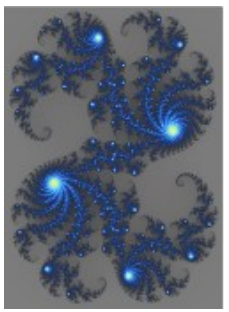
Using mass spectrometry to elucidate complex biological systems

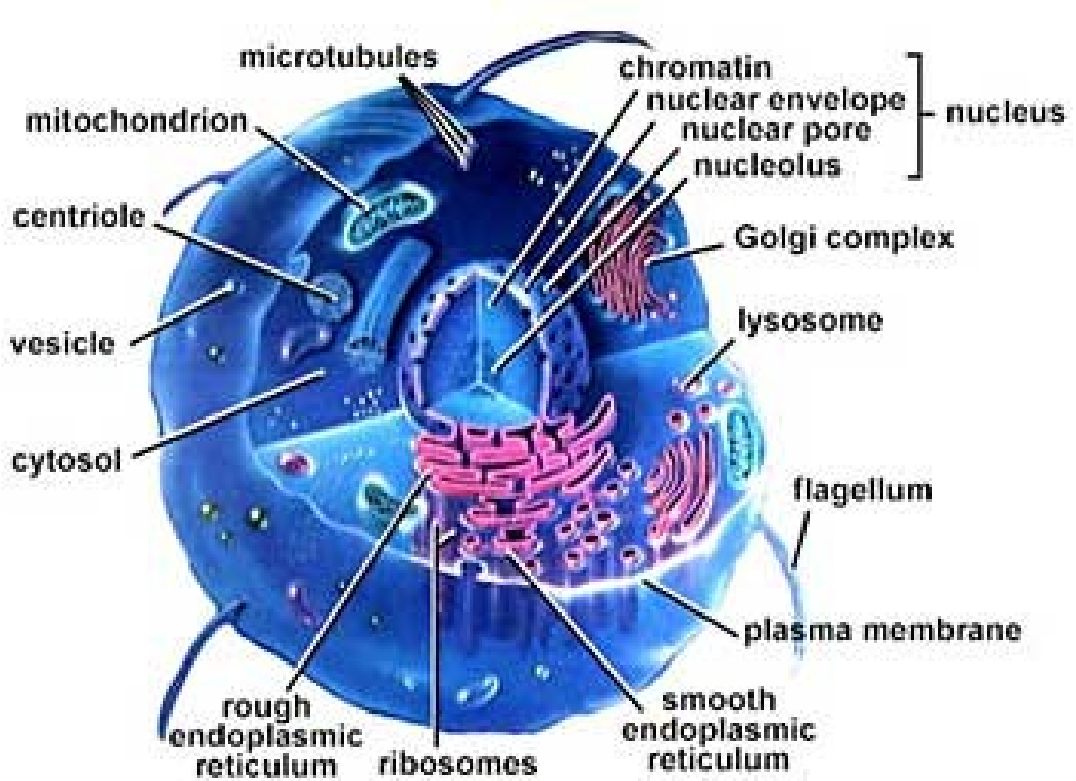


PRINCE
LAB

DEPARTMENT OF
CHEMISTRY AND BIOCHEMISTRY
BRIGHAM YOUNG UNIVERSITY

December 24, 2013

Biochemists are good at measuring the blueprints for cellular life (RNA, DNA), but we are not very good yet at measuring all the machinery and structures of which life is mostly composed (proteins, lipids, metabolites)!



http://www.beyondbooks.com/lif71/4.asp

proteins

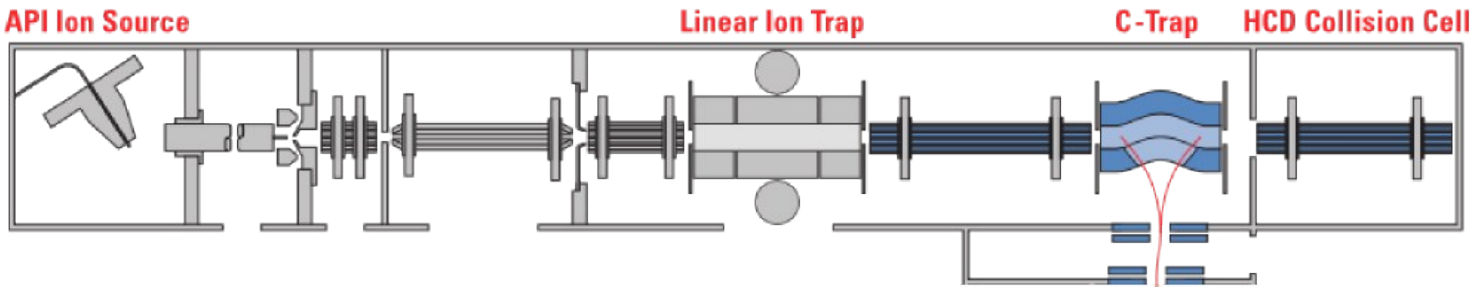
lipids

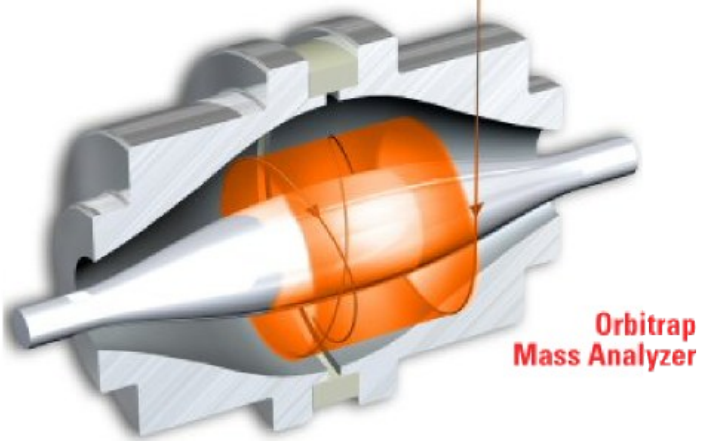
metabolites

RNA

DNA

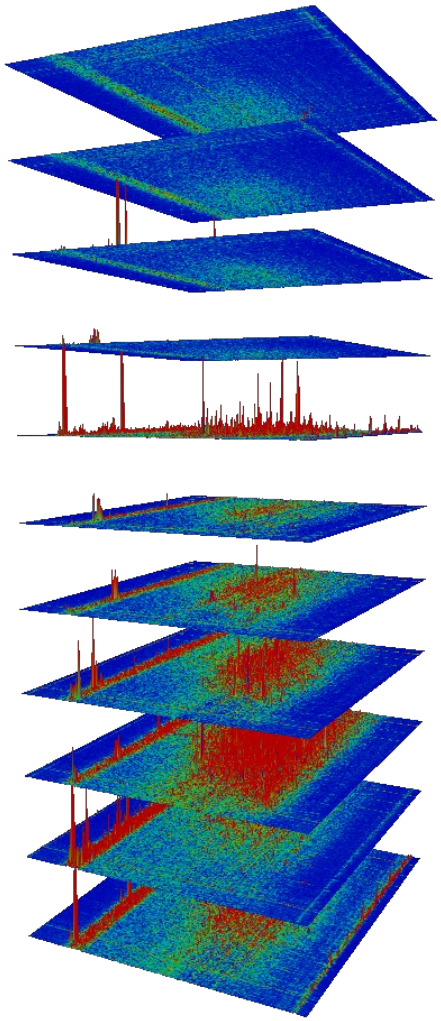
Mass spectrometry is the leading method for the high-throughput measurement of proteins, lipids, and metabolites. We can measure 100's to 10,000's of these biomolecules in a single experiment.

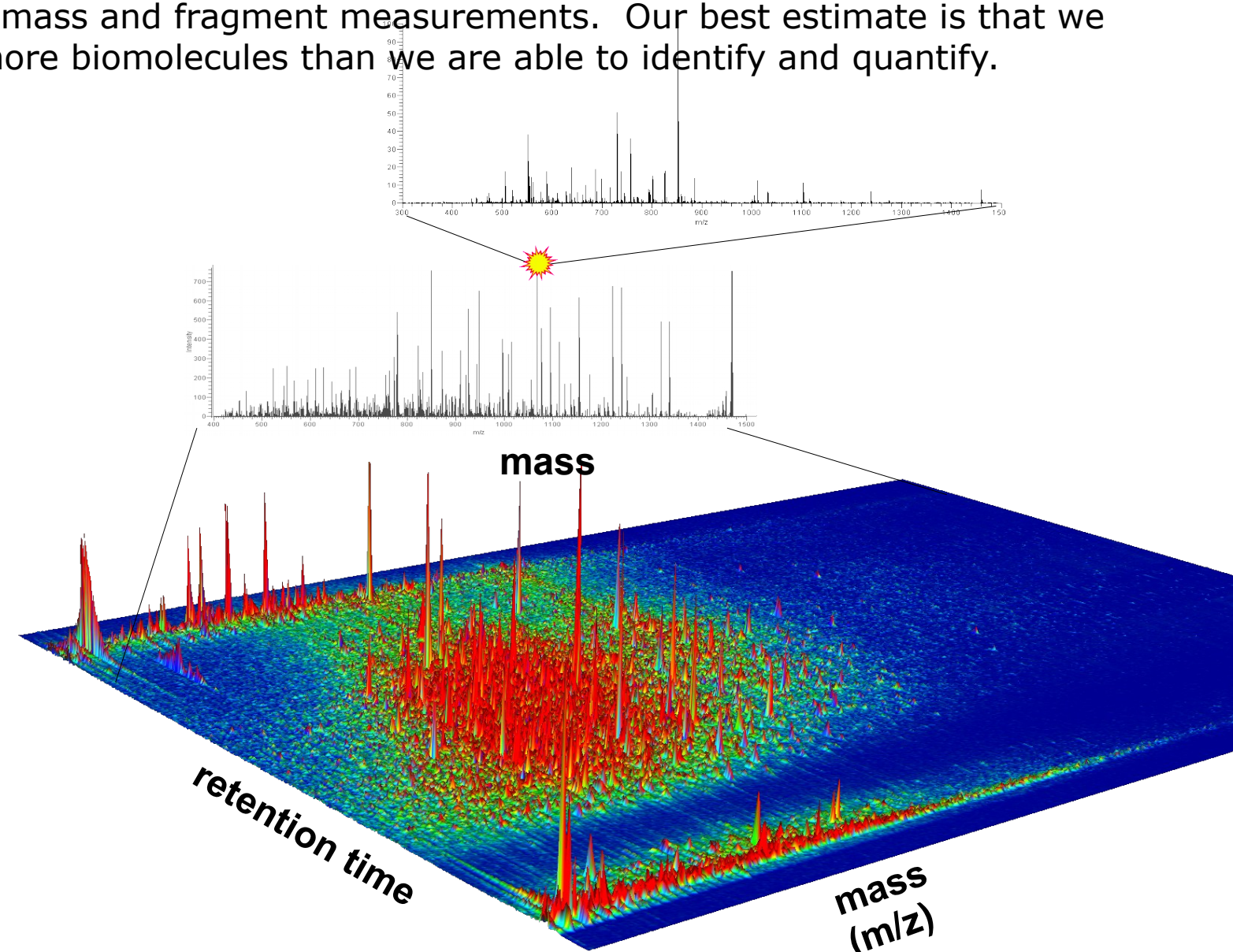




http://planetorbitrap.com/data/fe/image/LTQXL_Schema(1).png
http://www.macroarc.de/bilder/equipment/orbitrap1.jpg
http://planetorbitrap.com/data/fe/image/POTC_OrbitrapElite_HESI_Angle.png

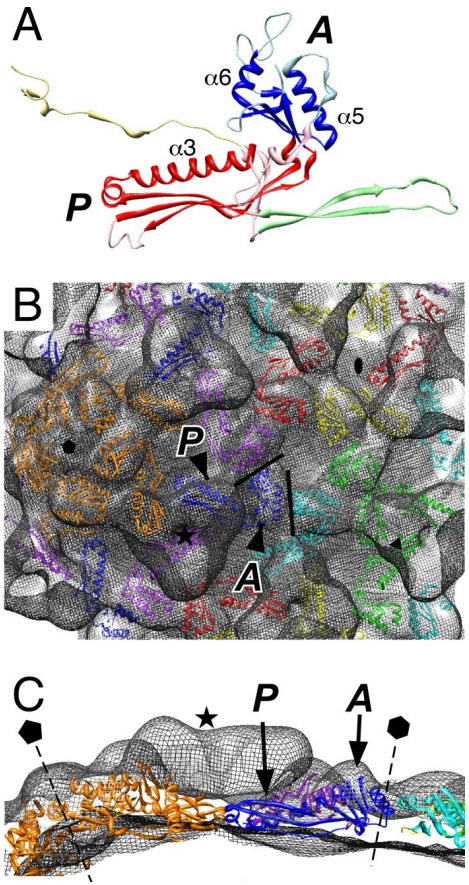
A key challenge in mass spectrometry is correctly inferring the identities and quantities of biomolecules from mass and fragment measurements. Our best estimate is that we collect data on 10X more biomolecules than we are able to identify and quantify.

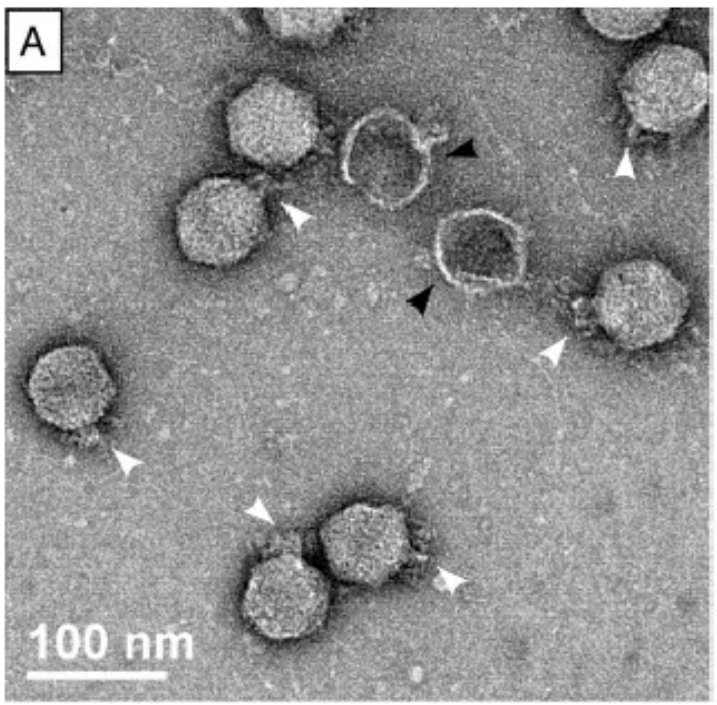




What kinds of things can we do right now with mass spectrometry?

We sequenced all the proteins in a Salt Lake bacteria virus.

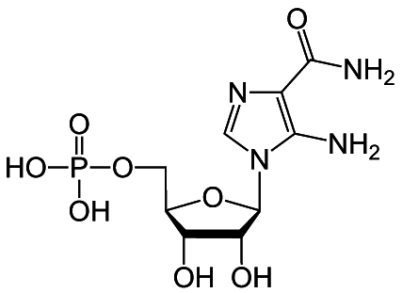




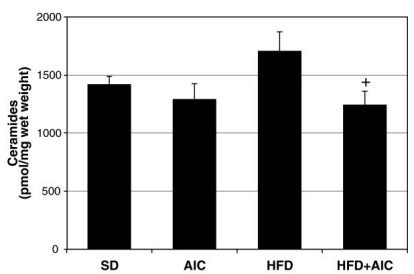
In collaboration with David Belnap

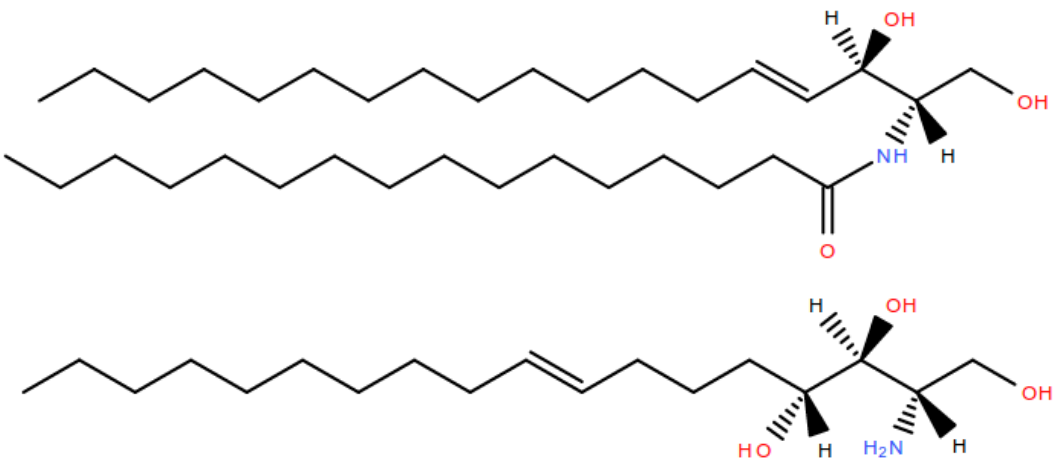
Shen PS, Domek MJ, Sanz-Gardia E, Makaju A, Taylor MJ, Hoggan R, Culumber MD, Oberg CJ, Breakwell DP, Prince JT, Belnap DM. *Journal of Virology*. **2012**

We quantified changing levels of ceramides, important lipids involved in metabolic diseases (obesity, heart disease, etc.)



AICAR



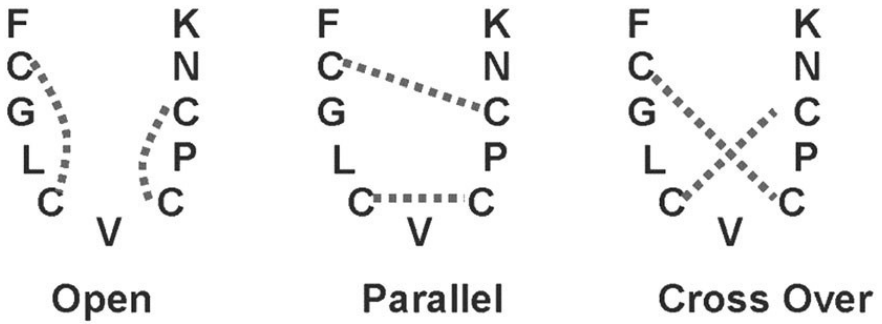


In collaboration with Ben Bikman

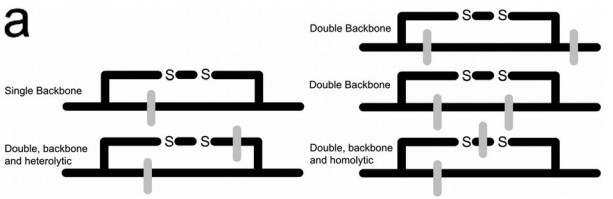
Erickson KA, Smith ME, Anthonymuthu TS, Evanson MJ, Brassfield ES, Hodson AE, Bressler MA, Tucker BJ, Thatcher MO, Prince JT, Hancock CR, Bikman BT. *Diabetol. Metab. Syndr.* **2012**

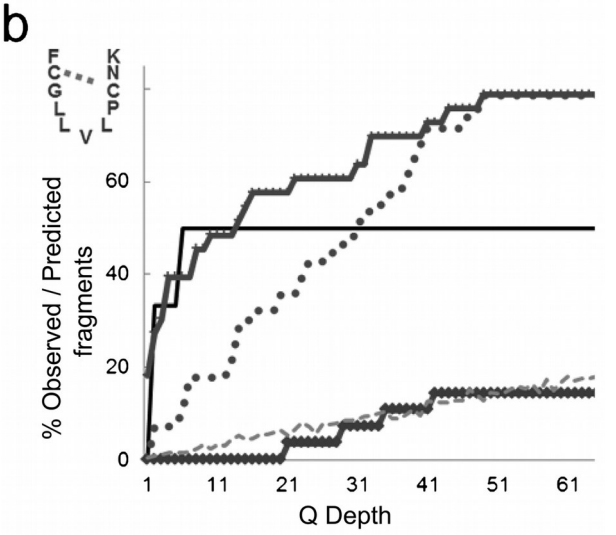
Smith ME, Tippetts TS, Brassfield ES, Tucker BJ, Ockey A, Swensen AC, Anthonymuthu TS, Washburn TD, Kane DA, Prince JT, Bikman BT. *Biochem J.* **2013**.

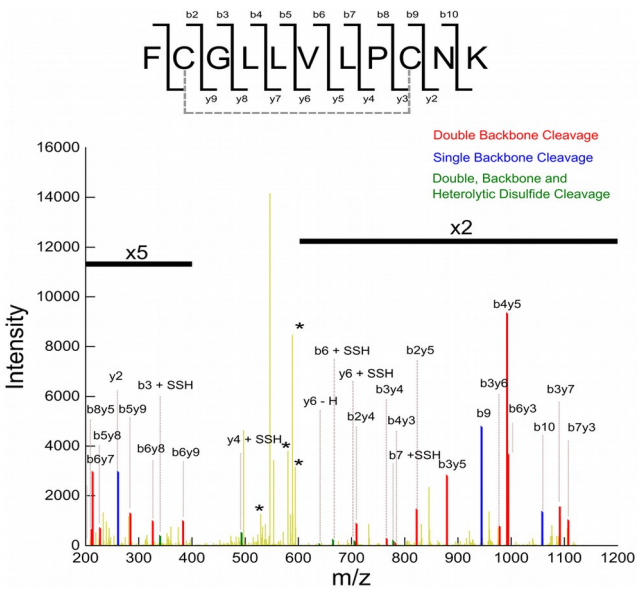
We deciphered the disulfide double bond configurations found in the vesicle fusion protein SNAP25, a key step in understanding how oxidative damage (e.g., aging) alters neurotransmission.



In collaboration with Dixon Woodbury

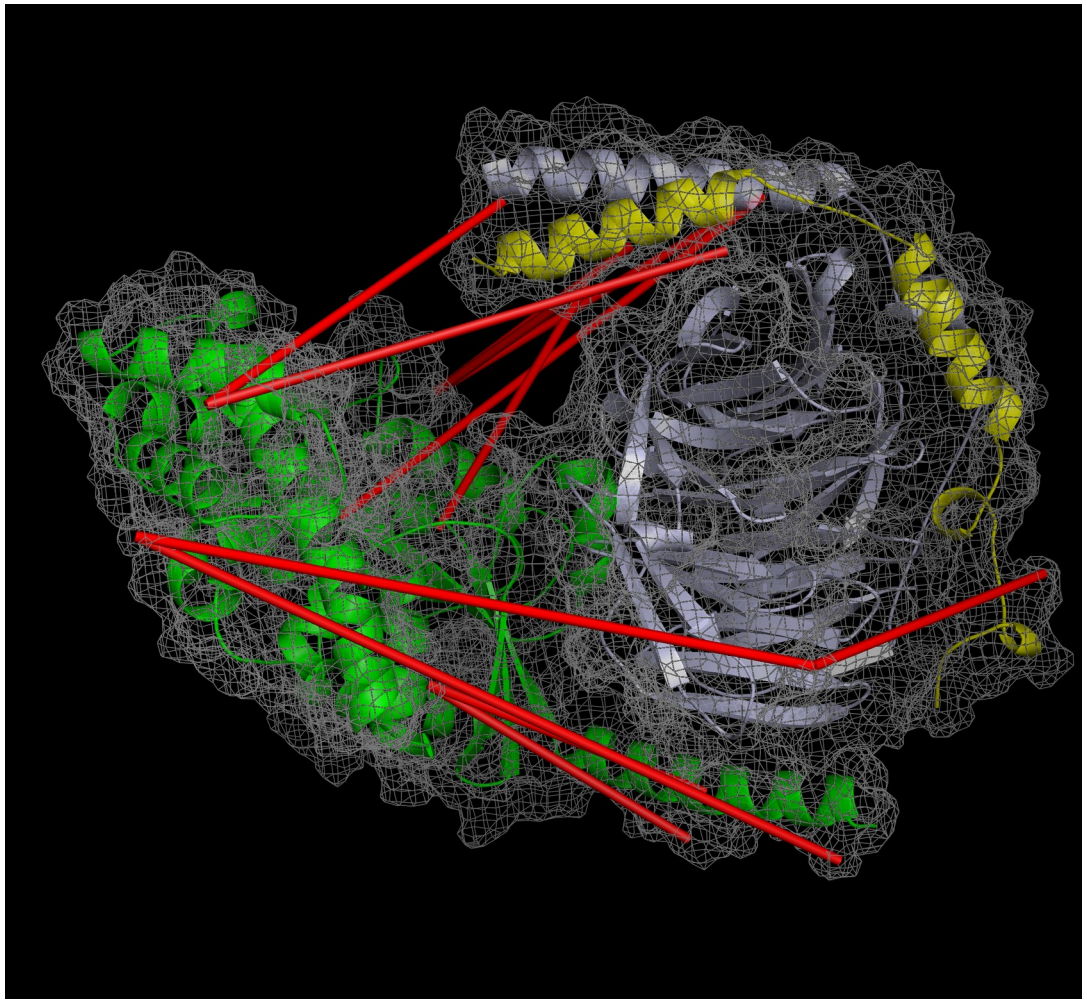


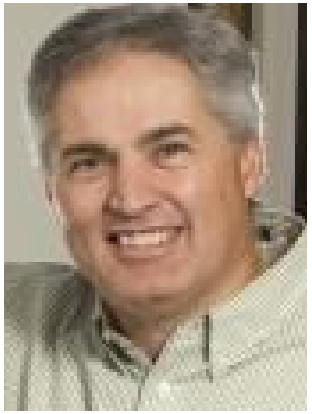




Ogawa N, Taylor RM, Woodbury DJ, Prince JT. *Journal of Mass Spectrometry*. **2013**

We are using chemical crosslinks and mass spectrometry along with cryoelectron microscopy to understand protein complexes important in a variety of disease (e.g., Bardet-Biedl syndrome)

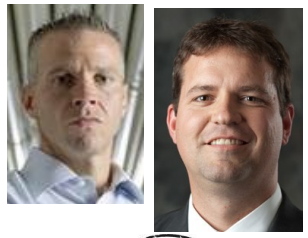




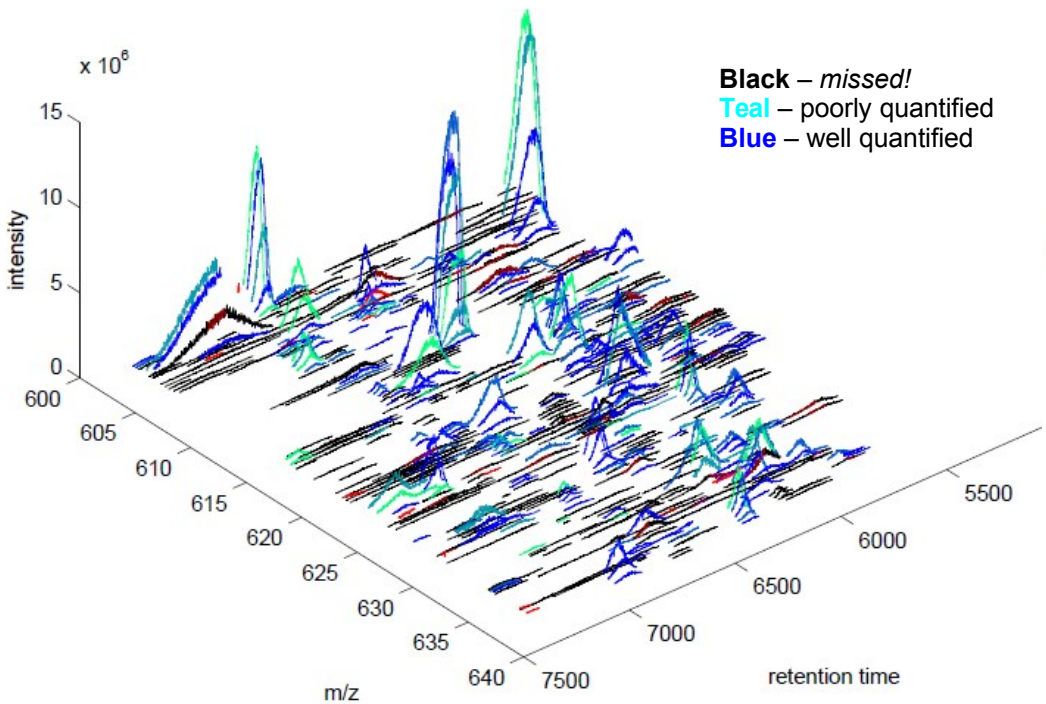
In collaboration with
Barry Willardson

The Prince Lab is working on methods to extract useful information to increase the reach of current approaches and develop new ways of understanding disease.

We wrote and characterized software that vastly increases the number of biomolecules that can be detected.

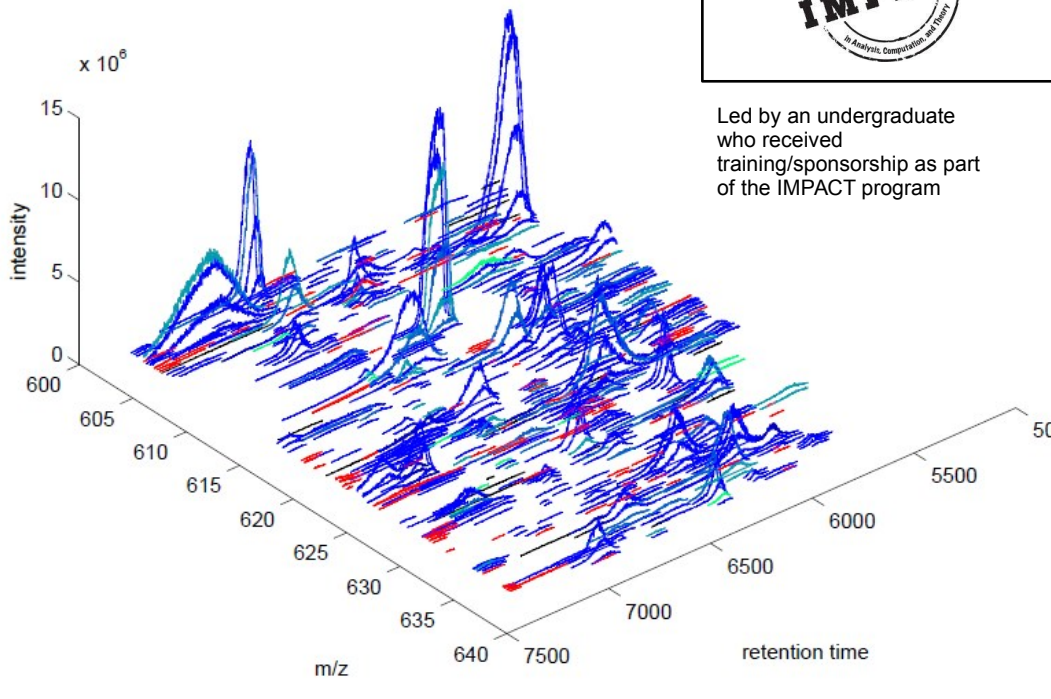


Led by an undergraduate who received training/sponsorship as part of the IMPACT program



Black – *missed!*
Teal – poorly quantified
Blue – well quantified

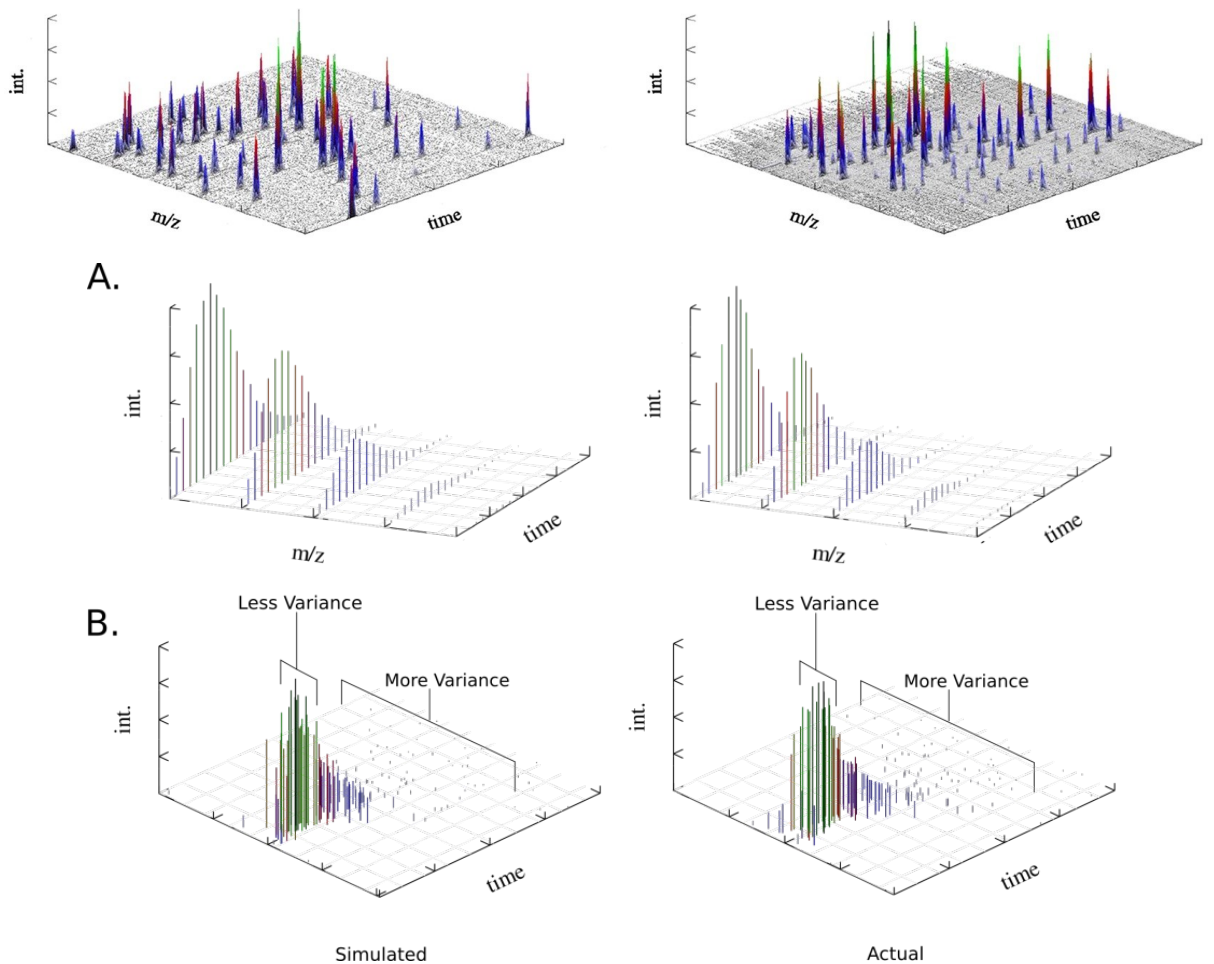
centwave



massifquant

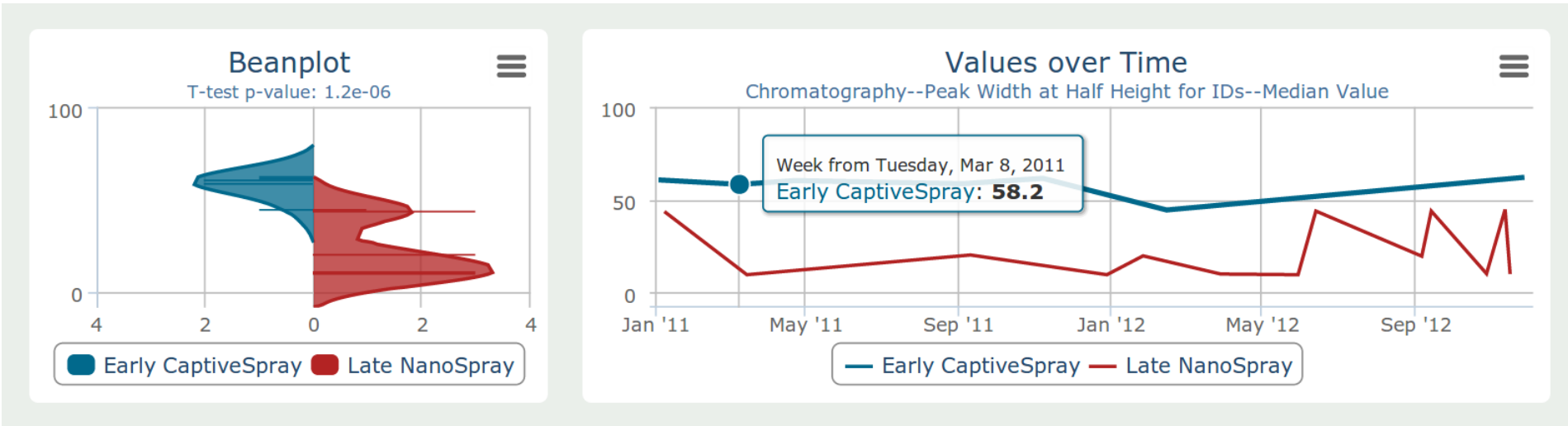
Conley C, Torgrip R, Taylor R, Tautenhahn R, Prince JT. *Bioinformatics* (in review)

We created a state-of-the-art mass spectrometry data simulator to help test software that extracts biomolecular signals.



Noyce A, Smith R, Dalgleish J, Taylor RM, Erb KC, Okuda N and Prince JT. *J Proteome Res.* **2013**

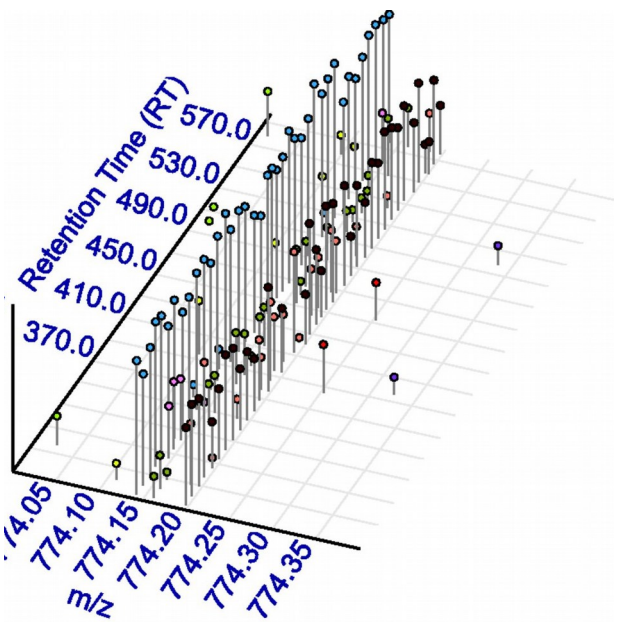
We developed a quality control web application that allows users to track over 300 quality metrics and alert them if performance is degrading.

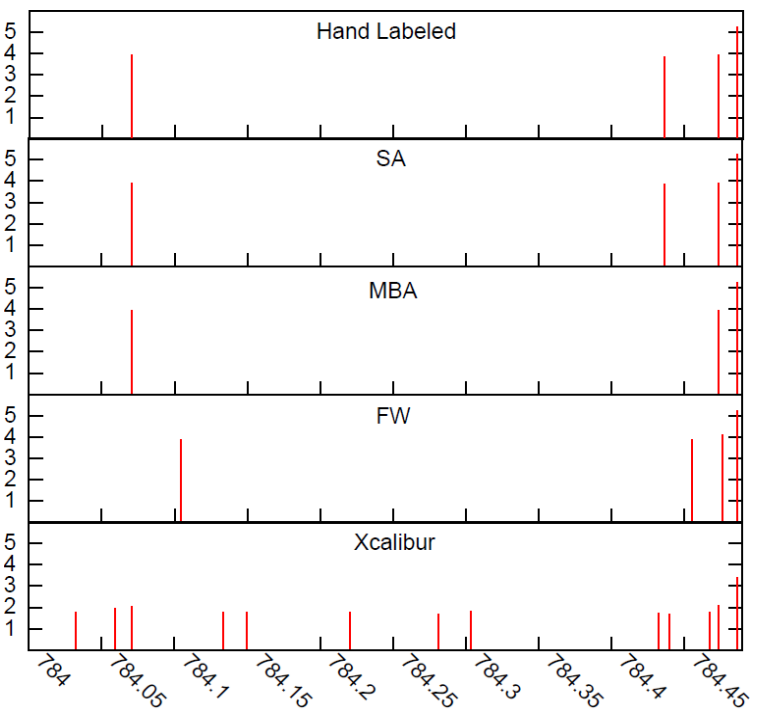


Taylor RM, Dance J, Taylor R, Prince JT. *Bioinformatics* **2013**.

We created software that is far more accurate at extracting lipid signals than current methods.

In collaboration with Dan Ventura and Rob Smith in Computer Science





Smith R, Anthonymuthu TS, Ventura D, Prince JT. *Bioinformatics*. **2013**.

Smith R, Ventura D, Prince JT. *Brief Bioinform.* **2013**.

Smith R, Ventura D, Prince JT. *Bioinformatics.* **2013**.

In order to dramatically boost the number of lipids that we can identify, we are developing software to predict how a lipid will fragment inside a mass spectrometer. As a first step, we developed a high-level chemistry library to help us model lipid fragmentation with greater ease.

In collaboration with Dan Ventura and Rob Smith in Computer Science

Draw

```
mol = Rubabel["NCC(O)C(=O)O"]
mol.write("file.svg")
```

Add

```
mol = Rubabel["OCC"]
# adds a carbon, then an oxygen to the previous carbon
mol << 6 << 8    # #<Mol "OCCCO">
mol << :C << :O  # same thing
```

Search

```
mol = Rubabel["NCC(O)C(=O)O"]
mol.each_match("CO") do |match|
  # match is just an array of atoms that matched
  match.first.el # => :C
  match.last.el # => :O
end
```

Split

```
bonds = mol.matches("CO").map {|c, o| c.get_bond(o) }
mol.split(*bonds)  # splits between every carbon single bonded to oxygen
```

Smith R, Williamson R, Ventura D, Prince JT. *Journal of Cheminformatics*. **2013**

Our software is now allowing us to predict how lipids will fragment in a mass spectrometer. We correctly predicted all the green peaks for this glycero-phosphoglyceride. Just this last month we modeled the rearrangement events that allow us to predict the two fragments pointed to in red.