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Visionary Software

Advancing Research

Fragment Based Drug Screening:

A study in visualization and processing

Agenda

- Look and feel
- Fragment based screening: a short primer
- Bits and pieces
- Outputs, options, and usage
- Conclusions

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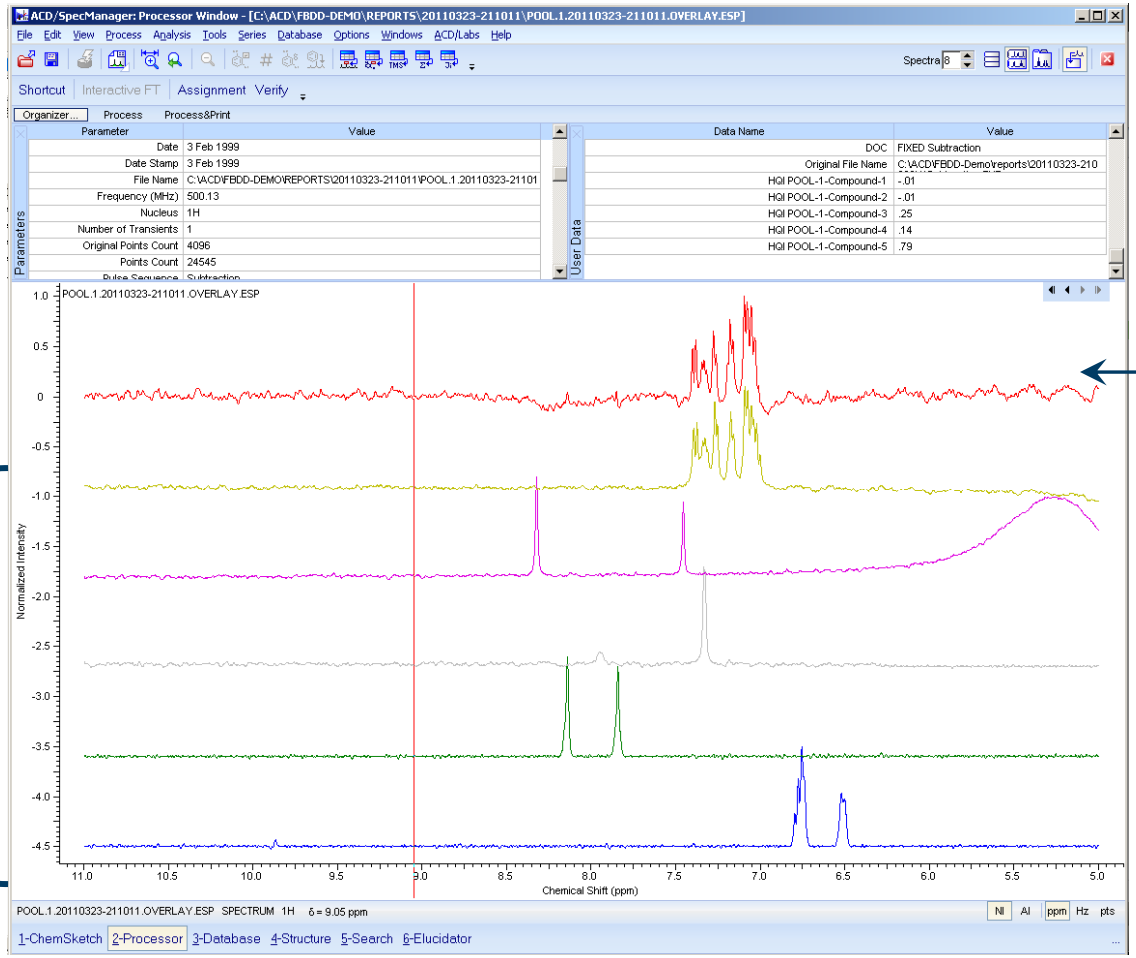
Visual Review of Data

Spectrum of Fragment Bound to protein



Fragment Spectra

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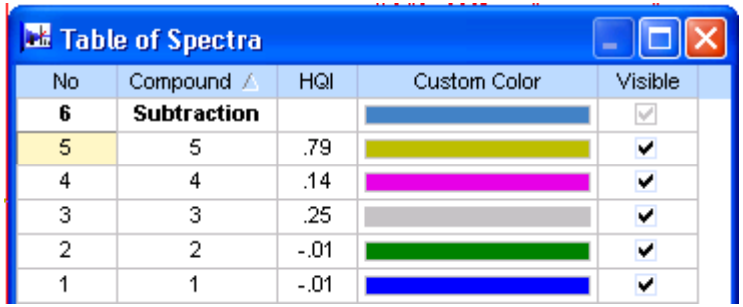
Quantitative Review

- Calculate similarity between “bound” spectrum and each ligand
- Use “Hit Quality Index” to quantify the similarity



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What is FBDD?

- Fragments: smaller space to span
- Proteins have multiple active sites
- Searching for fragments that can be combined to interact with proteins
- Five or more fragments per well
- Five, ten, or more plates in fragment library
- Each protein screened against the library

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NMR Screening Options

- Saturation Transfer Difference (STD): saturate protein with rf – signals are transferred via spin diffusion to bound ligands, which appear in spectra.
- WaterLOGSY: magnetization transfer from water.
- TINS: ligand signal suppressed by shortened T_2 – protein target coupled to solid phase.
- T2-Based Screening – Ligand relaxation is affected by binding to protein and thus signals are attenuated during a spin-lock period.

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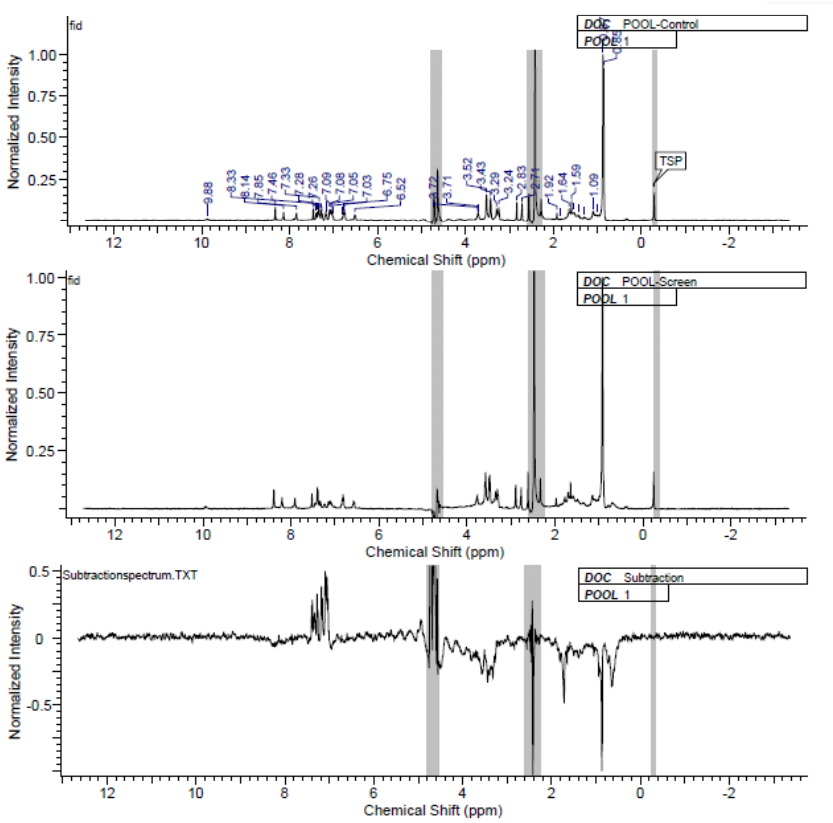
NMR Screening Mechanics

- Take spectrum without interaction “turned on”
- Take spectrum with interaction in place
- Subtract to find NMR signal of “bound” ligands



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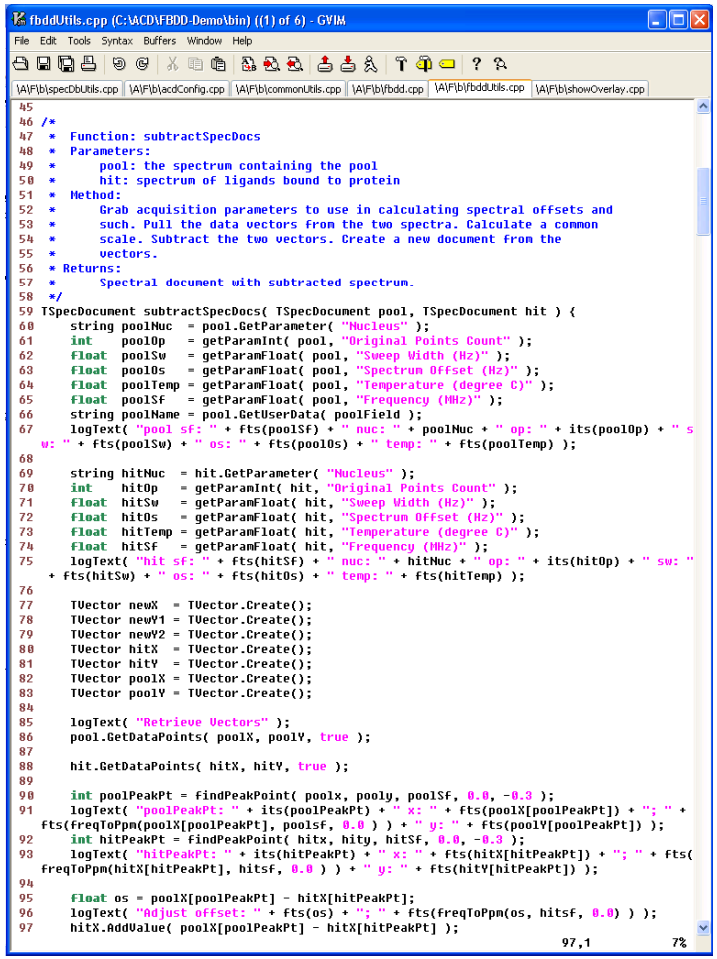
ACD Scripting



- Versatile environment to allow for custom data processing
- Hosted within ACD Automation products and now in ACD Desktop products, too

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Subtraction in Scripting

- Pull raw data from spectra
- Reference and normalize each based on TSP peak
- Subtract point to point
- Store in ASCII format and load as subtracted spectrum

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HQI in Scripting

- Truncate to window for calculation
- Pull raw data from spectra as vectors
- Harmonize both vectors
- Normalize each vector
- HQI is dot product

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Alternatives

- Do subtraction by phase cycling
- Spectrometer can perform subtraction
- Use peak-by-peak accounting instead of HQI
- Renormalize HQI by ligand mass

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Script Flow for FBDD

- Read in bound and unbound, calculate subtracted, and truncate to clear window
- Read in ligand spectra (or pull from library) and truncate to clear window
- Measure HQI for each truncated ligand spectrum against truncated subtracted spectrum

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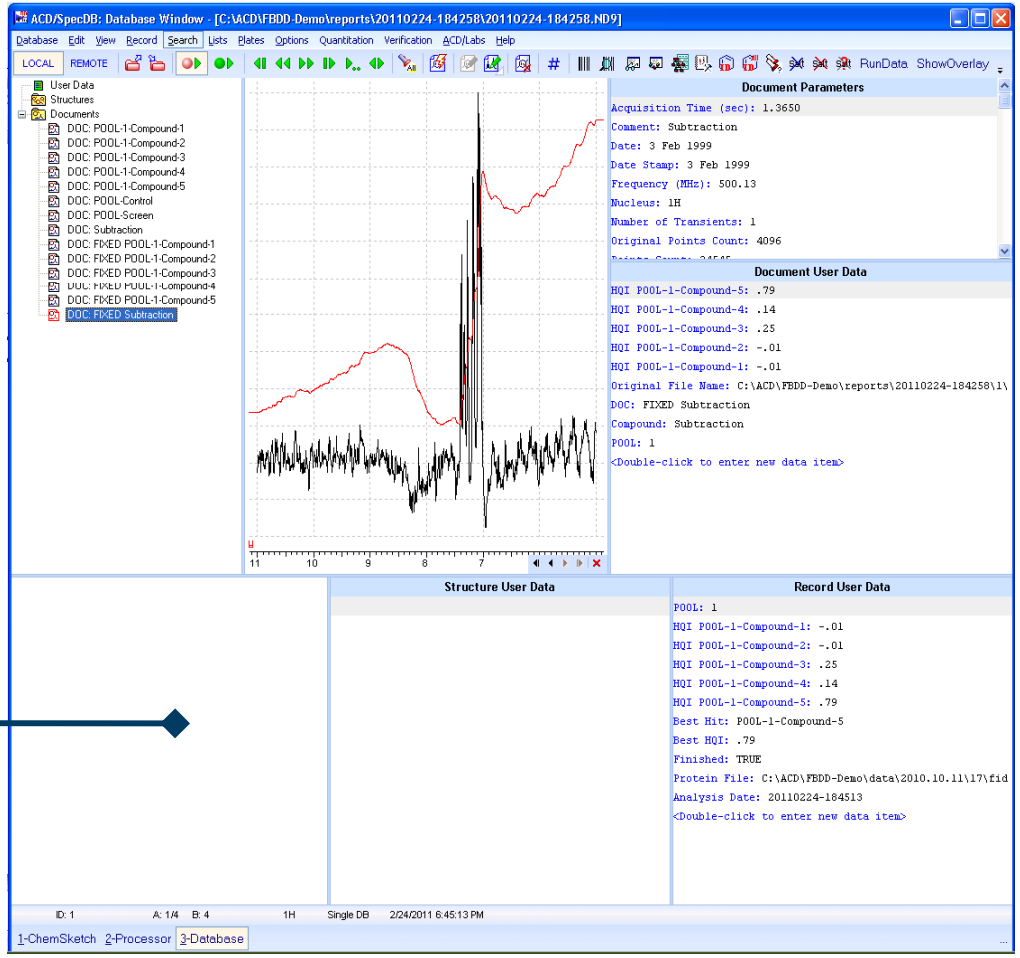
Analysis Output: ND9

Use document Tree for quick selection



Can populate Structures from Mol, SD, database

Summary Of HQI

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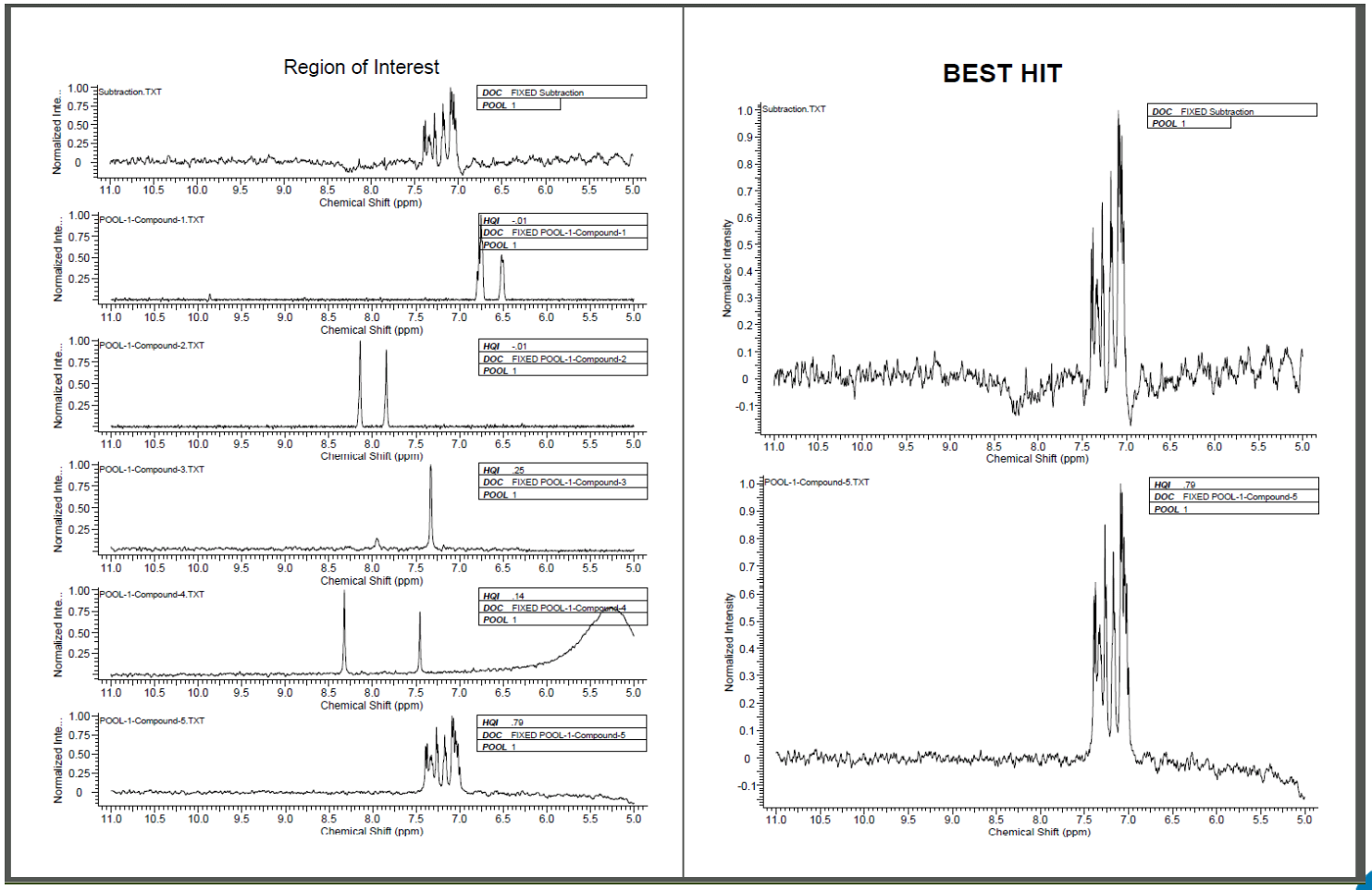
Analysis Output: PDF Report



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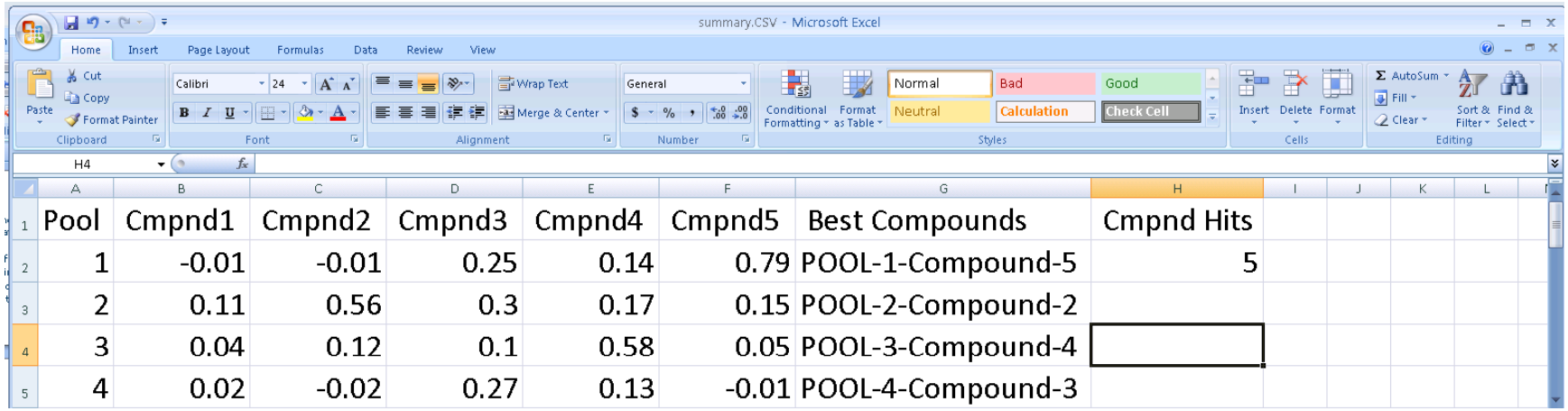
Analysis Output: CSV Report



	A	B	C	D	E	F	G	H
1	Pool	Cmpnd1	Cmpnd2	Cmpnd3	Cmpnd4	Cmpnd5	Best Compounds	Cmpnd Hits
2	1	-0.01	-0.01	0.25	0.14	0.79	POOL-1-Compound-5	5
3	2	0.11	0.56	0.3	0.17	0.15	POOL-2-Compound-2	
4	3	0.04	0.12	0.1	0.58	0.05	POOL-3-Compound-4	
5	4	0.02	-0.02	0.27	0.13	-0.01	POOL-4-Compound-3	

Well of Five compounds

HQI of each compound

Compound in Well with Highest HQI

List of compounds with HQI above threshold

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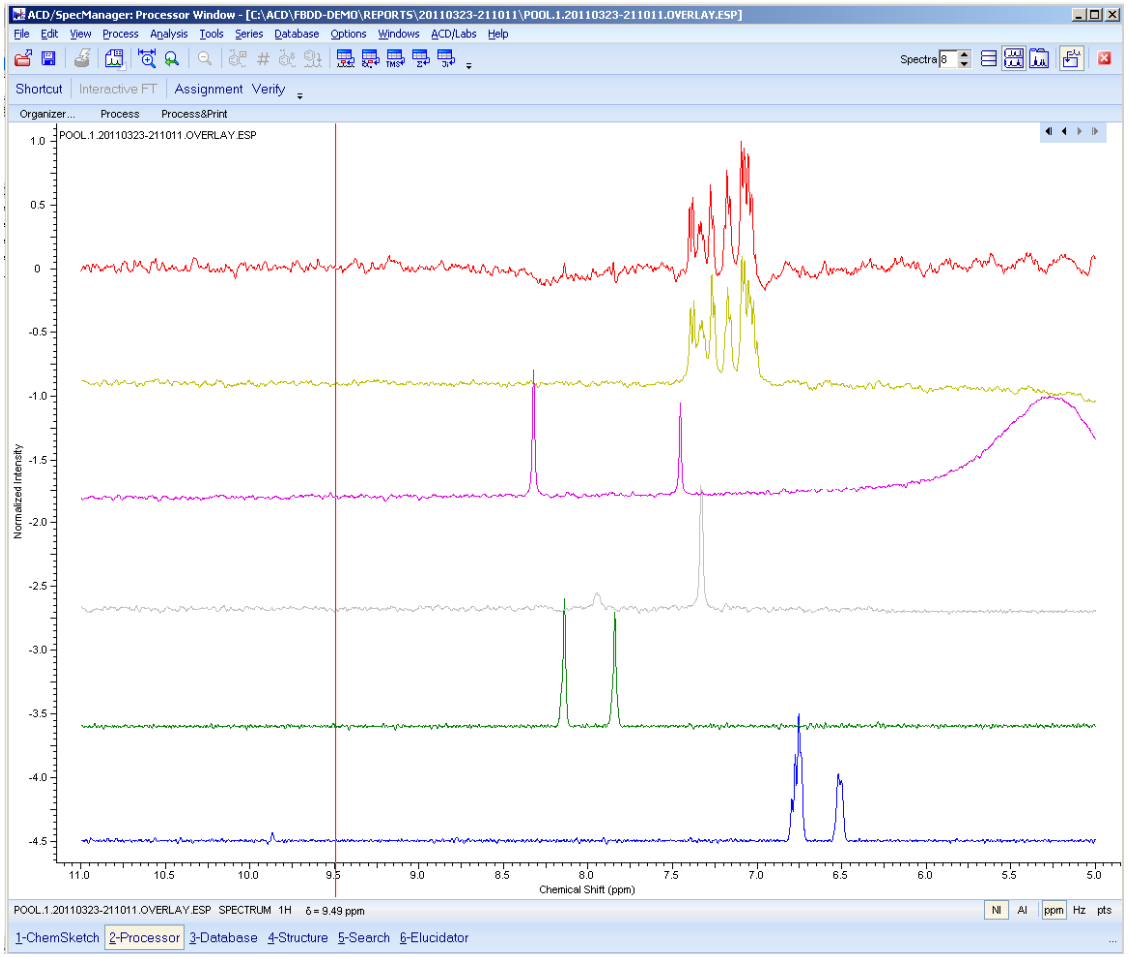
So… putting it all together

Subtracted

Well-bound ligand

Not bound



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Future Work

- Improve subtraction algorithms: especially alignments and normalizations
- Evaluate alternative hit recognitions and quantifications
- Work with other screening methods

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