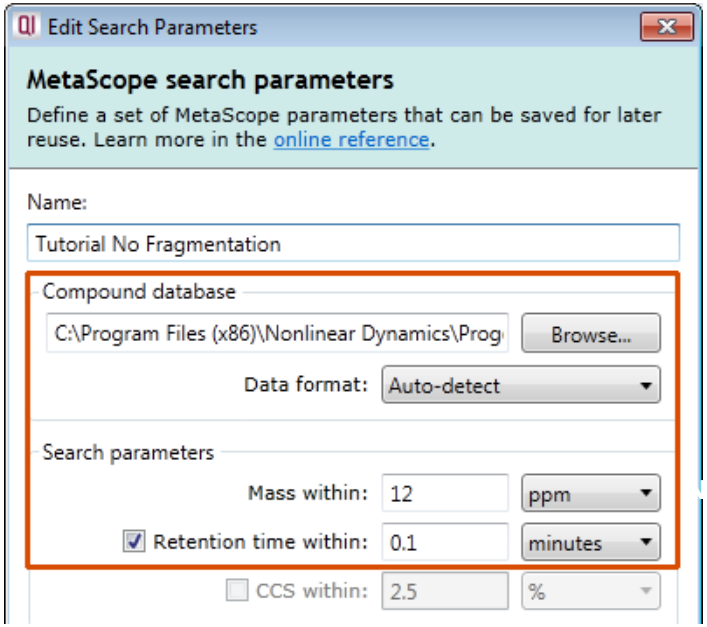
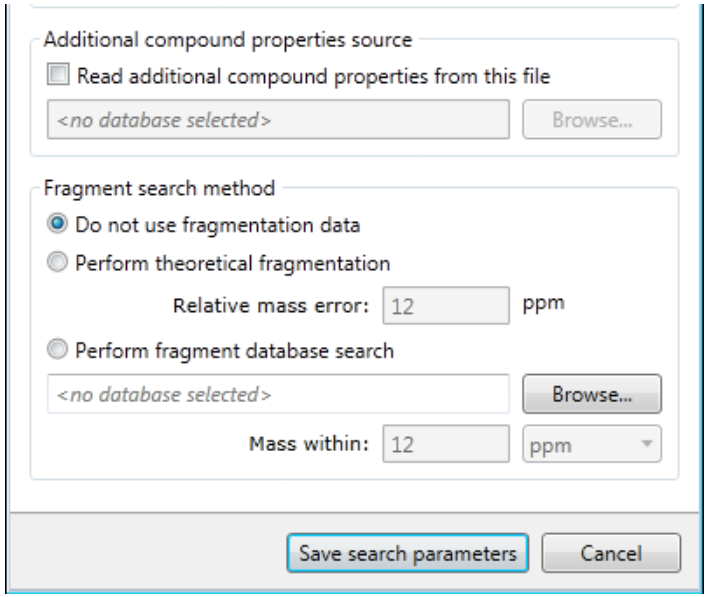
Compounds are identified using the integral MetaScope search engine and a compound database in Structure Data File (SDF)





- More search parameters **for increased specificity** for ID
  - Dt/CCS, fragment ion data

Theoretical fragmentation search result

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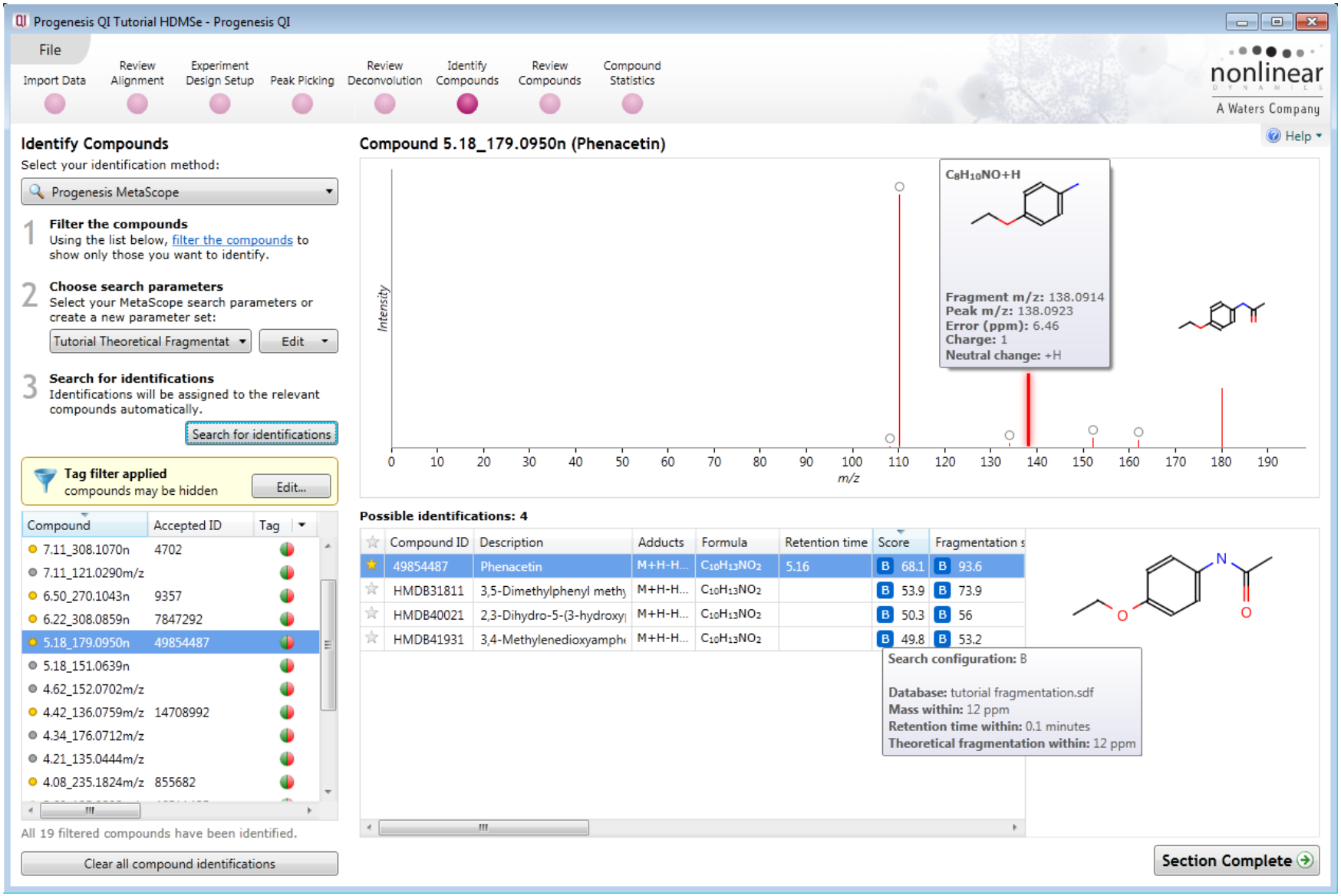

Fragment database search result Mirror plot

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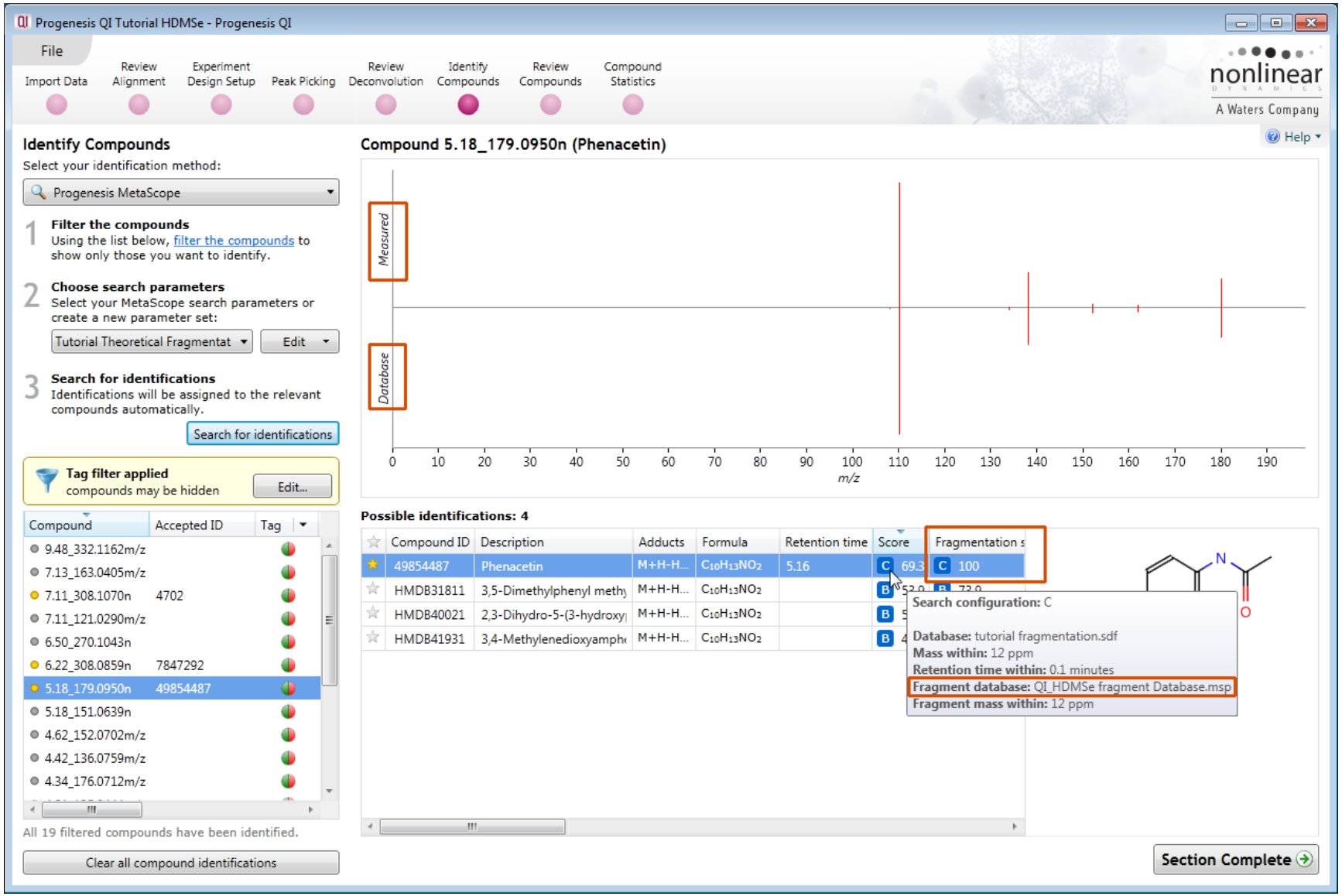

Conclusion

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- The “best” analytical system is worth nothing if the experiment is flawed.
- Good chromatography benefits mass analysis and gives you information as well.
- Find the right balance between coverage and method robustness.
- Ion mobility coupled with TOF gives more depth of coverage and an important useful measurement.
- DIA strategies such as HDMSE allow more information content to be extracted from each injection.
- Solutions are available today to routinely apply LC-IMS-MS approaches to Metabolomics.