Selecting and planning for the right mass spectrometer

MSACL US 2018
Palm Springs, CA

Wednesday, January 24th

Deborah French Ph.D., DABCC, FACB
University of California San Francisco
Learning Objectives

After this presentation, you should be able to:

- explain what specifications are important to consider when selecting a mass spectrometer

- explain what ancillary components are required for installation of a mass spectrometry system
Overview

- factors to consider when choosing instrumentation
- which type of instrument do you require?
- what else do you need?
- what resources are available?
Audience Poll

Have you used mass spectrometry before?

A. yes

B. no
Audience Poll

Are you

A. considering mass spectrometry for your lab?

B. in the process of bringing in mass spectrometry?

C. expanding existing mass spectrometry testing?
Initial factors to consider when choosing instrumentation

- what do you actually need for the applications you wish to implement?
  - analytes you wish to measure
  - quantitative vs qualitative methods
  - targeted vs untargeted methods
  - accurate mass determination required
  - sensitivity
  - throughput
  - robustness requirements
Initial factors to consider when choosing instrumentation (cont)

- what expertise do your technologists possess?
  - mass spectrometer has to be optimized for every single analyte you want to measure
  - not a “plug and play” technology

- what is the cost – direct and indirect – of implementation?
What are the components of a mass spectrometry system?

- **Ionization**
  - **Ion Source**: Components of sample are ionized (become charged)

- **Mass Sorting**
  - **Mass Analyzer**: Ions separated by mass (m) to charge (z) ratio (m/z)

- **Detection**
  - **Ion Detector**: Detects ions

**Inlet**
- Sample is introduced into mass spectrometer (e.g. liquid or gas chromatography, matrix-assisted laser desorption)

**Data Analysis**
Mass Analyzers

Types of mass analyzers:

- single quadrupole
- triple quadrupole
- quadrupole ion trap
- time of flight/quadrupole time of flight
- fourier transform ion cyclotron resonance (FTICR)
Single quadrupole mass spectrometer

- only ions of desired mass to charge ratio reach detector when using optimized voltages for analyte of interest
- all analytes with that mass will be detected
- can also scan across a mass range by varying voltages
- not as specific as other instruments
Triple quadrupole mass spectrometer

- Components of sample become charged
- All ions
- Precursor ion selection
- Sample ions of selected mass
- Product ions from selected precursor ion
- Product ion selection/full scan
- Sample inlet from liquid chromatography
- Detection and recording of fragment ions

Q1. Ions of interest are selected (precursor/parent ions)
Q2. Fragmented into smaller product ions
Q3. Product ions separated by mass (m) to charge (z) ratio (m/z)

- Also known as a tandem mass spectrometer (MS/MS)
- Very selective so best for quantitative analysis
- Poor scanning capabilities
Quadrupole Ion trap mass spectrometer

- quadrupole used to generate a field that functions to “trap” ions without destroying them
- ideal for qualitative analysis and elucidation of ion structure
- not as useful for quantitative analysis due to capacity limitations of the trap
- can be used to produce product ion spectra if used with MS/MS
  - an extra layer of selectivity
How is triple quadrupole mass spectrometry commonly used in the clinical laboratory?

- small molecules
  - steroid hormones
    - testosterone, estradiol, 25-hydroxyvitamin D
  - thyroid hormones
    - free T4, free T3, T4, T3
- therapeutic drug monitoring
  - cyclosporine, tacrolimus, sirolimus, busulfan, voriconazole, posaconazole, ketoconazole, itraconazole
- toxicology
  - drug confirmations (opioids, amphetamines, cocaine metabolite etc), comprehensive drug screens
- proteins/peptides
  - thyroglobulin, insulin-like growth factor 1 (IGF-1)
High resolution mass analyzers
Time of flight MS (TOF-MS)

Sample inlet from liquid chromatography → Components of sample become charged → All ions → Reflectron → Detector

Quadrupole time of flight MS (QTOF-MS)

Sample inlet from liquid chromatography → Components of sample become charged → All ions → Reflectron → Detector

Q1  /  Q2
Fourier transform ion cyclotron resonance MS

- FTICR-MS (Orbitrap technology uses similar principles)

- Ions trapped in a cell inside a strong magnetic field and move in circular orbits in a plane perpendicular to magnetic field.

- RF electrical potential is applied to transmitter plates causing trapped ions to be excited into larger circular orbits.

- Frequency of motion of ion is inversely proportional to its mass.
How is high resolution mass spectrometry commonly used in the clinical laboratory?

- toxicology
  - comprehensive drug screens
- microbiology (with MALDI ionization source)
  - identification of bacteria, fungi and mycobacteria
- proteins/peptides
  - thyroglobulin, insulin-like growth factor 1 (IGF-1)
Which type of instrument do you require?

<table>
<thead>
<tr>
<th></th>
<th>LC-MS</th>
<th>LC-MS/MS</th>
<th>LC-TOF-MS</th>
<th>LC-QTOF-MS</th>
<th>FTICR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Resolution</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>Mass Accuracy</td>
<td>~0.1 units</td>
<td>~0.1 units</td>
<td>~0.01 units</td>
<td>~0.01 units</td>
<td>~0.0001 units</td>
</tr>
<tr>
<td>Operational difficulty</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Suited for which</td>
<td>Targeted Quant</td>
<td>Targeted Quant</td>
<td>Targeted or untargeted Qual</td>
<td>Targeted or untargeted Quant</td>
<td>Targeted or untargeted Quant</td>
</tr>
<tr>
<td>Applications?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>$$</td>
<td>$$$-$$$$$</td>
<td>$$</td>
<td>$$$$</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

DO NOT FORGET THE COST OF A SERVICE CONTRACT - SIGNIFICANT $$$

(Quant: quantitative analysis; Qual: qualitative analysis)
Problem solving

Your lab manager has asked you to develop a method to quantify total testosterone by mass spectrometry in pediatric and female patients.

What type of mass spectrometer would be best suited for this application?

A. TOF
B. FTICR
C. MS
D. MS/MS
Other considerations for implementing mass spectrometry

- mass specs are heavy! and large!
- and they generate heat

- need to move cabinets?
- electrical supply
- gas supply - nitrogen, argon
- exhaust
- UPS or back up power
- roughing pump and oil (and disposing of oil)
Other considerations for implementing mass spectrometry (cont)

- mass spectrometry vendor should be able to give you a site guide documenting the requirements for the instrument

- optional (but really nice!) - interface between mass spectrometer and laboratory information system

All of these components can add $$$ to the cost of implementation!
What resources are available?

- colleagues already running mass spectrometry methods
  - invaluable resource
  - can give you “real world” experience with instrumentation
- mass spectrometry vendors
- attend conferences specializing in mass spectrometry
  - e.g. MSACL, ASMS, AACC/MSSS
- literature search
  - can see what instrumentation other clinical laboratories use to measure specific analytes in clinically relevant concentration ranges
Conclusions

- make a list of what your laboratory needs ahead of time with regards to sensitivity, robustness, throughput etc

- mass analyzers vary in specificity, sensitivity, cost and ease of use - should be chosen wisely in terms of desired applications

- don’t forget the “extras” such as gas and electrical supply, exhaust, service contract etc as the cost is significant
References/Resources

- Clinical and Laboratory Standards Institute (CLSI). *Mass Spectrometry in the Clinical Laboratory: General Principles and Guidance; Approved Guideline*. CLSI document C50-A
- French D, Terrazas E. *The successful implementation of a licensed data management interface between a Sunquest laboratory information system and an AB SCIEX mass spectrometer*. J. Pathol. Inform. 2013. 4:1

- [https://www.aacc.org/publications/cln/articles/2015/february/implementing-mass-spec-part-one](https://www.aacc.org/publications/cln/articles/2015/february/implementing-mass-spec-part-one)
- [https://www.aacc.org/publications/cln/articles/2015/may/implementing-mass-spectrometry-in-the-clinical-lab](https://www.aacc.org/publications/cln/articles/2015/may/implementing-mass-spectrometry-in-the-clinical-lab)
Deborah French
University of California San Francisco
Email: deborah.french@ucsf.edu