Automated mass spectra comparison algorithm for high-throughput compound QC applications

SCIEX: Chang Liu; Gordana Ivosev; Thomas R. Covey
Pfizer: Alandra Quinn; Jeff Chin; Hui Zhang

ASMS 2021, Philadelphia, PA, November 1, 2021

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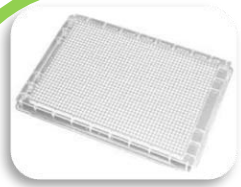
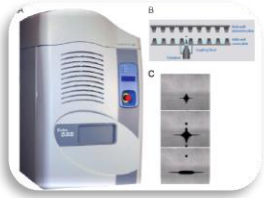
Compound management and distribution

Echo® MS System





Direct Dilutions

Sample Logistics

1.4ml tube Inventory

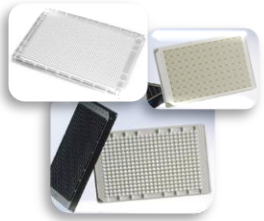
~70,000 cpds supporting lead optimization

Liquid Store

Plate based Inventory

~4.5 million cpds in Echo® plates* supporting HTS

***Plates are available from Beckman Coulter Life Sciences**



Assay ready plates

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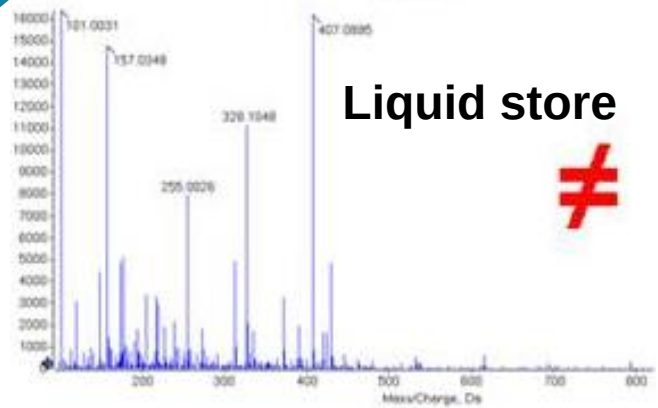
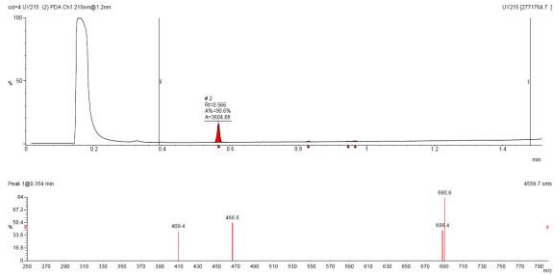
Compound QC challenge

Echo® MS System



LC-UV/MS



Sample logistics and liquid store submits compounds for analysis

1,500- 2,000 cpds a week

Project teams see this

sQC Summary	sQC Purity (Num)	sQC Purity(Txt)	sQC Result Load Date
Suspect		No Peak	8/19/2021
Pass	91		8/19/2021
Pass	94		8/17/2021
Fail	54		8/19/2021
Fail	40		8/19/2021
Pass	90		8/17/2021

High throughput compound QC is required

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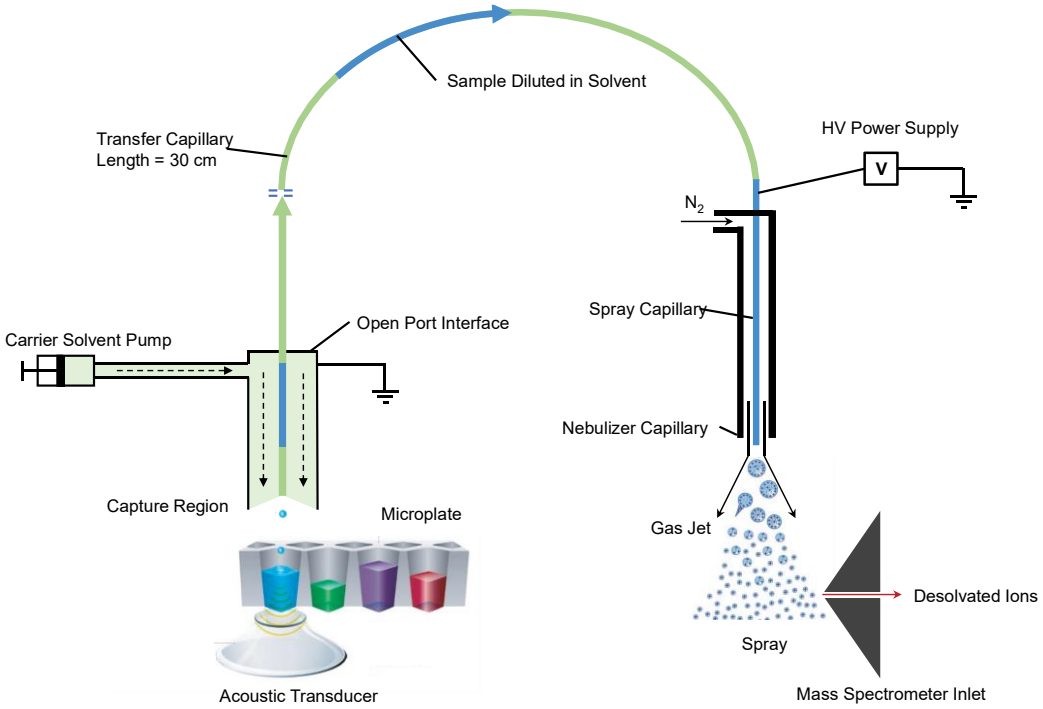
AEMS system

Echo® MS System



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AEMS for high-throughput analysis

Echo® MS System

ACS Medicinal Chemistry Letters

Ultra-High-Throughput Acoustic Droplet Ejection-Open Port Interface-Mass Spectrometry for Parallel Medicinal Chemistry

Kenneth J. DiRico,[§] Wenyi Hua,[§] Chang Liu, Joseph W. Tucker, Anokha S. Ratnayake, Mark E. Flanagan, Matthew D. Troutman, Mark C. Noe, and Hui Zhang*

analytical chemistry

Acoustic Ejection Mass Spectrometry for High-Throughput Analysis

Hui Zhang,* Chang Liu,* Wenyi Hua, Lucien P. Ghislain, Jianhua Liu, Lisa Aschenbrenner, Stephen Noell, Kenneth J. Dirico, Lorraine F. Lanyon, Claire M. Steppan, Mike West, Don W. Arnold, Thomas R. Covey, Sammy S. Datwani,* and Matthew D. Troutman

analytical chemistry

Ultrahigh-Throughput ESI-MS: Sampling Pushed to Six Samples per Second by Acoustic Ejection Mass Spectrometry

Tim T. Häbe,* Chang Liu, Tom R. Covey, Roman P. Simon, Wolfgang Reindl, Frank H. Büttner, Martin Winter, Daniel Bischoff, Andreas H. Luippold, and Frank Runge*

Original Research

Acoustic Ejection/Full-Scan Mass Spectrometry Analysis for High-Throughput Compound Quality Control

Jun Zhang[1], Yong Zhang[1], Chang Liu[2], Tom Covey[2], Julia Nielsen[3], Shu Li[1], Harold Weller[1], and Wilson Shou[1]

analytical chemistry

Ultrahigh-Throughput and Chromatography-Free Bioanalysis of Polar Analytes with Acoustic Ejection Mass Spectrometry

Andrew Wagner, Jun Zhang, Chang Liu, Thomas R. Covey, Timothy V. Olah, Harold (Bud) N. Weller, and Wilson Z. Shou*

analytical chemistry

Direct Analysis from Phase-Separated Liquid Samples using ADE-OPI-MS: Applicability to High-Throughput Screening for Inhibitors of Diacylglycerol Acyltransferase 2

Xiujuan Wen,*[,⊥] Chang Liu,[⊥] Lucien Ghislain,[⊥] Kiersten Tovar, Vinit Shah, Steven J. Stout, Steven Cifelli, Santhosh Satapati, Gregory O'Donnell, Payal R. Sheth, Mary Jo Wildey, Sammy S. Datwani, Thomas R. Covey, Kevin P. Bateman, and David G. McLaren

analytical chemistry

Operational Modes and Speed Considerations of an Acoustic Droplet Dispenser for Mass Spectrometry

Chang Liu,* Gary J. Van Berkel, David M. Cox, and Thomas R. Covey*

analytical chemistry

Fluid Dynamics of the Open Port Interface for High-Speed Nanoliter Volume Sampling Mass Spectrometry

Chang Liu,* Gary J. Van Berkel, Peter Kovarik, J. Blair Perot, Venkatesh Inguva, and Thomas R. Covey*

Journal of Pharmaceutical Sciences

Rapid Communication

Acoustic Droplet Ejection and Open Port Interface for Rapid Analysis of Metabolic Stability Assays

Tom Hollenbeck[A,*], Stefan Thibodeaux[b], Patrick White[a], Lucas Westling[a], Ashley Chong[a], John Isbell[a]

ACS Medicinal Chemistry Letters

analytical chemistry

SLAS Discovery

Advancing the Science of Drug Discovery

Special Collection

slas

. Dev. Pte. Ltd.

TOF based AEMS system prototype

Echo® MS System

OPP MS	Found	Not Found	Review	total cpds
Plate 1	304	10	6	320
Plate 2	299	20	1	320
Plate 3	308	10	2	320
Plate 4	287	31	2	320
Plate 5	285	34	1	320
Plate 6	285	30	5	320
Plate 7	281	28	11	320
Plate 8	288	31	1	320
Plate 9	297	16	7	320
Plate 10	291	14	15	320
Plate 11	317	3	0	320
Plate 12	307	11	2	320
Plate 13	304	15	1	320
Plate 14	308	12	0	320
Plate 15	311	9	0	320
Plate 16	309	10	1	320
Plate 17	303	17	0	320
Plate 18	289	26	5	320
Plate 19	298	16	6	320
Plate 20	73	3	4	80
Plate 21	310	9	1	320
Plate 22	300	16	4	320
Total cpds	6354	371	75	6800
	% mass match	93%		
	% not Found	5%		
	% review	1%		

22 plates by AEMS within <1 day

Same samples would take > 1 month with current LC/MS based QC

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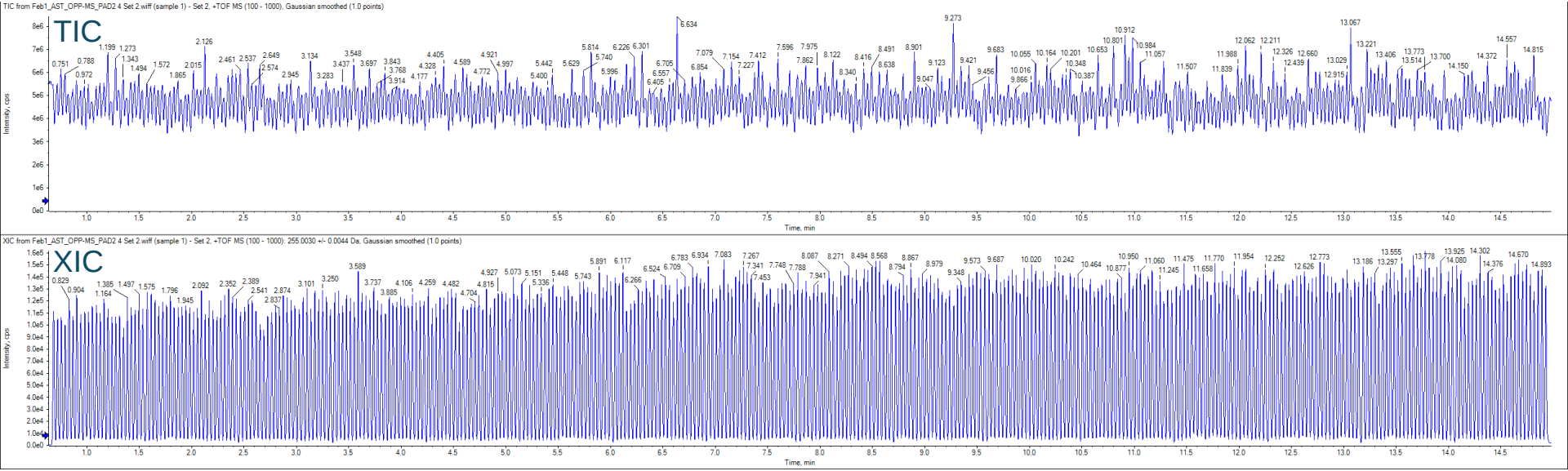
TOF based AEMS data

Echo® MS System



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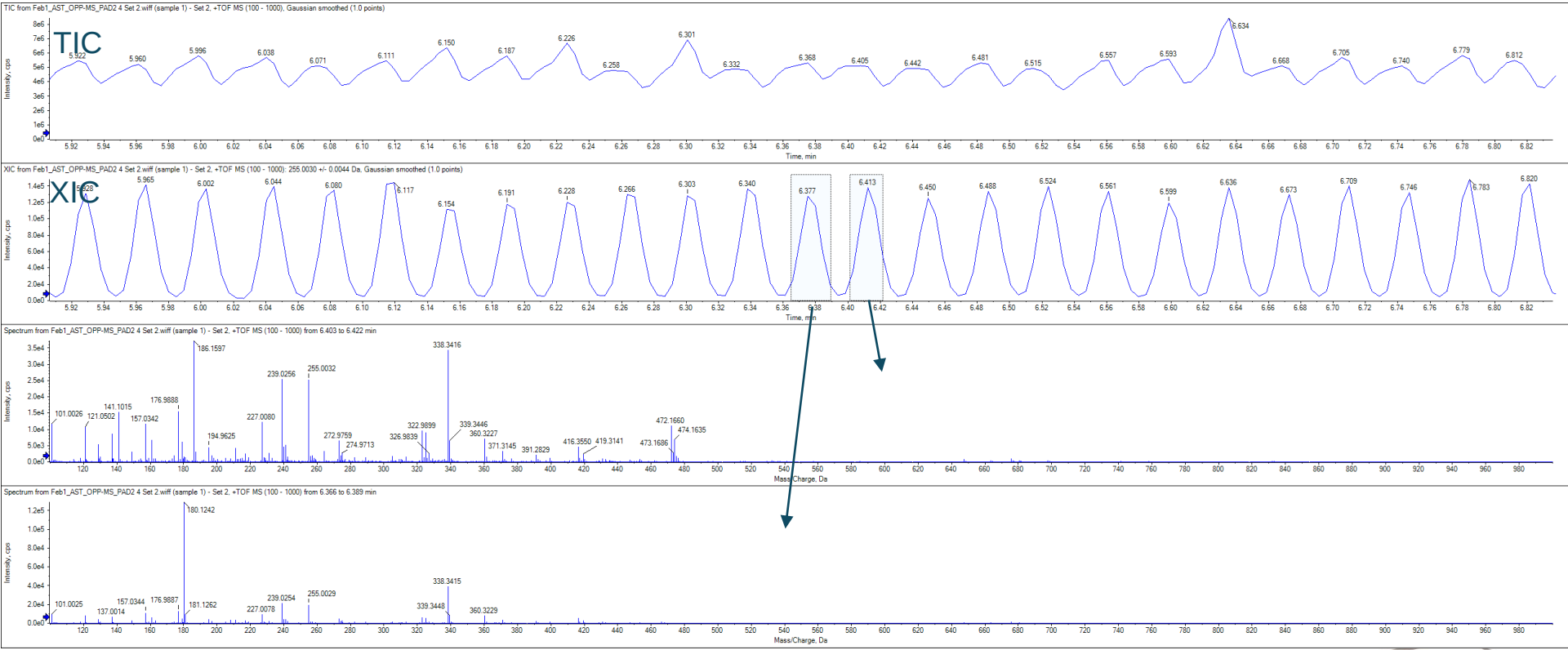
TOF based AEMS data

Echo® MS System



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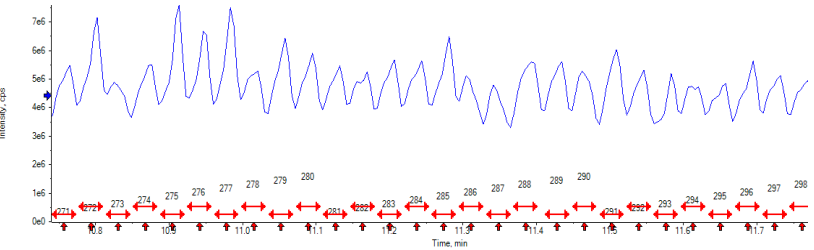
Automated data processing overview

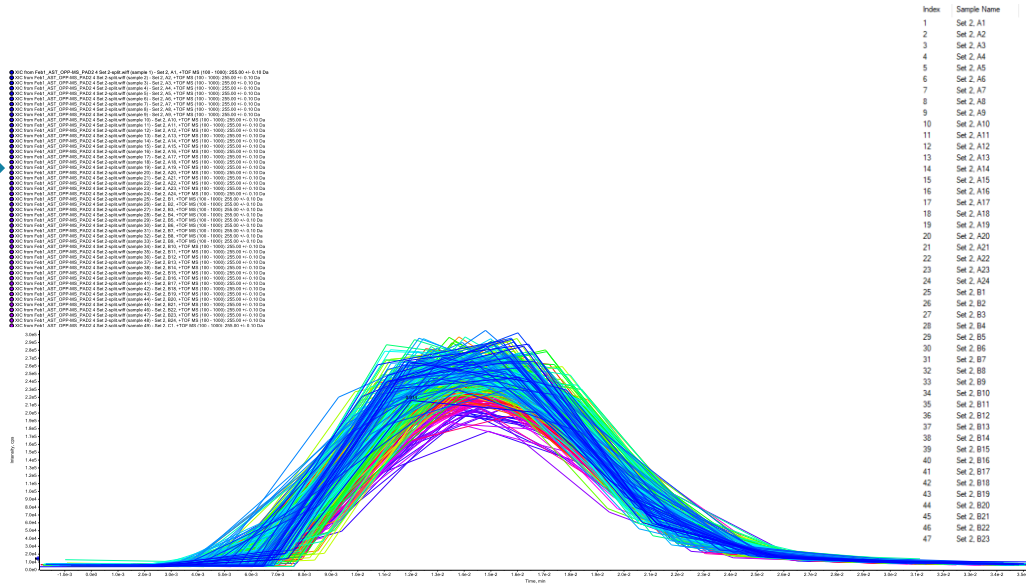
- Data splitting: correlate well position with each signal peak
- Integration and visualization
- Background identification and subtraction
- Spectra comparison

Data splitting

Echo® MS System

CORRELATE WELL POSITION WITH EACH SIGNAL PEAK





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Integration and report

Echo® MS System

- Input information
  - Split data (MS signal correlated with well position)
  - Compound information table
  - Integration settings (MS window width, etc.)
- Report table
  - Intensity, mass accuracy, isotope pattern matching score, S/N, etc.

sample	formula_group_1	charge_agent_group_1	formula_group_2	charge_agent_group_2	formula_group_3	charge_agent_group_3
A1	C5H9NO2	H+	C5H9NO3	H+	C5H9NO4	H+
A2	C6H13NO	H+	C5H9NO3	H+	C5H9NO4	H+
A3	C6H11NO2	H+	C6H11NO3	H+	C6H11NO4	H+
A4	C6H11NO2	H+	C6H11NO3	H+	C6H11NO4	H+
A5	C5H9NO2	H+	C5H9NO3	H+	C5H9NO4	H+
A6	C5H9NO2	H+	C5H9NO3	H+	C5H9NO4	H+
A7	C5H9N	H+	C5H9NO	H+	C5H9NO2	H+
A8	C5H9N	H+	C5H9NO	H+	C5H9NO2	H+
A9	C7H13N	H+	C7H13NO	H+	C7H13NO2	H+
A10	C7H13N	H+	C7H13NO	H+	C7H13NO2	H+
A11	C6H13N	H+	C6H13NO	H+	C6H13NO2	H+
A12	C6H13N	H+	C6H13NO	H+	C6H13NO2	H+
A13	C6H13NO	H+	C6H13NO2	H+	C6H13NO3	H+
A14	C6H13NO	H+	C6H13NO2	H+	C6H13NO3	H+
A15	C6H9NO2	H+	C6H9NO3	H+	C6H9NO4	H+
A16	C6H9NO2	H+	C6H9NO3	H+	C6H9NO4	H+
A17	C7H11NO2	H+	C7H11NO3	H+	C7H11NO4	H+
A18	C7H11NO2	H+	C7H11NO3	H+	C7H11NO4	H+
A19	C7H11NO2	H+	C7H11NO3	H+	C7H11NO4	H+
A20	C7H11NO2	H+	C7H11NO3	H+	C7H11NO4	H+
A21	C6H9NO2	H+	C6H9NO3	H+	C6H9NO4	H+

Sample	MZ (1)	Status (1)	Intensity (1)	S/N (1)	Abs Mz Error (1)	Error Type (1)	AVG Ratio Diffs (1)
A17	470.1145		379850.1	17067.9	1	Positive	0.0364375691427
A18	465.1356		680719.1	10490.3	1	Positive	0.0414579539151
A19	474.1247		705874.2	32371.8	0	-	0.0409172184878
A20	465.1356		218335.2	3208.2	2	Positive	0.0361845186639
A21	471.1713		23219.5	413.1	1	Positive	0.0785033672792
A22	465.0913		1670878.0	63492.6	0	-	0.0485186411711
A23	471.1713		78104.9	1617.3	3	Positive	0.0320035385586

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Data review and visualization

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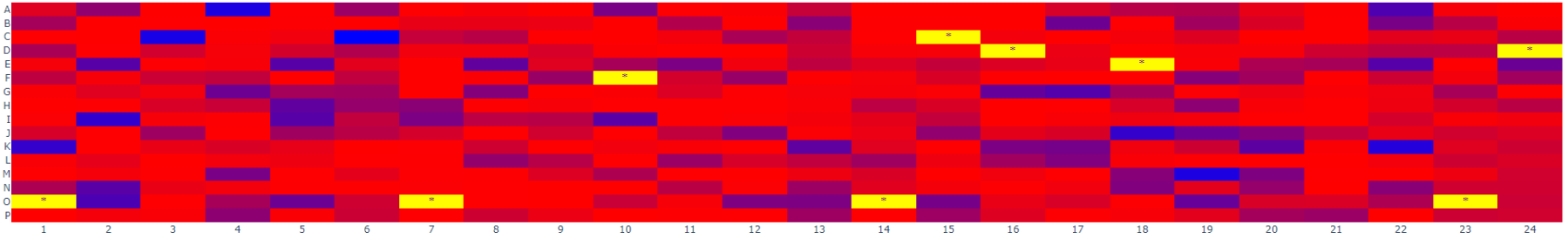
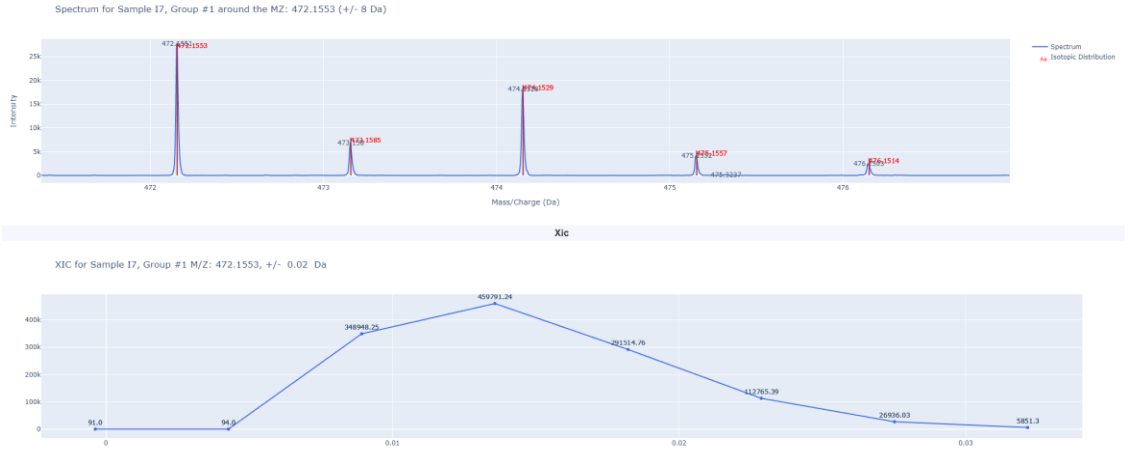
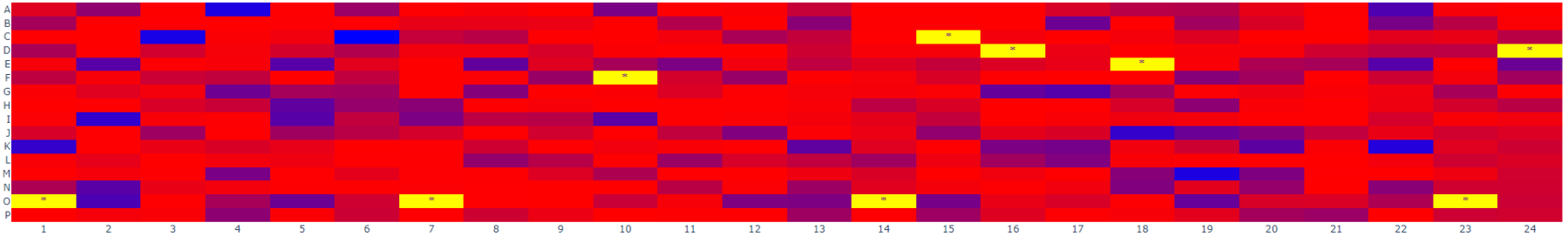
HEAT MAP



MASS SPECTRA AND XIC VISUALIZATION



Validation rules

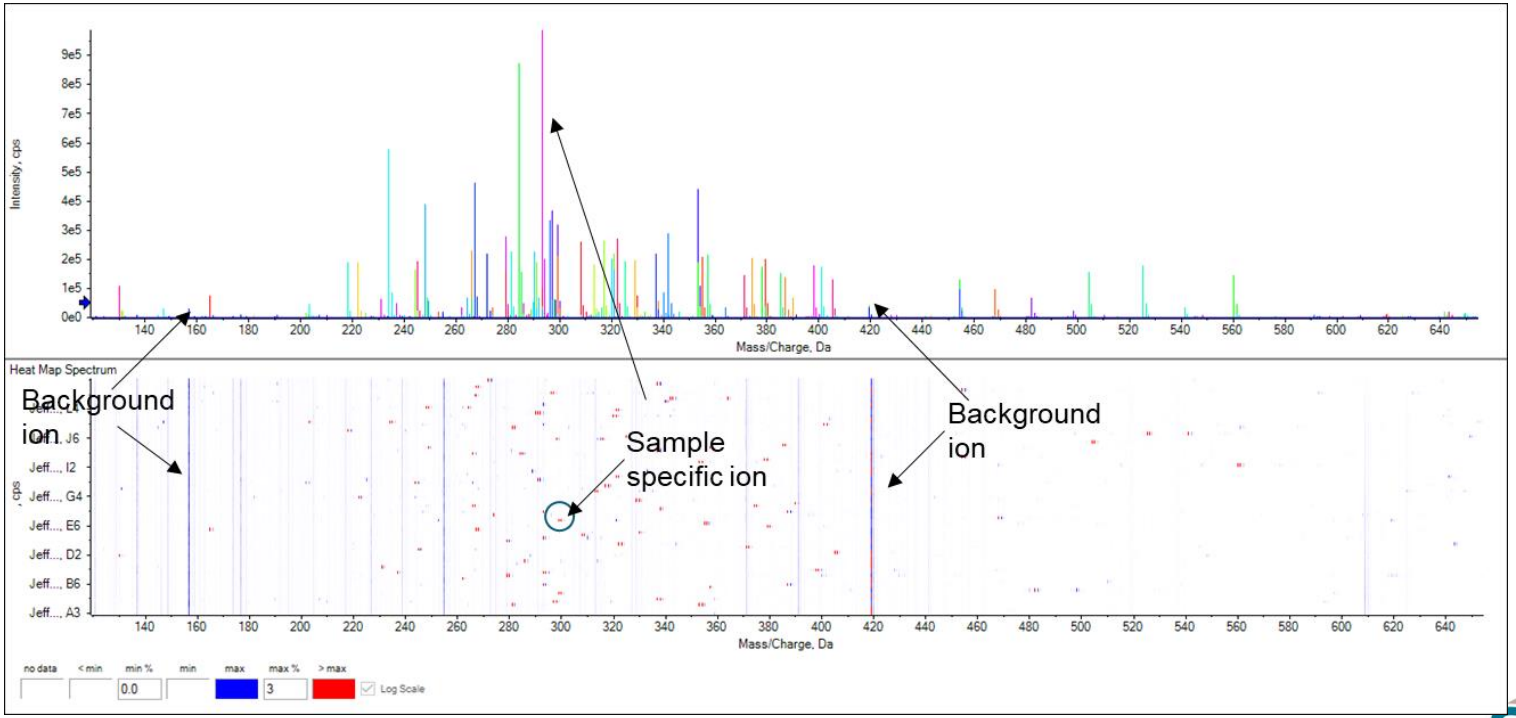


- Validation rules
  - Mass accuracy
  - Isotope pattern
  - S/N

Background mass spectra pemoval

Echo® MS System

- Background identification and subtraction (with well-specific scaling factor)



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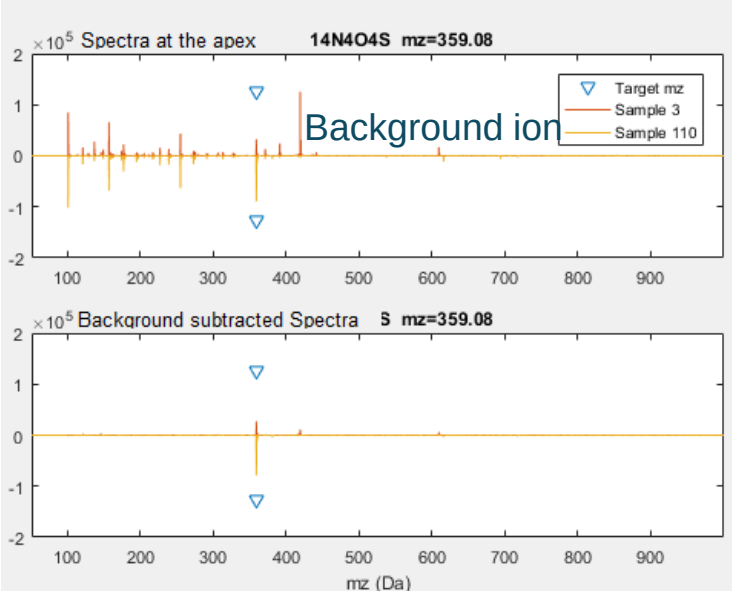
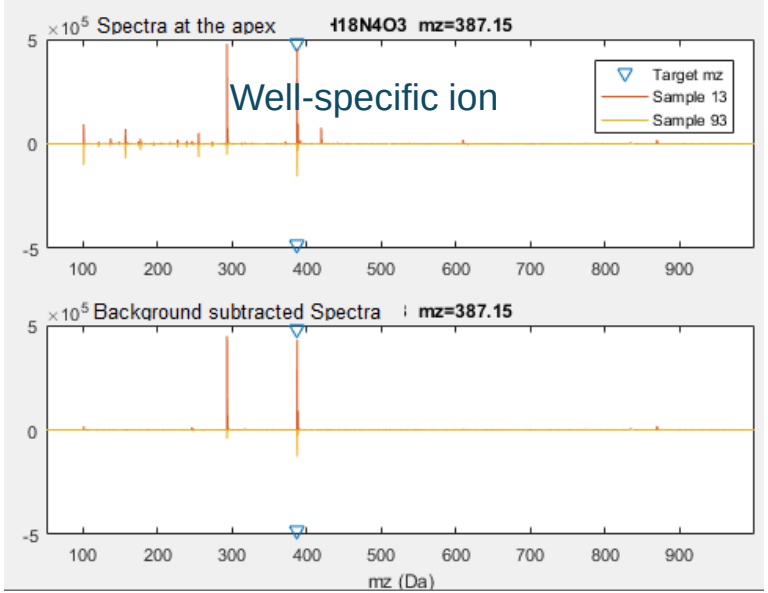
The Power of Precision

Background mass spectra removal

Echo® MS System

- Background identification and subtraction (with well-specific scaling factor)





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Spectra comparison

Echo® MS System

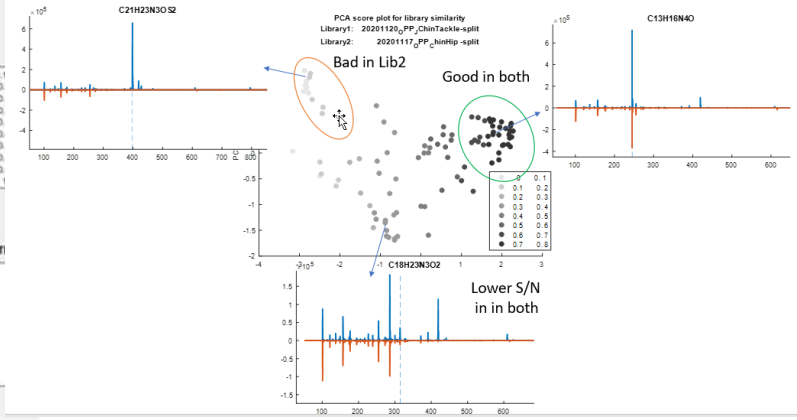
- Auto pairing from two sets of data (reference and test sets)
- Calculating the spectra similarity score

L1_20201120_OPP_JChinTackle_split	formula1	ChargeAgent1	ind1	L2_20201117_OPP_ChinHip__split	formula2	ChargeAgent2	ind2	SumOfSquares_orig	SumOfSquares_log	SumOf_ABS_orig	DotProd_orig	DotProd_log	chebychev_orig	chebychev_log	hamming
A1	C11H13N3O	H+	1	K7	C11H13N3O	H+	77	0.959456172	0.955820259	0.645442795	0.959456172	0.95582026	0.796880899	0.849142716	0.7540124
A2	C21H25N3S	H+	2	L1	C21H25N3S	H+	78	0.012769056	0.035536743	0.024073165	0.012769056	0.03553674	0	0	0.63627819
A3	C16H14N4O4S	H+	3	P5	C16H14N4O4S	H+	110	0.376369085	0.521629264	0.431661871	0.376369085	0.52162926	0	0	0.57399973
A4	C15H16ClNO3	H+	4	L7	C15H16ClNO3	H+	84	0.575450241	0.798650943	0.59424423	0.575450241	0.79865094	0	0	0.57098524
A5	C20H30N2O2	H+	5	E2	C20H30N2O2	H+	30	0.246982531	0.514444398	0.360448312	0.246982531	0.5144444	0	0	0.57540668
A6	C22H28N2O2	H+	6	B5	C22H28N2O2	H+	12	0.934506833	0.934983036	0.673043026	0.934506833	0.93498304	0.710370764	0.815177024	0.69882028
A7	C19H24N2O	H+	7	J5	C19H24N2O	H+	68	0.975984359	0.975293725	0.717011186	0.975984359	0.97529373	0.807628839	0.876087665	0.67489348
B1	C20H20N2OS	H+	8	M4	C20H20N2OS	H+	88	0.942930052	0.923079481	0.579466376	0.942930052	0.92307948	0.760249987	0.803224657	0.61001602
B2	C18H20O2	H+	9	A5	C18H20O2	H+	5	0.629982577	0.806256346	0.571039906	0.629982577	0.80625635	0	0	0.58906072
B3	C19H26N2O	H+	10	A3	C19H26N2O	H+	3	0.97830618	0.969743791	0.668430451	0.97830618	0.96974379	0.865575518	0.880806797	0.61427126
B4	C28H31N7O	H+	11	N6	C28H31N7O	H+	97	0.455716805	0.55414278	0.388890379	0.455716805	0.55414278	0	0.057437431	0.56637181
B5	C19H24N4O3	H+	12	M3	C19H24N4O3	H+	87	0.720422371	0.737543874	0.595474874	0.720422371	0.73754387	0.02396553	0.325962775	0.58712939
B6	C22H18N4O3	H+	13	N2	C22H18N4O3	H+	93	0.784752158	0.801449044	0.491496274	0.784752158	0.80144904	0.285153155	0.57117613	0.58073362
B7	C29H31N7O2	H+	14	G1	C29H31N7O2	H+	43	0.513106546	0.689543154	0.458382234	0.513106546	0.68954315	0	0	0.57883667
C1	C16H23NO2	H+	15	O2	C16H23NO2	H+	100	0.600978976	0.677178713	0.508897909	0.600978976	0.67717871	0	0.308279677	0.57361002
C2	C17H18N4	H+	16	D4	C17H18N4	H+	25	0.953061801	0.942710098	0.601272225	0.953061801	0.9427101	0.803503805	0.86625866	0.61351478
C3	C20H24N2	H+	17	M7	C20H24N2	H+	91	0.961009919	0.965121483	0.700107091	0.961009919	0.96512148	0.782007216	0.863901431	0.70986386
C4	C21H23N3OS2	H+	18	H2	C21H23N3OS2	H+	51	5.56523E-05	0.000763311	0.000416035	5.56523E-05	0.00076331	0	0	0.58622389
C5	C14H18N2O	H+	19	P6	C14H18N2O	H+	111	0.800553535	0.772565728	0.518654281	0.800553535	0.77256573	0.424909407	0.548170368	0.60166026
C6	C16H14N2O3	H+	20	K5	C16H14N2O3	H+	75	0.665656906	0.768897344	0.604907656	0.665656906	0.76889734	0	0	0.58993183
C7	C18H23N3O2	H+	21	L6	C18H23N3O2	H+	83	0.639113904	0.758830027	0.499500931	0.639113904	0.75883003	0	0	0.56209077
D1	C12H14N2O3	H+	22	J2	C12H14N2O3	H+	65	0.667574896	0.774567625	0.550112697	0.667574896	0.77456763	0	0	0.57328049
D2	C12H12F3N3S	H+	23	I7	C12H12F3N3S	H+	63	0.74729223	0.729210257	0.449139073	0.74729223	0.72921026	0	0	0.60106138
D3	C25H28N2O3	H+	24	O3	C25H28N2O3	H+	101	0.008131822	0.03555204	0.019647503	0.008131822	0.03555204	0	0	0.62086475
D4	C13H16N4O	H+	25	H7	C13H16N4O	H+	56	0.948149344	0.929838929	0.61596809	0.948149344	0.92983893	0.759258155	0.800922094	0.63014892
D5	C23H34N2O2	H+	26	H4	C23H34N2O2	H+	53	0.959585554	0.950042239	0.681816781	0.959585554	0.95004224	0.812018621	0.828515384	0.61561804
D6	C21H23NO2	H+	27	J4	C21H23NO2	H+	67	0.955406317	0.941799395	0.591993253	0.955406317	0.9417994	0.829509871	0.855498614	0.62816314
E1	C16H10N2OS	H+	28	F2	C16H10N2OS	H+	37	0.794237262	0.775753339	0.471712523	0.794237262	0.77575334	0.41179044	0.583293401	0.58171648

Spectra comparison

Echo® MS System

- Background removing feature enabled
- UI for data review
- PCA analysis included for direct visualization



Summary

- AEMS enables the high-throughput compound QC
- The automated data processing workflow enabling
  - Target ion integration
  - Data visualization
  - Background processing
  - Spectra comparison across data set

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