

# Intro to MS & Mass Analyzers 1: Time-of-flight Mass Spectrometry

CU- Boulder

CHEM-5181

Mass Spectrometry & Chromatography

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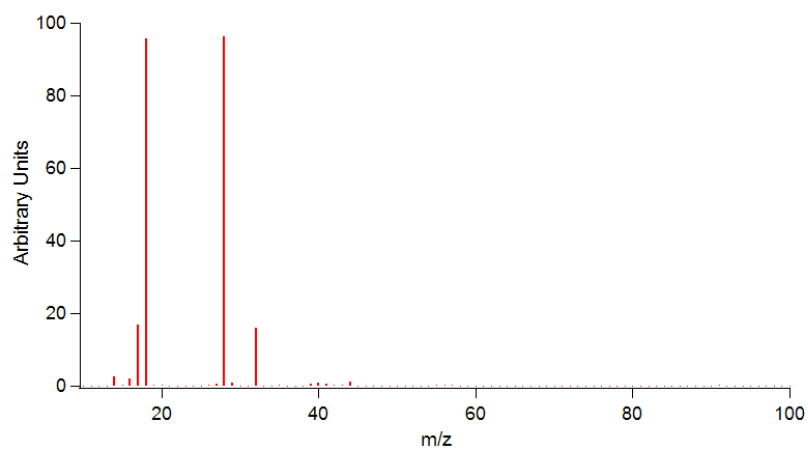
Lecture Slides adapted from 2007 lecture by Dr. Joel Kimmel, CU-Boulder

## Business Items

- Review calendar for labs
- Small change to pre-lab
  - Instead of matrices of CHCA, SA, DHB and *urea*, you will be using CHCA, SA, DHB and "*no matrix*".
- TOFMS HW assigned later today by email
  - Igor simulation of TOFMS
- Start looking for articles to present
  - 1<sup>st</sup> journal skim due on Thu next week

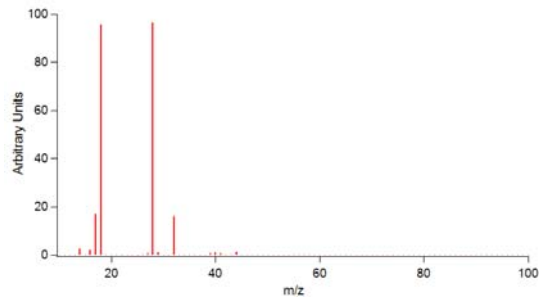
A mass spectrometer determines the mass-to-charge ratio ( $m/z$ ) of gas-phase ions by subjecting them to known electric or magnetic fields and analyzing their resultant motion.

## Mass Spectrum



Signal intensity vs mass-to-charge ratio

## m/z



The **mass-to-charge ratio** is often referred to as **m/z** and is typically considered to be unitless:

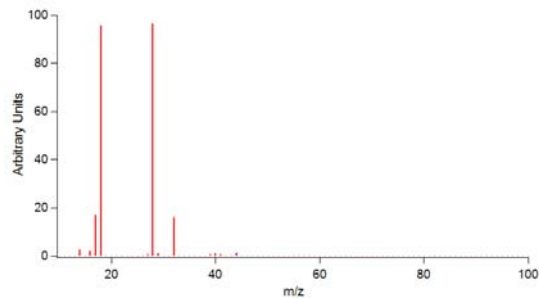
**m**: the mass number = atomic mass/u      ( $u = 1/N_A \text{ g}$ )

**z**: the charge number =  $Q/e$       ( $e = 1.6022 \times 10^{-19} \text{ C}$ )

The **Thompson** has been proposed as a unit for m/z, but is only sometimes used.

Historically, most ions in MS had  $z = 1$ , which is likely the cause for the confusion in units. But, due to new ionization techniques, this is no longer true.

## Signal Intensity



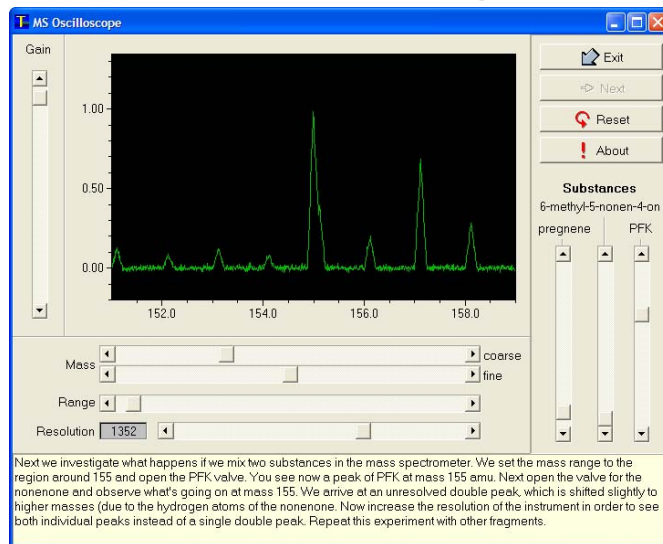
Depending on the type of mass spectrometer, ions may be detected by direct impact with a detector or by monitoring of an induced current image.

**Recorded signal can be measured in:**

- Counts per unit time (Digital)
- Voltage per unit time (Analog)
- Power (Frequency domain)

To a first approximation, **relative signal intensity reflects relative ion abundance**

## MS Oscilloscope



[http://www.vias.org/simulations/simusoft\\_msscope.html](http://www.vias.org/simulations/simusoft_msscope.html)

An ion with  $m/z = m$  has charge equal:

- (a) 1 Coulombs
- (b)  $m$  Coulombs
- (c)  $1.6022 \times 10^{-19}$  Coulombs
- (d)  $e$  Coulombs
- (e) I don't know

- Early stages of MS:** Precise determination of atomic masses and isotope abundances.
- Last 50 years:** Shift towards analytical applications involving molecules of greater complexity
- Last 15 years:** Explosion of biological applications

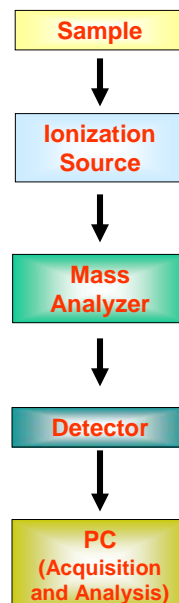
- 1897: J.J Thompson discovers electron and determines  $m/z$
- 1912: JJ Thompson constructs first mass spectrometer
- 1918: Demster develops electron ionization source
- 1942: First commercial instrument for organic analysis
- 1956: First GC-MS
- 1974: First HPLC-MS
- 1987: MALDI demonstrated; 1988 ESI Demonstrated; shared Nobel Prize in 2002

*See extended history in introduction of DeHoffmann*

## “A Universal Technique”

- Analysis by MS does not require:
  - Chemical modification of the analyte
  - Any unique or specific chemical properties
- In theory, MS is capable of measuring any gas-phase molecule that carries a charge
- Analyzed molecules range in size from  $H^+$  to mega-Dalton DNA and intact viruses
- As a result, the technique has found widespread use
  - Organic, Elemental, Environmental, Forensic, Biological, Reaction dynamics ...

**All experiments have this basic backbone, but range of applications implies a diversity of experimental approaches.**





“A mass spectrometer determines the mass-to-charge ratio ( $m/z$ ) of **gas-phase ions** by subjecting them to known electric or magnetic fields and **analyzing their resultant motion.**”

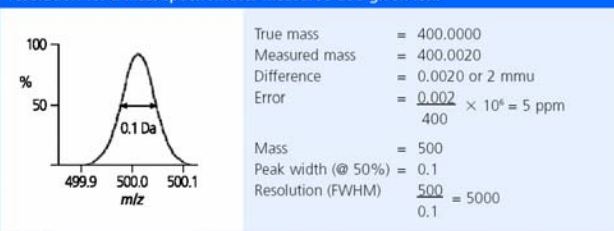
The **ionization source** imparts energy into the sample in order to drive (i) conversion to gas-phase (if necessary) and (ii) ionization of molecule

The **mass analyzer** manipulates the motion of the ions. **Requires vacuum!** (Consider mean free path)

Many systems will require **transport of gas-phase sample from atmospheric pressure to vacuum**, before or after ionizations step.

## Mass Analyzer Resolving Power

Figure 1: Mass accuracy determination and the FWHM method for determining resolution for a mass spectrometer measured at a given ion.



### Mass peak width ( $\Delta m_{50\%}$ )

Full width of mass spectral peak at half-maximum peak height

### Mass resolution / Resolving Power ( $m / \Delta m_{50\%}$ )

Quantifies ability to isolated single mass spectral peak

### Mass accuracy

Mass accuracy is the ability to measure or calibrate the instrument response against a known entity. Difference between measured and actual mass

Figure from: M. P. Balogh, *LC-GC Europe*, 17(3), 152–159 (2004)

Which of the following pairs requires the greatest mass resolving power to distinguish:

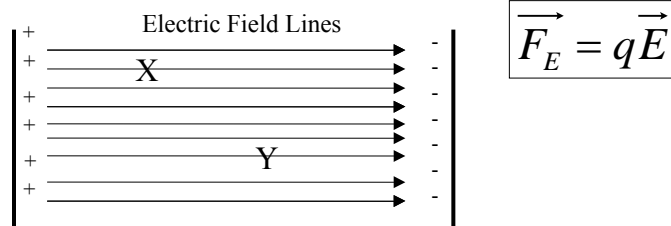
- (A)  $\text{Ar}^+$  from  $\text{Ar}^{2+}$
- (B)  $\text{CO}^+$  from  $\text{N}_2^+$
- (C)  $\text{CH}_3^+$  from  $\text{CDH}_2^+$
- (D) I don't know
- (E) I need a coffee

*Info:*

$\text{Ar} = 39.9623837 \text{ u}$ ,  $\text{C} = 12 \text{ u}$ ,  $\text{O} = 15.9949 \text{ u}$ ,  $\text{N} = 14.003 \text{ u}$ ,  
 $\text{H} = 1.007 \text{ u}$ , and  $\text{D} = 2.0141 \text{ u}$

## Ion Motion in Electrostatic Fields

- Electrical force on an ion:

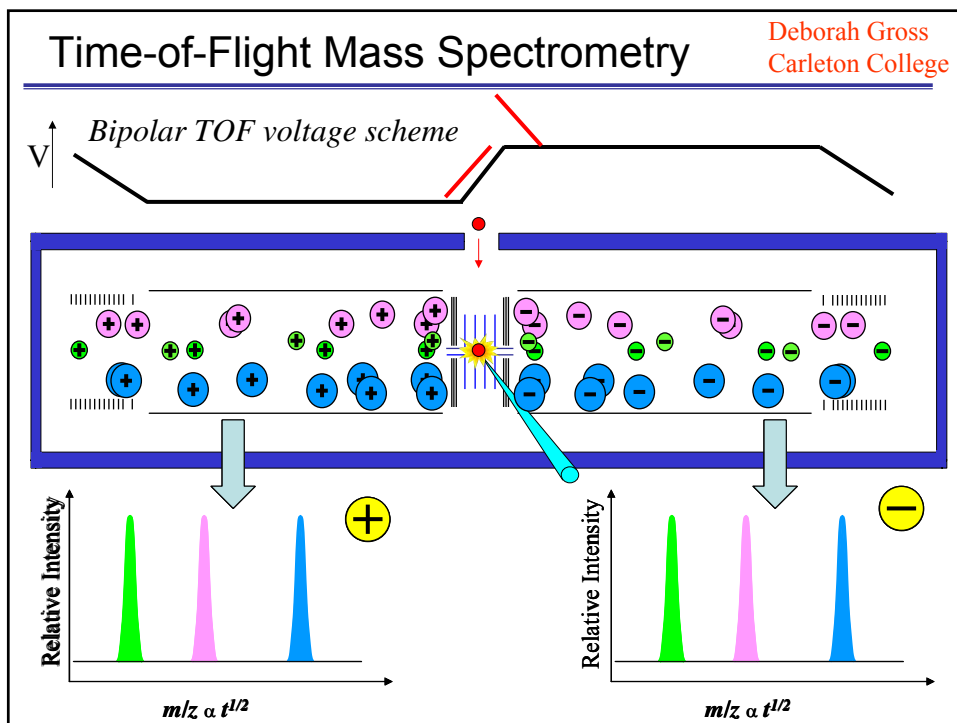


Q: Would ions originating at X and Y be arrive at negative surface at the same time?

- A. Yes
- B. X will arrive before Y
- C. Y will arrive before X
- D. I don't know
- E. I still need a coffee

# Types of Mass Analyzers

- **Time-of-flight (TOF)**
- Sector
  - Magnetic
  - Electric
- Quadrupoles
- Ion traps
- Orbitrap
- Ion-Cyclotron Resonance (ICR)
  - Fourier Transform (FTMS)
- Hybrids



# Time-of-Flight Mass Spectrometry

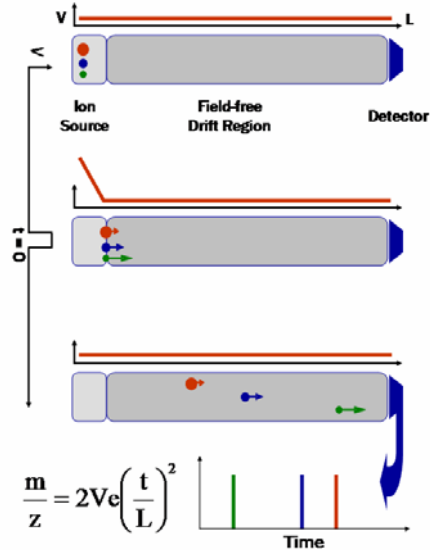
## To determine $m/z$ values

A packet of ions is accelerated by a known potential and the flight times of the ions are measured over a known distance.

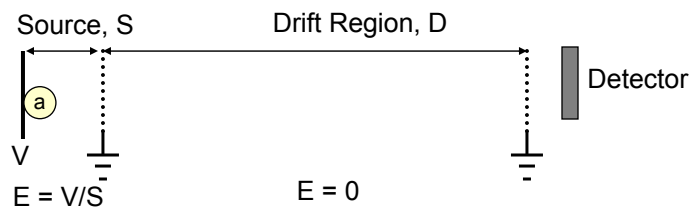
Q: What are  $V$ ,  $e$ , and  $z$ ?

## Key Performance Notes

- Based on dispersion in time
- Measures all  $m/z$  simultaneously, implying potentially high duty cycle
  - “Unlimited” mass range
  - DC electric fields
  - Small footprint
  - Relatively inexpensive



# TOFMS



$$U = qV_a = qEs_a$$

$$qEs_a = \frac{1}{2}mv_D^2$$

$$v_D = \sqrt{\frac{2qEs_a}{m}}$$

$$t_D = \frac{D}{v_D} = \frac{D}{\sqrt{2qEs_a/m}}$$

Ions accelerated by strong field,  $E$ , within short source region,  $S$ .

Drift times recorded across long, field-free drift region,  $D$ .

$v_D$  depends on starting position of ion – ideally all ions start from same plane.

Q: What else is ideally assumed ( $U_0$ ,  $E$ ,  $D$ , ...)?

Q: What figures of merit will non-ideality affect?

Drawing adapted from p20 of Cotter reference on next slide.

## Actual Picture More Complex

$$TOF = t_o + t_a + t_D + t_d$$

TOF = total recorded flight time of an ion

$t_o$  = Ion formation time after  $T_0$  of TOF measurement

$t_a$  = Time in acceleration region, which depends on initial position and initial energy

$t_D$  = Time in drift region, which depends on initial position and initial energy

$t_d$  = Response time of detector

For detailed discussion see: Guilhaus, *J. Mass. Spec.*, 1519, 1995.  
Cotter, "Time-of-flight Mass Spectrometry: Instrumentation and Applications in Biological Research," ACS, 1997.

## Resolution

For any  $m/z$  in a time-of-flight mass spectrum, the recorded peak will be the **sum of signals corresponding to multiple, independent, ion arrival events**

**Each ion arrival will be recorded at a unique TOF**, as determined by expression on previous slide

**TOF'**, which is the center of the peak in the mass spectrum, will be an average of all individual ion arrival TOFs

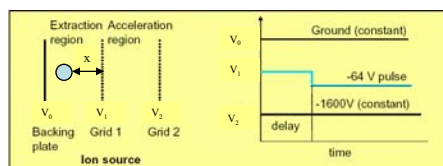
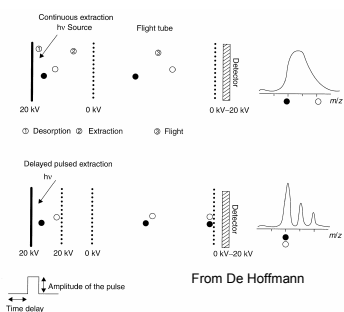
The width of TOF',  $\Delta t$ , will depend on the distribution of the individual ion arrival TOFs (and other factors ...)

$$R = \frac{TOF'}{2 \Delta t}$$

# Improving Resolution

- TOFMS was first commercialized in 1950s
- Early instruments had limited resolution
  - Speed of electronics
  - Energy distribution
- Recent “Renaissance ....”

## Delayed Ion Extraction / Time-Lag Focusing



Modified from Cotter:  
[http://www.hopkinsmedicine.org/mams/MAMS/middleframe\\_files/teaching\\_files/ME330.884/2005/MS2005-Lecture-5-Instrumentation.pdf](http://www.hopkinsmedicine.org/mams/MAMS/middleframe_files/teaching_files/ME330.884/2005/MS2005-Lecture-5-Instrumentation.pdf)

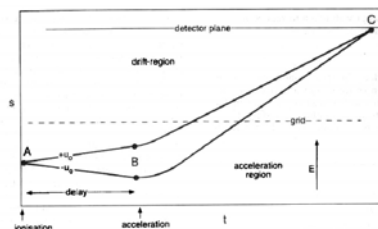
### Delay between ionization and extraction events.

At ionization:  $U = U_0$  (Initial Energy of Ion)

At exit of extraction:  $U = U_0 + E_{ext}xq$

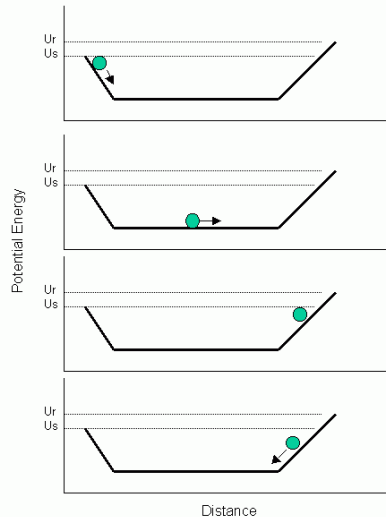
At beginning of drift:  $U = U_0 + E_{ext}xq + (V_1 - V_2)q$

Tune source voltages and/or delay to compensate for  $\Delta U_0$  and create space focus at detector. Mass dependent.

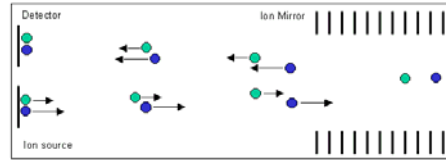


From Guilhaus, *J. Mass. Spec.*, 1519, 1995.

# Reflectron



From: <http://www.chemistry.wustl.edu/~msf/damon/reflectrons.html>



Reflectron consists of a series of electrodes, forming a linear field in direction opposite of initial acceleration.

Ions are slowed by this field, eventually turning around and accelerating back in direction of detector.

Penetration depth depends on  $U_s$ , which is function of  $U_0$  and acceleration field,  $E$ .

Reflectron voltages are tuned to create a space focus at the plane of the detector.

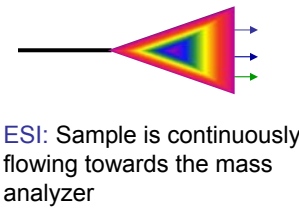
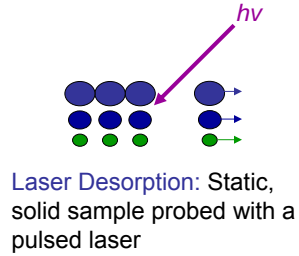
## Comparison of DE vs Reflectron

- In Delayed Extraction, we give ions different  $U$  to achieve same TOF.
- In Reflectron, ions possess different  $U$ . We force them to travel different  $D$  to achieve same same TOF

# An Inherent Dilemma

TOFMS is an ideal detector for pulsed ionization methods  
 If ionization event is synchronized with time zero, high duty cycle is achieved

Because of pulsing, ions are wasted when TOFMS is applied to a continuous source  
 &  
 Increased efficiency comes at the expense of mass range and mass resolution  
 Still, figures of merit and cost make the technique desirable



## Performance Trade-offs: On Axis

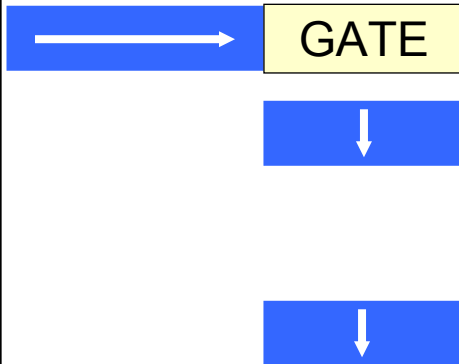


$$Duty Cycle \approx \frac{Sampling\ Time}{Sampling\ Time + Drift\ Time}$$

$\Delta t$  proportional to sampling time  
 Mass Range proportional to drift time



## Orthogonal Extraction

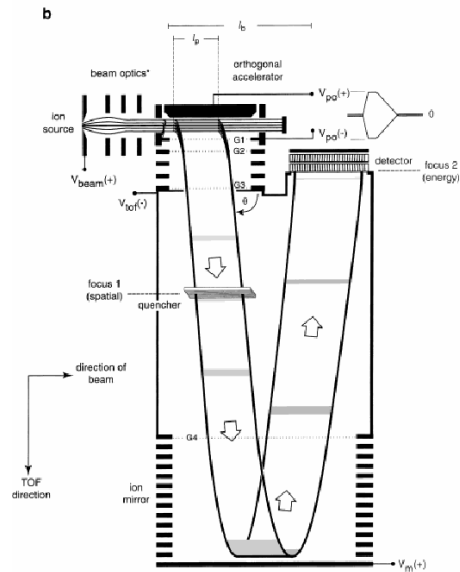


Ions are extraction in a direction orthogonal to source trajectory

Extraction event is still rapid ( $\Delta t$ ), but extraction volume is determined by length of gate region.

## oTOFMS

- Able to reduce average initial energy in ToF direction to 0 (resolution and accuracy).
- Independent control of beam energy and drift energy, allows maximum duty cycle.
- Want tightly collimated beam in extraction region



See: Guilhaus, *et al. Mass Spec Rev*, 2000, 65-107

## TOFMS Animation from Agilent:

<http://www.chem.agilent.com/en-us/products/instruments/ms/6210time-of-flightlcms/pages/gp10184.aspx>

