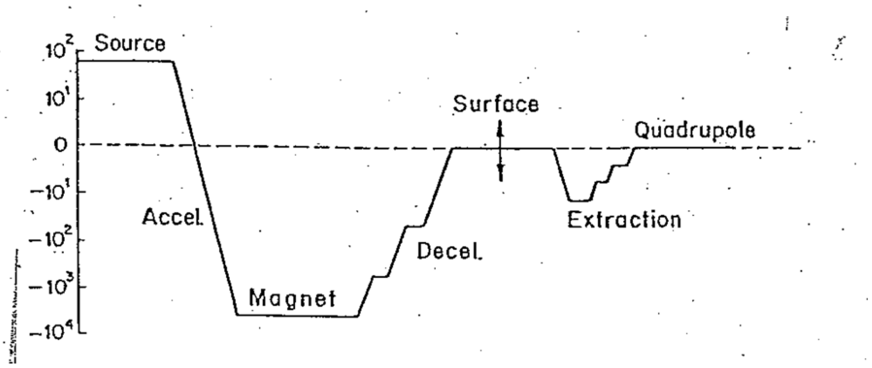
MS Short Course at Tsinghua
Lecture 8 – 9
Mass Analyzer and MS Instrumentation

Ion Optics

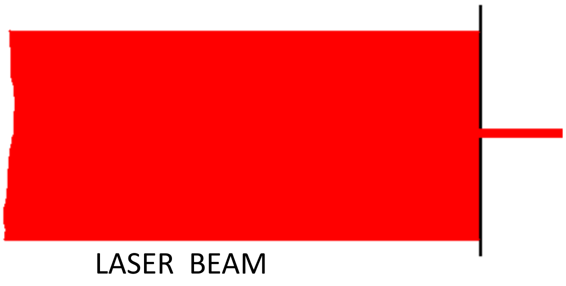
1. Potential along ion optical axis



2. Comparison with light optics

Same objective

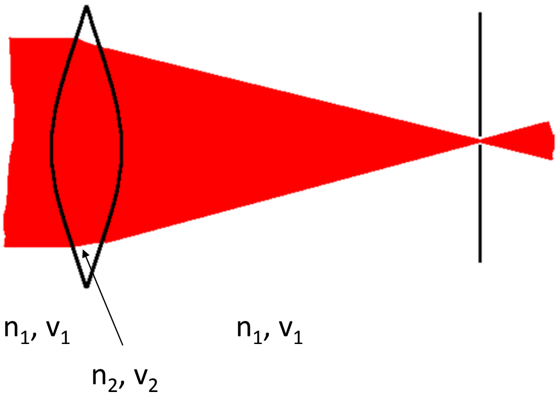
Shine laser onto small slit:



no focusing lenses

only small fraction of light makes it thru slit

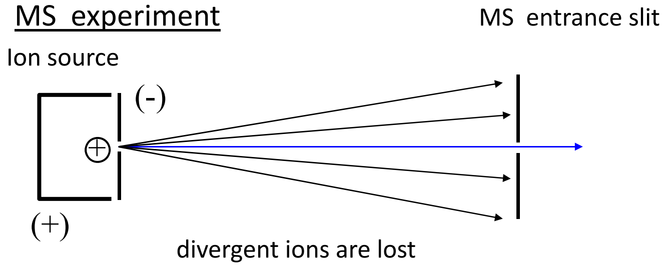
Use lens to focus beam into slit



velocity of beam changes inside lens

lens surface curved ⇒
off-axis rays are deflected and focused

MS experiment



Insert lens between source and slit

collimate divergent ions thru slit

improve transmission and sensitivity

set of metal lenses: circular apertures or cylinders
apply DC voltages to focus

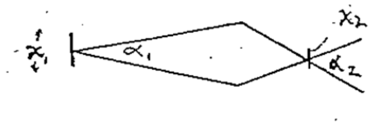
Objective	Optical Lens	Ion Lens
CHANGE VELOCITY	pass beam into medium of different density	pass beam thru region of different E field
DEFLECT BEAM	curve/tilt boundary of different media	curve/tilt potential contours

Conservation Theorem: Liousville's Theorem

Product x. α . υ = constant , x dimension, α angle and υ velocity

At constant velocity phase space x, α is constant, can only reduce size of image by increasing angle.

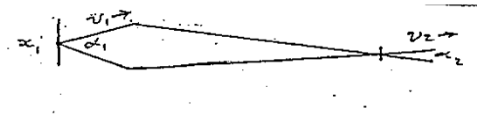
Aceleration is easiest way to focus (but many expts don't allow!)



$\alpha_2 > \alpha_1$
$x_2 < x_1$

If one focuses without change in energy it is necessarily done at expense of angular divergence [which means any error in position of image is magnified in image size]

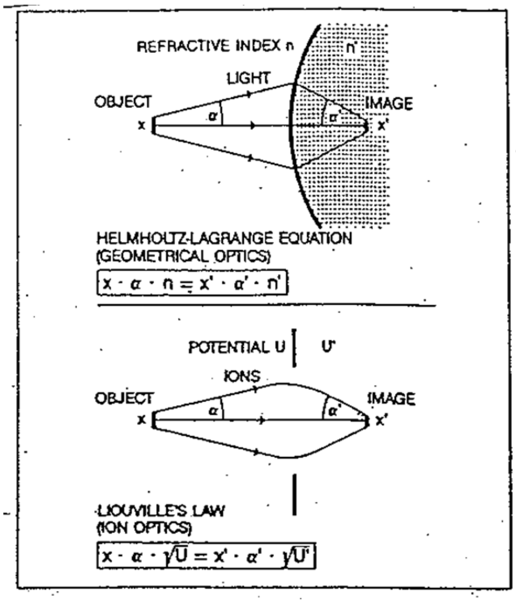
One can get good focusing ($x_2 < x_1$) without angular divergence only by acceleration beam:



$x_2 < x_1$
$\alpha_2 < \alpha_1$
$v_2 > v_1$

Post acceleration is part of high quality ion optics but it simply hides errors--the quality of the pre-accelerated beam the essential matter.

Helmholtz-Lagrange equation and Liouville's theorem



$$\boxed{x \cdot \alpha \cdot n = x' \cdot \alpha' \cdot n'}$$

$$\boxed{x \cdot \alpha \cdot \sqrt{U} = x' \cdot \alpha' \cdot \sqrt{U'}}$$

3. Electrostatic weak lenses

Field penetration produces curvature in equipotential lines, this second order effect is used for focusing: [fringe fields]

Immersion lens (two sections w. difference in potentials and hence velocities) not good for focusing. –necessarily chance KE

Electrostatic lenses are always convergent, never divergent as light, optic lenses often are. To get divergence in an optical lens one uses a "cross—over" which means one focuses the beam to a point, after which the trajectories diverge. The small spot on a tube is an image of a cross-over made near the cathode of the electrode gun.

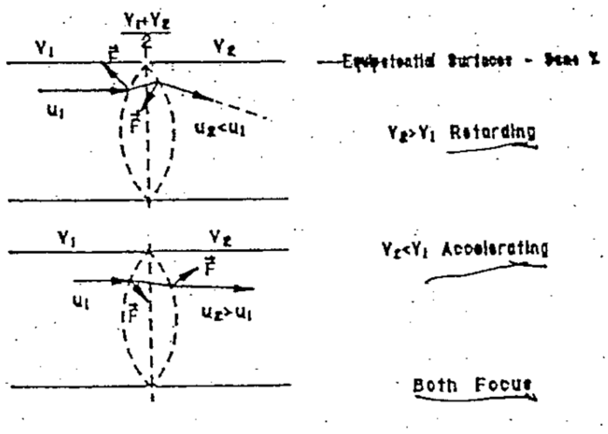


Fig. 11A

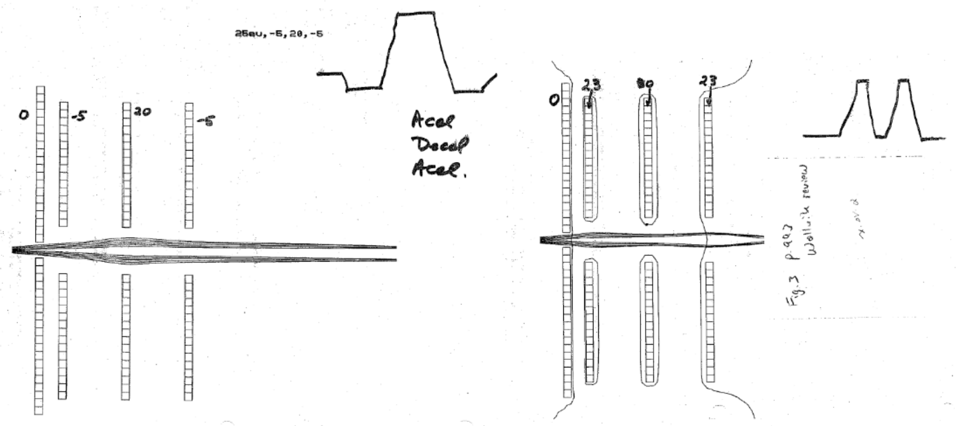
Thin Lens: Einzel lenses

Einzel = single

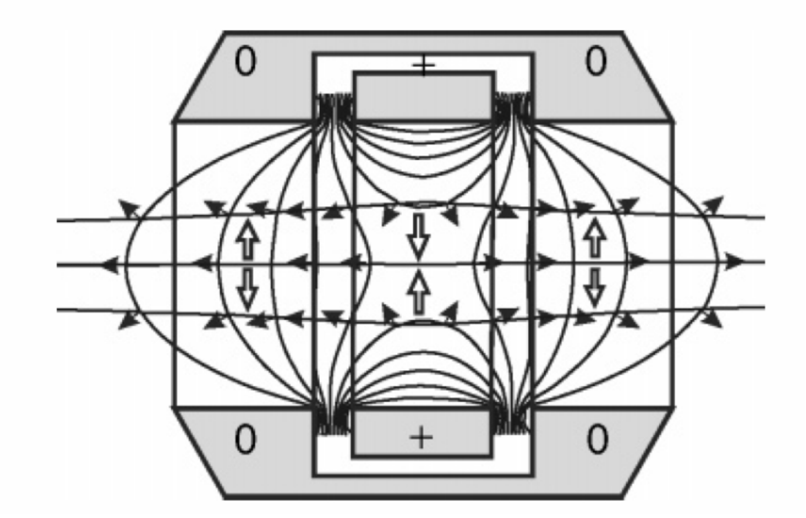
Good lens for focusing requires three lens elements this gives two lens element intersections which can be acel -- decel -- acel OR decel -- acel –decel

So even w/o changing overall energy of the beam there are strong potential changes which form the basis for the forces at right angles to beam direction which are basis for focusing.

As usual, there is no force on beam along ion optical axis.

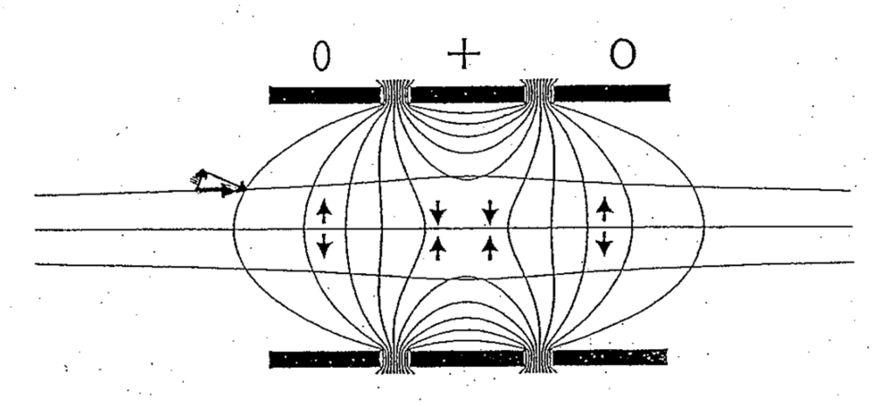


Thick Lens



Convergence

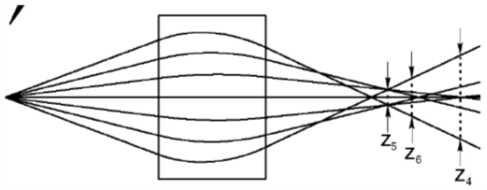
Electrostatic lens intersections are always convergent (unlike light optics) forces are always towards the ion optical axis



4. Aberrations in Ion Optics

Spherical- ions farther from axis cross at different pts than those near axis center (field strength)

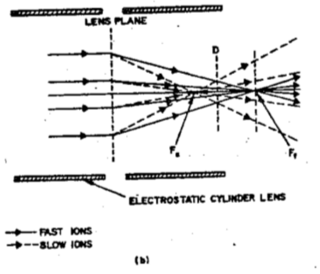
Solution:
- -skim off outer part of beam (lose ions)
- -keep lens diameter >> ion beam size



H. Wollnik, J. Mass Spectrom., *34*, 991-1006 (1999).

Chromatic- ions with different KE have different focal pts

Solution:
- -brute force (keep KE/∆KE large)

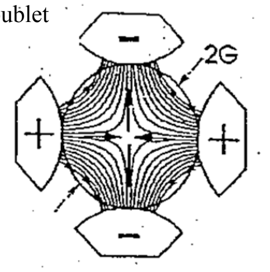


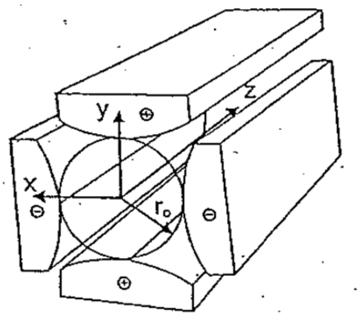
Thick and thin lenses
As stated.
Thin need higher potentials, might need surrounding potential defining screen, but use distance more effectively, allow pumping, etc

5. Strong focusing

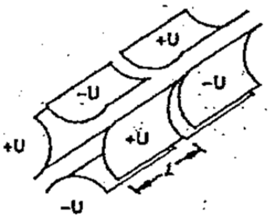
Weak focusing uses forces due to second order (fringe or lens element intersection) effects with no force in radial direction except due to fringe effects; strong focusing uses lens elements with radial forces directly proportional to distance from axis or higher.

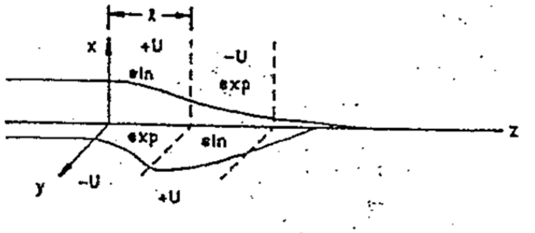
These forces will be focusing in one direction but will disperse in the other so a second lenses with opposite polarity is used to focus in the other
Most common case is a quadrupole doublet.
DC: 1quad of doublet
RF: 1 quad only





Combination of DC quadrupole provide flexibility in shaping/focusing the beam





This example illustrates a quad pair that leads to astigmatic focusing (focal points for x and y are not coincident on z)

3-element quad lens system with stigmatic focus

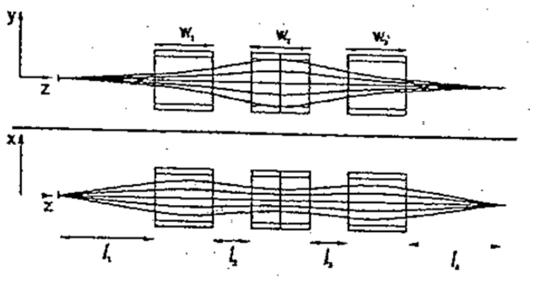
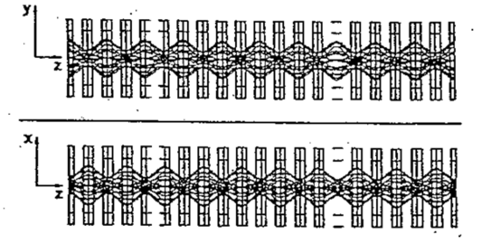
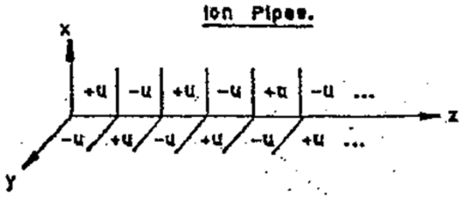
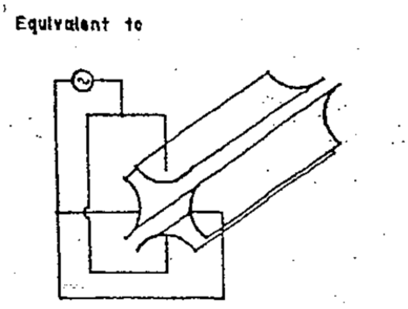


Figure 9 A quadrupole triplet that achieves stigmatic focusing (x/a) = (y/b) = 0 and a 1:1 magnification in both the x and y-directions, i.e. (x/x)(y/y)= -1. Note that the ion trajectories, that diverge from one point initially, are all parallel in the middle of the quadrupole triplet at which position the x, y beam envelopes differ considerably.

An ion pipe







Stable trajectories if $\frac{m}{e} \geq \frac{2u}{(3.78)^2 f^2 r^2}$

All multipoles consist of 2n
symmetrically arranged element
n=2 quadrupole
3 hexapole
4 octapole
5 decapole
6 dodecapole

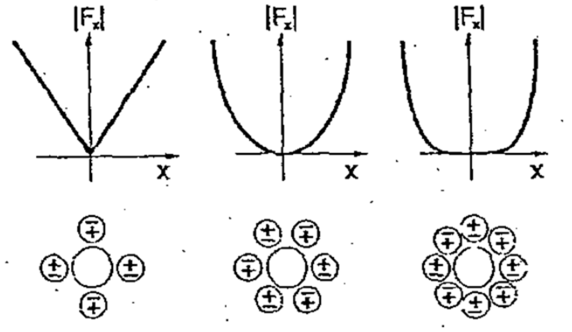
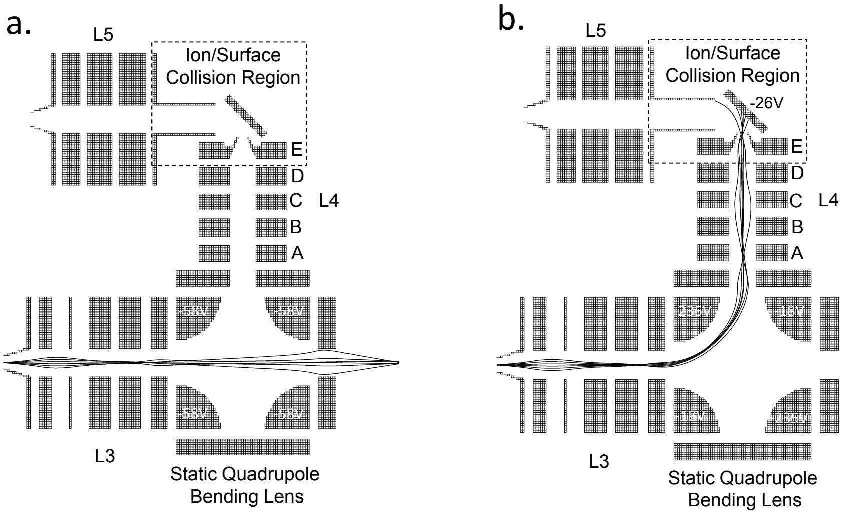
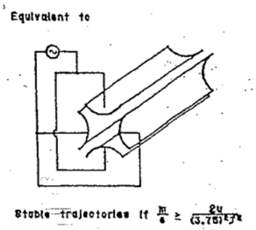


Figure 20. The absolute values of the back-driving forces *F* in the x-direction that ions experience in an electric quadrupole (2n=4*)*, hexapole (2n = 6) or octupole (2n= 8) are plotted as a function of the distance r from the optical axis.
All multipole devices exhibit a high pass filtering action

Static Bending lens
1. initialize ion beams with certain m/z, KE and dispersion angle, etc.
2. Use Einzel lens set 1 to focus the ion beam
3. Use reflection quadruple electrodes to bend the ion beam by 9O°
4. Use Einsel Lens set to focus the bent ion beam to get maximum output.

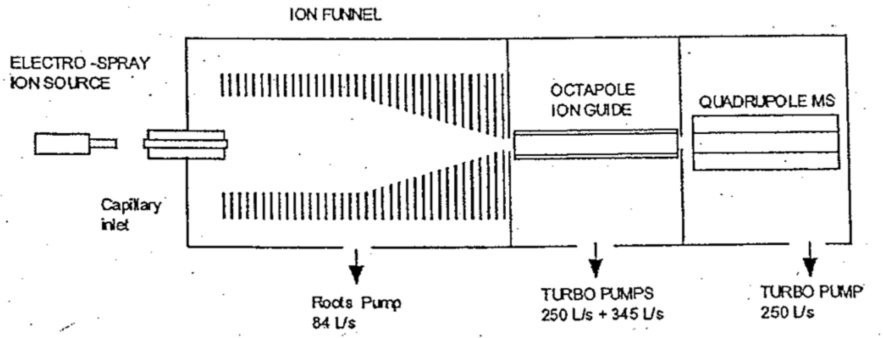


6. Electrical Dynamic Lens:



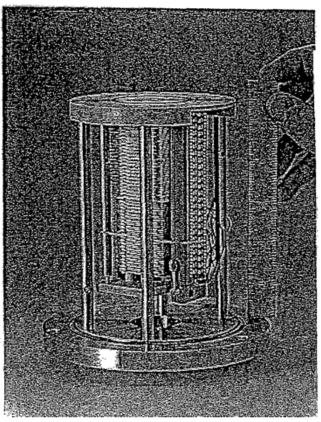
Ion funnel

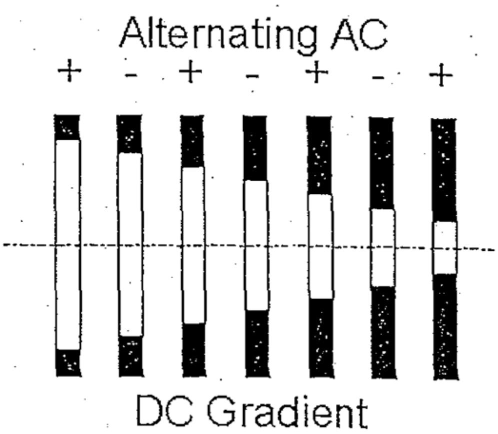
Deceleration, especially by large factor without defocusing is difficult; decal with strong focusing is very hard. Solution is the ion funnel.



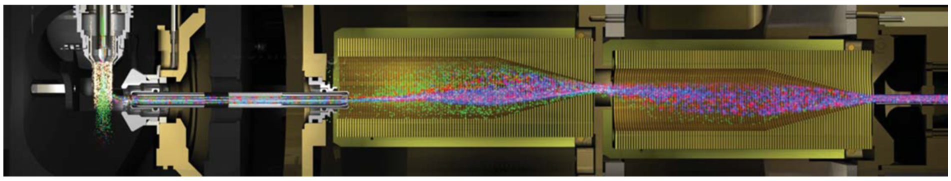
Schematic diagram of the ion funnel interface in the context of the overall instrumentation

PNNL

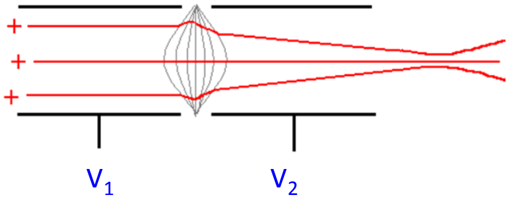




Agilent iFunnel



7. Space Charge- limits minimum beam diameter



+ ions repel each other
if beam current
too high

$$Force = \frac{eI_0}{2\pi\varepsilon_0 vr} = eE_r$$

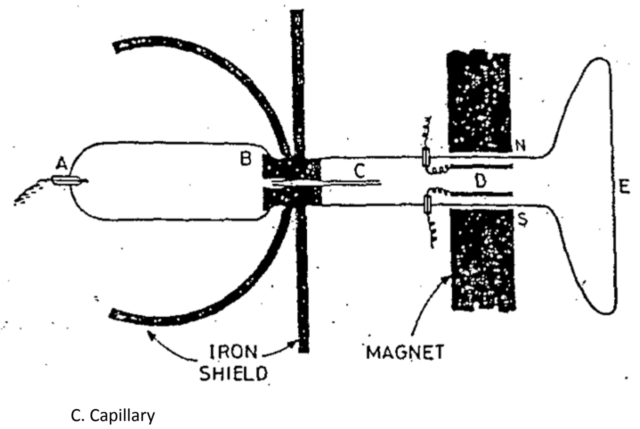
assume beam is cylindrical

Space charge increases with:

↑I_0
↓v
↓r

Mass Analyzers

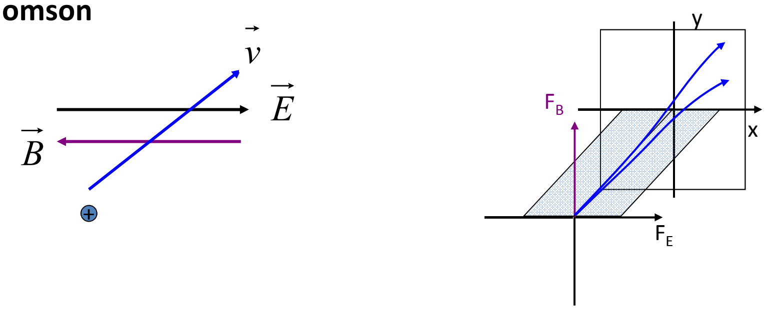
Thomson' apparatus



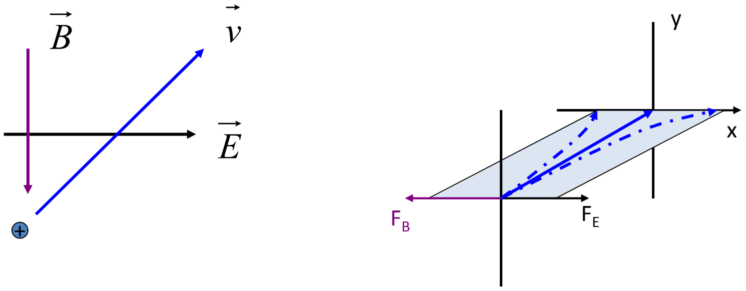
C. Capillary
B. Cathode
A. Al anode 20 kV
E. Detection (willenite) fluorescence o photoplate
Vacuum using rotary pump
Parallel B, E fields

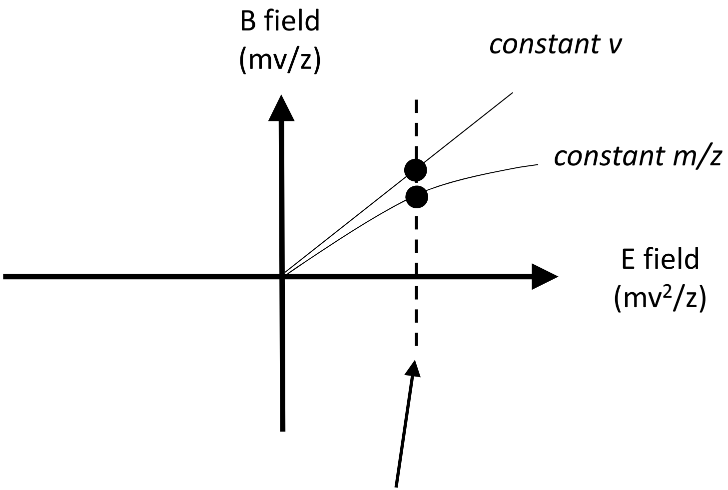
$$\vec{F} = q(\vec{E} + \vec{v} \times \vec{B})$$

Thomson



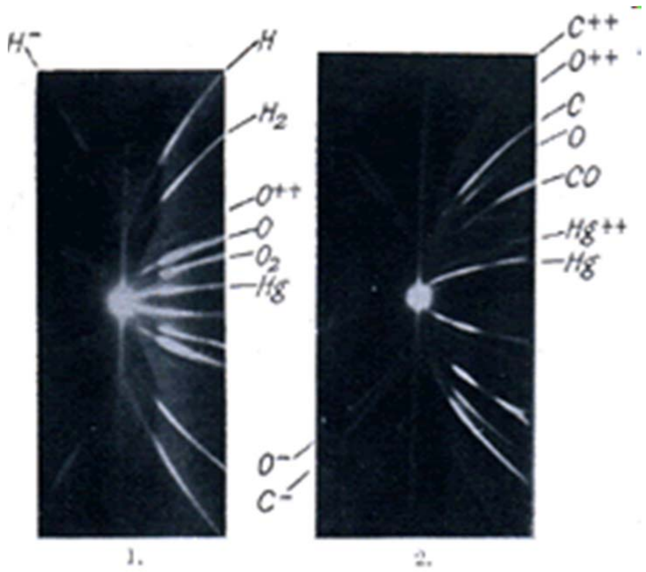
Wien





Constant KE/z
“mass” spectrum if all ions have same KE

Photo of Thomson's data



http://www.phy.cam.ac.uk/camphy/index.htm

Mass Analysis and Mass Analyzers

- The mass of a molecule cannot be directly weighed.
- The m/z value of an ion cannot be directly measured.

- Mass analysis is a gas phase separation of the charged particles.

- Separation in space –trajectory based MS analyzers
  - Sectors
  - Time of Flight
- Separation in motion frequency –Trap type MS analyzers
  - Quadrupole filter/ion trap
  - Ion cyclotron resonance (ICR)
  - Orbi-trap

Characteristics of Mass Analyzers

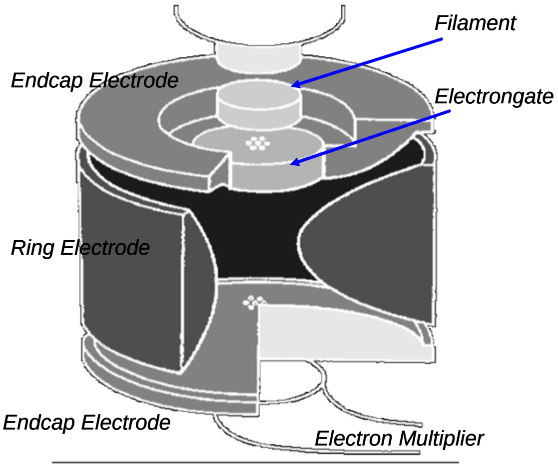
Method	Quantity measured	Mass/Charge range (Da/charge)	Resolution at 1000 (Da/charge)	Mass Accuracy at 1000 Da/charge	Dynamic range[b]	Operating Pressure (Torr)
Sector Magnet	Momentum / charge	10^4	10^5	<5 ppm	10^7	10^{-6}
Time of flight	flight time	10^6	10^3	0.01%	10^4	10^{-6}
Quadrupole ion trap	frequency	10^4-10^5	10^3-10^4	0.1%	10^4	10^{-3}
Quadrupole	filters for m/z	10^3-10^4	10^3	0.1%	10^5	10^{-5}
Cyclotron resonance	frequency	10^5	10^6	<10 ppm	10^4	10^{-9}
Orbi Trap	Frequency	10^5	10^6	<10 ppm	10^4	10^{-9}

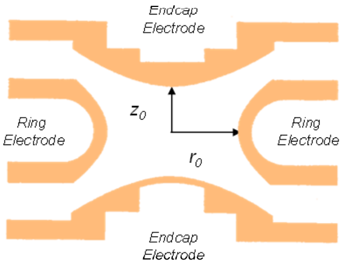
[a] Mass/peak width
[b] Number of orders of magnitude of concentration over which response varies linearly.

Quadrupole MS Filter and Quadrupole Ion Trap

1.Geometry of MS analyzer and Instrument Configurations

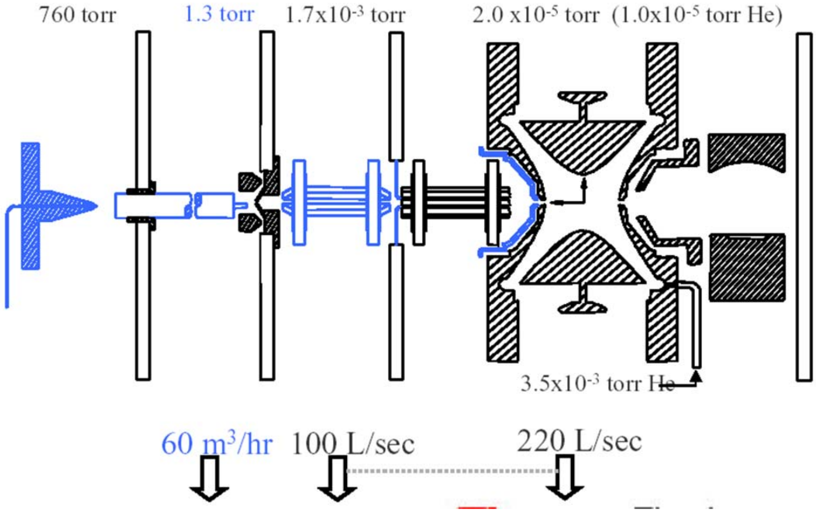
Geometry of ion trap/ internal EI



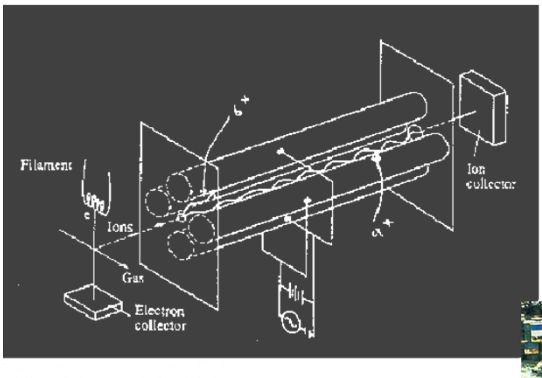


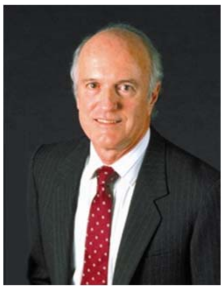
Instrument with atmospheric pressure ionization

Operating pressures and optics



Quadrupole Mass Spectrometer



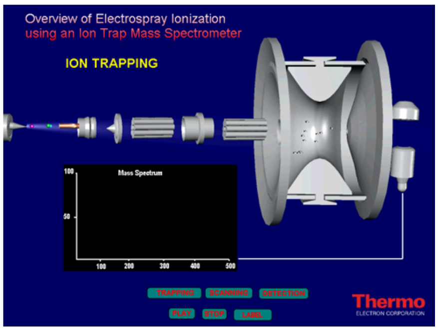


Finnigan

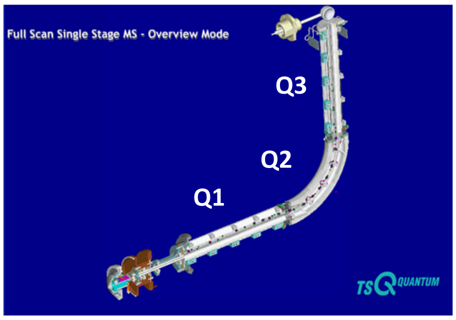
Valley of the Drums
Superfund Site

Quadruple
Mass Spectrometer

http://www.chm.bris.ac.uk/~paulmay/misc/msc/msc3.htm



Overview of Electrospray Ionization
using an Ion Trap Mass Spectrometer

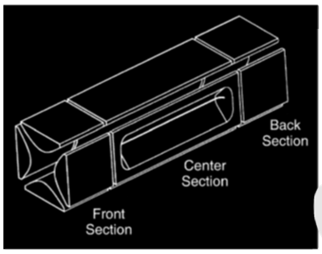


Full Scan Single Stage MS - Overview Mode

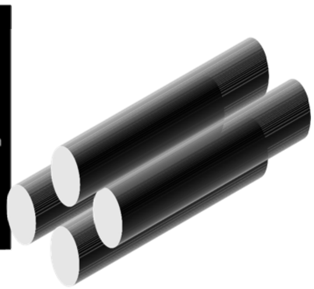
3D vs. Linear

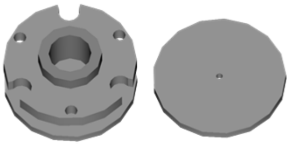
Paul Trap

Linear Trap

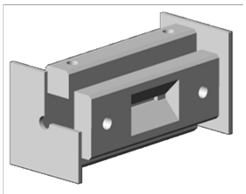


Quadrupole Filter



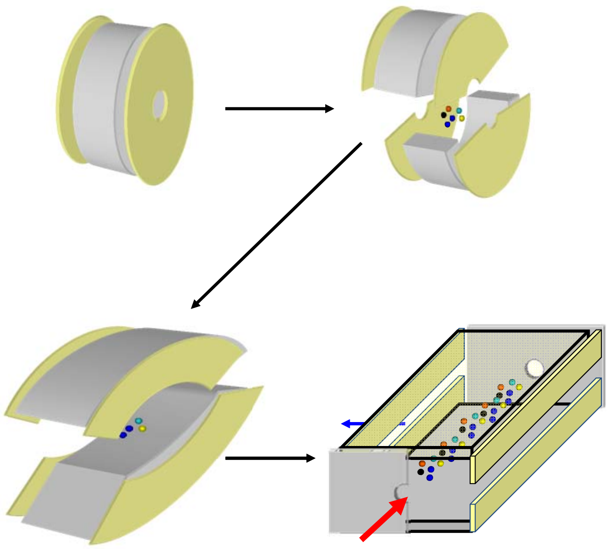


Cylindrical Ion Trap



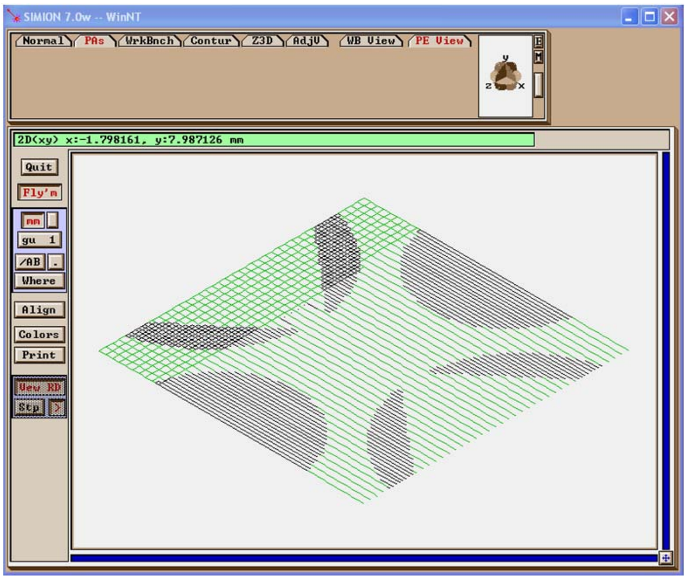
Rectilinear Ion Trap

3D vs Linear



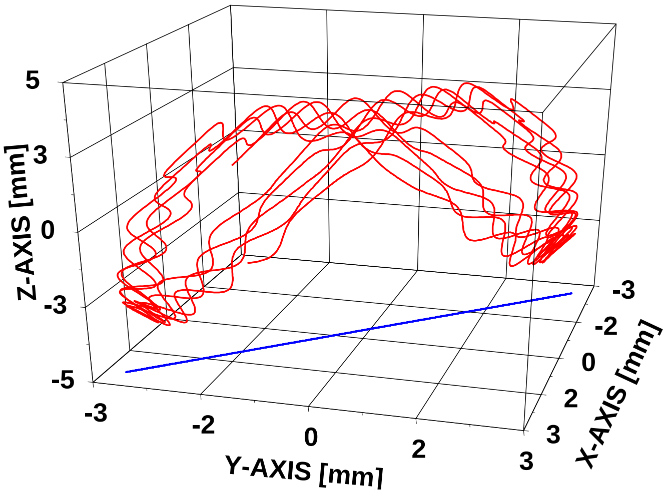
2. Theory

SIMION Simulation of Ion Trap RF Field



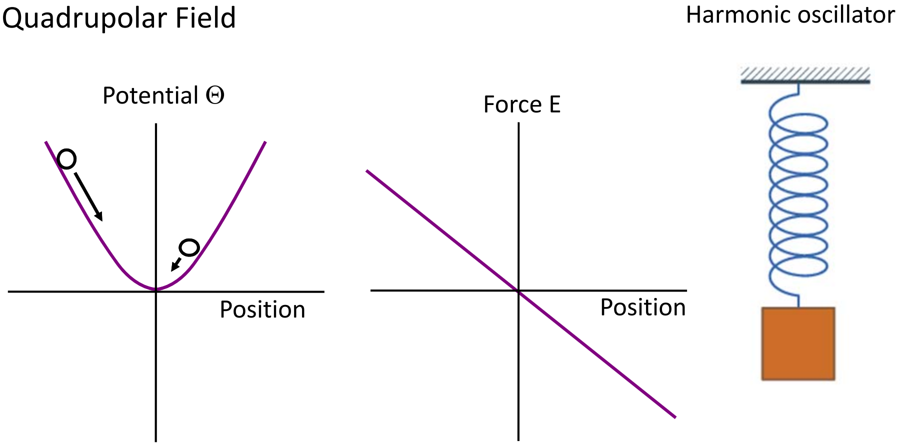
2D(xy) x:-1.798161, y:7.987126 mm

Ion Trajectory



Ion Trap RF Field

Quadrupolar Field



$$F = -kx \qquad \omega_0 = \sqrt{\frac{k}{m}}$$

Circular frequency is INDEPENDENT on the KE and Position of the ion.

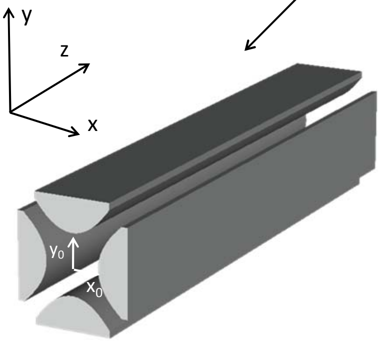
$$E = E_0(\lambda x + \sigma y + \gamma z) \qquad \nabla \bullet E = 0$$

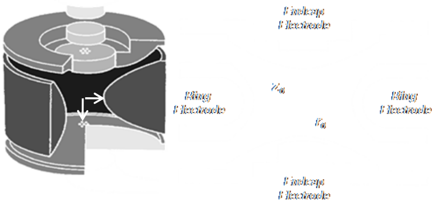
Laplace's equation

$$\lambda + \sigma + \gamma = 0$$

$$\lambda = -\sigma; \quad \gamma = 0$$

$$\lambda = \sigma; \quad \gamma = -2\lambda = -2\sigma$$





$$\Phi(x,y,t) = \frac{U + V\cos(\omega t)}{r_0^2}\left(x^2 - y^2\right)$$

$$\Phi(x,y,t) = \frac{U + V\cos(\omega t)}{2r_0^2}\left(r^2 - 2z^2\right)$$

Quadrupole filter

$$\Phi(x,y,t)=\frac{U+V\cos(\omega t)}{r_0^{\ 2}}\left(x^2-y^2\right)$$

3D Trap

$$\Phi(x,y,t)=\frac{U+V\cos(\omega t)}{2r_0^{\ 2}}\left(r^2-2z^2\right)$$

$$m\frac{d^2u}{dt^2}=\boxed{ma=F}=eE_u=e\frac{d\Phi}{du}$$

$$\frac{d^2x}{dt^2}+\frac{e}{mr_0^{\ 2}}(U-V\cos(\omega t))x=0$$

$$\frac{d^2y}{dt^2}-\frac{e}{mr_0^{\ 2}}(U-V\cos(\omega t))y=0$$

$$\frac{d^2z}{dt^2}-\frac{2e}{mr_0^{\ 2}}(U-V\cos(\omega t))z=0$$

$$\frac{d^2r}{dt^2}+\frac{e}{mr_0^{\ 2}}(U-V\cos(\omega t))r=0$$

$$a_u=a_x=-a_y=\frac{4eU}{mr_0^{\ 2}\Omega^2}$$

$$q_u=q_x=-q_y=\frac{2eV}{mr_0^{\ 2}\Omega^2}$$

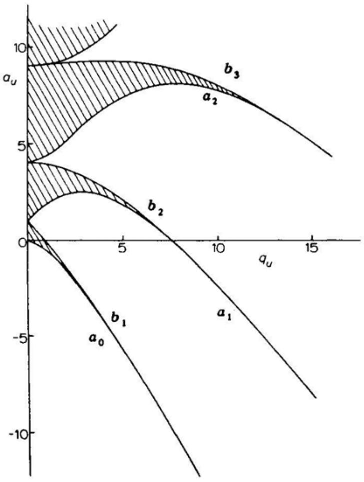
$$a_z=-2a_r=-\frac{8eU}{mr_0^{\ 2}\Omega^2}=-\frac{4eU}{mz_0^{\ 2}\Omega^2}$$

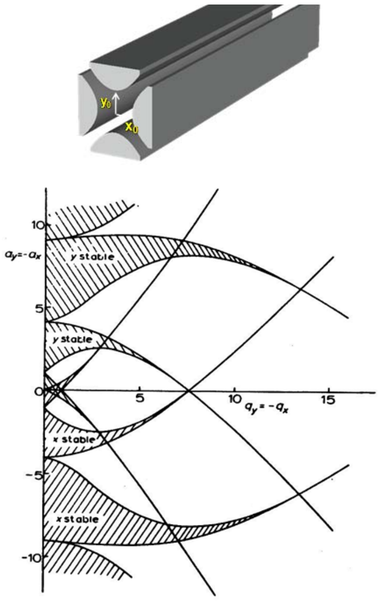
$$q_z=-2q_r=-\frac{4eV}{mr_0^{\ 2}\Omega^2}=-\frac{2eV}{mz_0^{\ 2}\Omega^2}$$

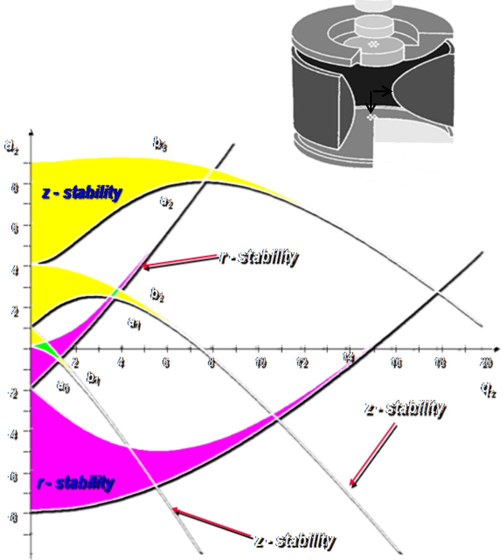
Mathieu equation

$$\frac{d^2u}{d\xi^2}+\left(a_u-2q_u\cos(2\xi)\right)u=0 \qquad \xi\equiv\frac{\Omega t}{2}$$

$$\xi\equiv\frac{\Omega t}{2}$$







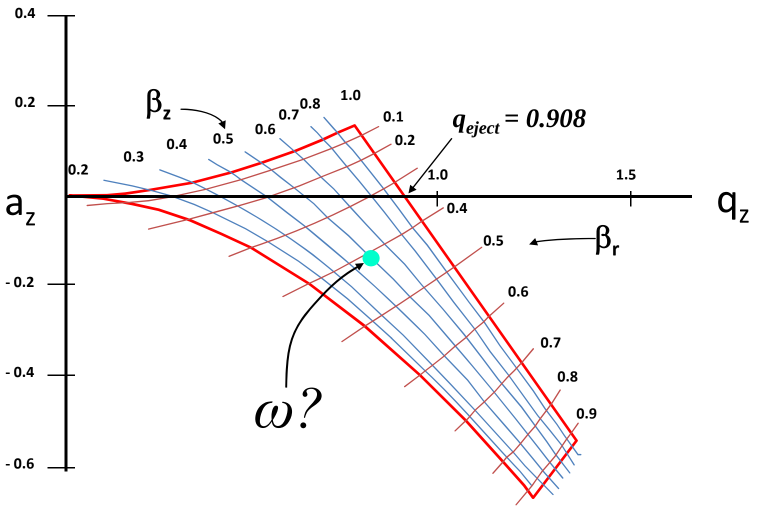
$$a_z=-2a_r=-\frac{8eU}{mr_0{}^2\Omega^2}=-\frac{4eU}{mz_0{}^2\Omega^2}$$

$$a_u=a_x=-a_y=\frac{4eU}{mr_0{}^2\Omega^2}$$

$$q_u=q_x=-q_y=\frac{2eV}{mr_0{}^2\Omega^2}$$

$$q_z=-2q_r=-\frac{4eV}{mr_0{}^2\Omega^2}=-\frac{2eV}{mz_0{}^2\Omega^2}$$

Mathieu Stability Diagram

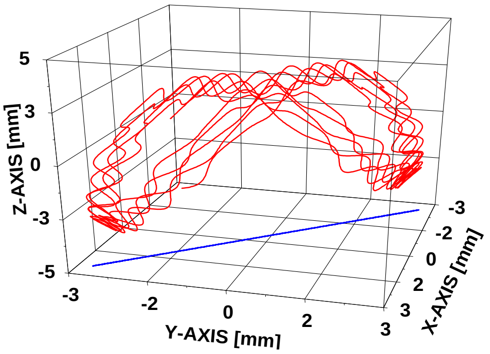


$$\beta_u^2 = a_u + \cfrac{q_u}{(\beta_u+2)^2 - a_u - \cfrac{q_u^2}{(\beta_u+4)^2 - a_u - \cfrac{q_u^2}{(\beta_u+6)^2 - a_u - \cdots}}} + \cfrac{q_u}{(\beta_u-2)^2 - a_u - \cfrac{q_u^2}{(\beta_u-4)^2 - a_u - \cfrac{q_u^2}{(\beta_u-6)^2 - a_u - \cdots}}}$$

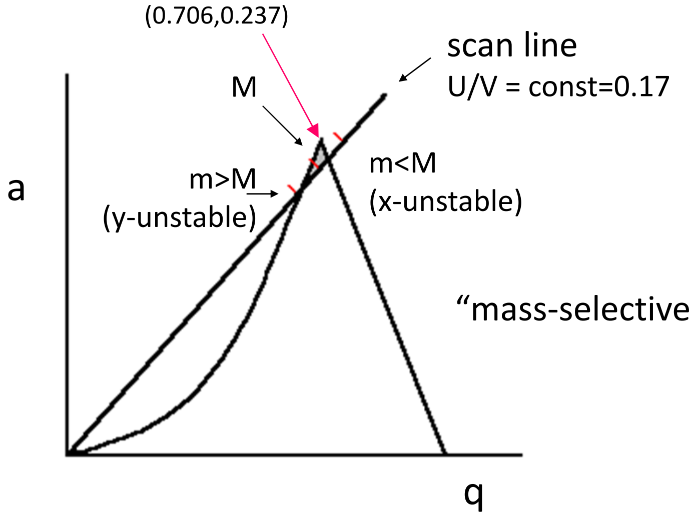
$$\beta_u \cong \sqrt{a_u + q_u^2/2}$$

(for q_u<0.4)

$$\omega_{n,u} = (2n \pm \beta_u)\frac{\Omega}{2}$$



3. RF and DC operation: Mass filter



$$a_u = \frac{4zeU}{m{r_0}^2\Omega^2}$$

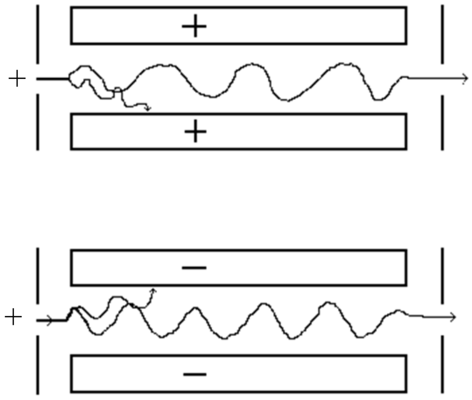
$$q_u = \frac{2zeV}{m{r_0}^2\Omega^2}$$

“mass-selective ***stability***”

*scan electronically, change stable m/z (1000 Th/s)

Filtering action

Positive Rods



M + heavier ions

(*high pass filter)*

M + lighter ions
(travel greater distance
during RF cycles)
(*low pass filter)*

Negative Rods

RF: light ions follow and are made unstable (when RF>DC) = high pass
DC: heavy ions made unstable (inertia) = low pass

Mass Filter - Mass range

$$q_{\max} = \frac{4zeV_{\max}}{mr_0^{\ 2}\Omega^2} = 0.706$$

$$\left(\frac{m}{z}\right)_{\max} = \frac{4eV_{\max}}{(0.706)r_0^{\ 2}\Omega^2}$$

- •Increase V- practical limits
- •Decrease r_0- practical limits
- •Decrease Ω- easy, but affects resolution

$$\left(\frac{m}{\Delta m}\right) \propto (\#cycles)^2$$

increase length, but then have mechanical limits

Quad calcs:

1) time of flight: m/z 100; 10 eV (= $1.602\text{x}10^{-18}$ J); L=20 cm

$E=0.5mv^2= 0.5m\,(d/t)^2$

$$t = d\sqrt{\frac{m}{2E}} = (0.2)\sqrt{\frac{1.66\times10^{-25}}{2*1.602\times10^{-18}}} = 45 \ \mu\text{s}$$

2) mass range (example is an Extrel quad)

f= 880 kHz $\Rightarrow$ Ω= (2πf)= $5.529\text{x}10^6$

V_{max}= 3600 V_{0p}

r_0= 4.14 mm

$$\left(\frac{m}{z}\right)_{\max} = \frac{4eV_{\max}}{(0.706)r_0^{\;2}\Omega^2} = \frac{4(1.602\times10^{-19})(3600)}{(0.706)(0.00414)^2(5.529\times10^6)^2}$$

=$6.236\text{x}10^{-24}$ kg/molecule = 3755 Da

Quad calcs:

2) mass range (example is an Extrel quad)

f= 880 kHz $\Rightarrow$ Ω= (2πf)= $5.529\text{x}10^6$

V_{max}= 3600 V_{0p}

r_0= 4.14 mm m/z max= 3755 Da

How much DC is needed?

$$U = a_u \frac{m}{z}\frac{r_0^{\;2}\Omega^2}{8e} = (0.237)(\frac{3755}{1000}\frac{1}{6.023\times10^{23}})\frac{(0.00414)^2(5.529\times10^6)^2}{8(1.602\times10^{-19})}$$

U = 604 V

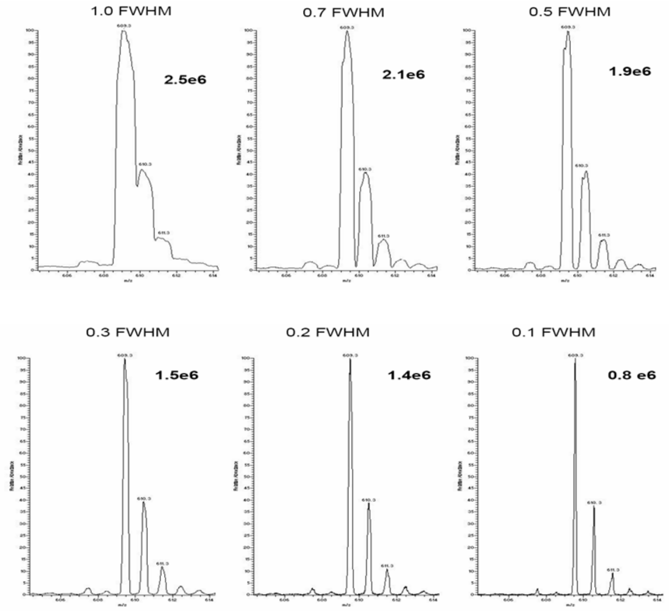
Quad (mass filter) Resolution

Resolution depends on (# cycles)^2

Trade-off between transmission and resolution (acceptance angle)

Mechanical limits: non-ideal fields (round rods)
rod alignment
fringing fields

Mass Filter - Mass resolution, intensity and peakshape



Quadrupoles

- 3 types: DC only, RF only,
  RF/DC (mass-selective stability)

- beam-type instrument

- Resolution controlled electronically (U/V scan)

- Resolution $\propto$(# cycles)^2

- m/z linear with U and V

- Focusing properties

Performance of Quadrupoles

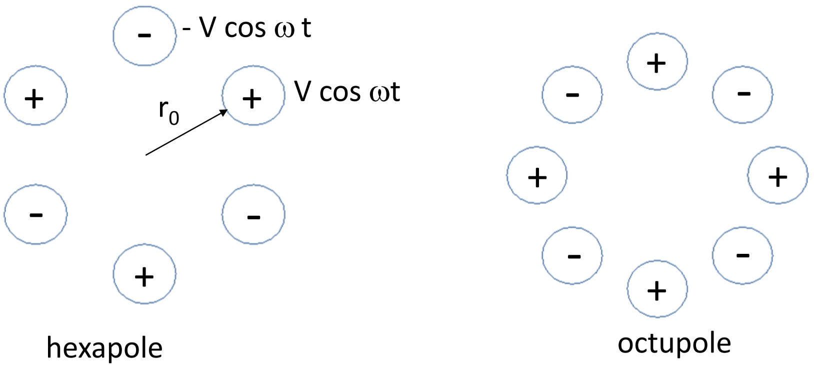
- R= 10^2-10^4
- 100 ppm accuracy
- m/z range <10,000
- LDR: 10^7

- Efficiency: <1-95%
- Speed: 1-20 Hz

- Ionizer: continuous
- Cost: low
- Size: benchtop

Very common mass analyzer

4. Higher order multipole ion guides (rf only)

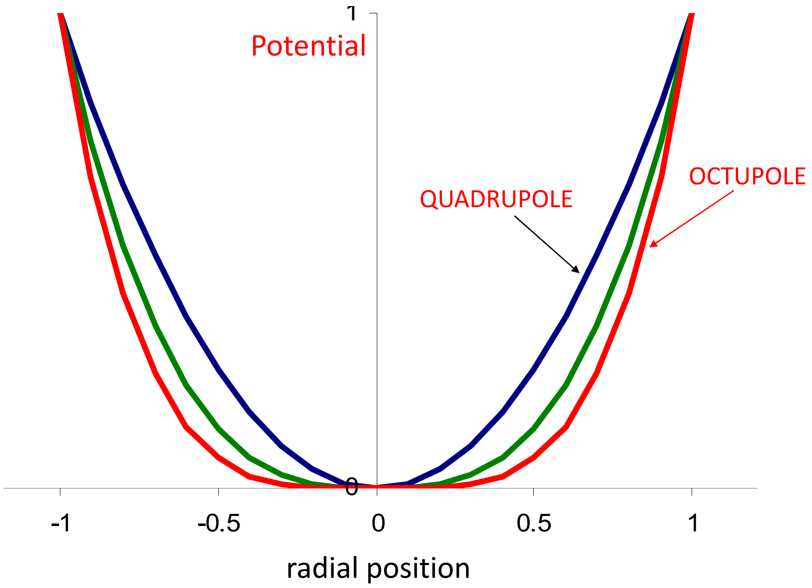


-collisional cooling (good for injection in TOF, sector, quad):
reduce velocity spread (thermal ions)

-more efficient collection of ions (compared to quad)

D. Gerlich, Adv. Chem. Phys. *82*, 176 (1992).

collision energy <u>more uniform</u> in higher multipoles



5. Quadrupolar Ion Trap

History

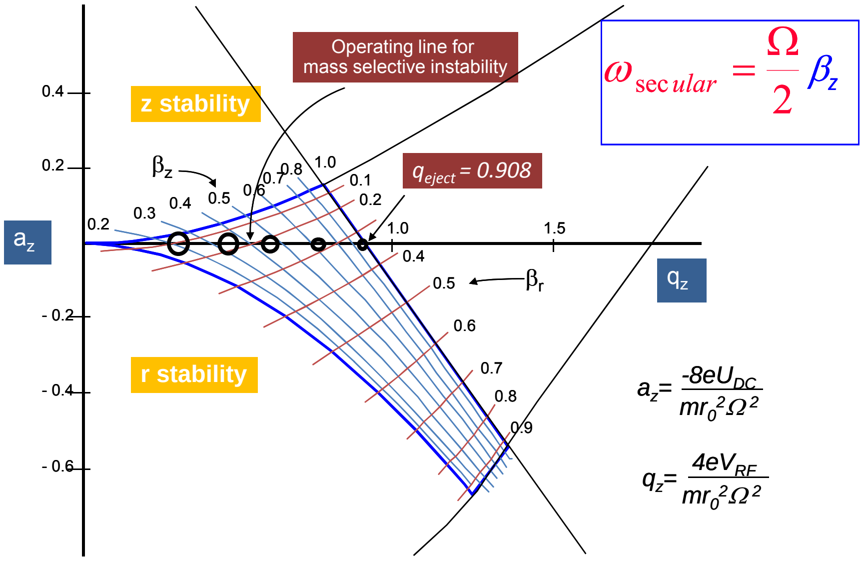
1953 Wolfgang Paul
1963 Hans Dehmelt
} Mass-selective Detection

1968 Dawson & Whetten
1972 John Todd
1972 Ray March
} Mass-selective Storage

1984 George Stafford
} Mass-selective Ejection

Ion Trap

Stability diagram



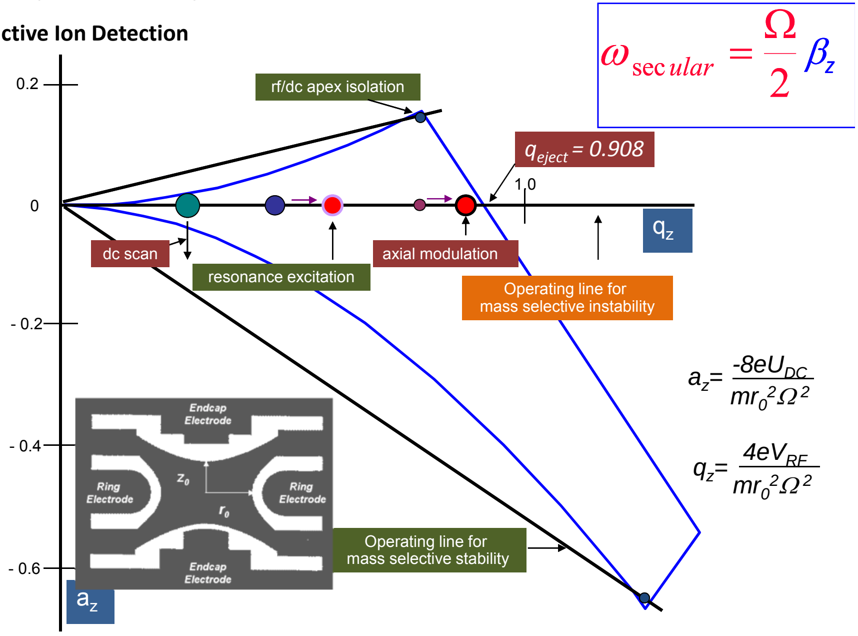
$$\omega_{secular} = \frac{\Omega}{2}\beta_z$$

$$a_z = \frac{-8eU_{DC}}{mr_0^2\Omega^2}$$

$$q_z = \frac{4eV_{RF}}{mr_0^2\Omega^2}$$

Ion Trap MS Analysis

Destructive Ion Detection

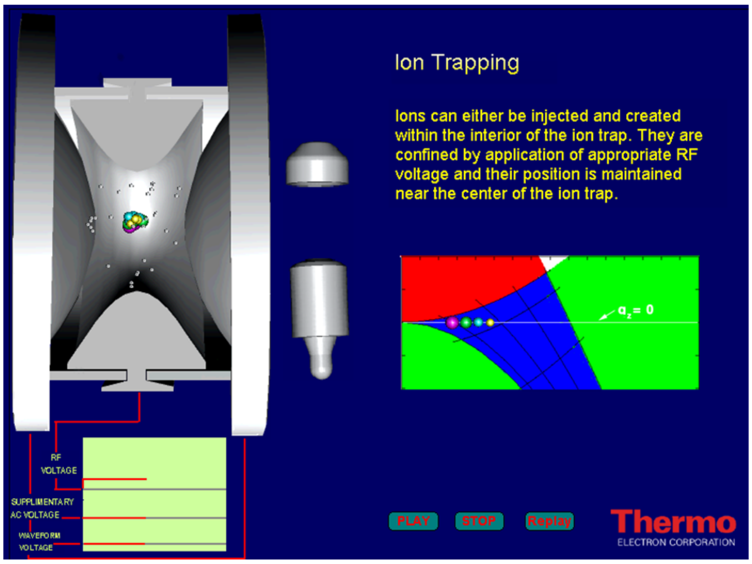


$$\omega_{secular} = \frac{\Omega}{2}\beta_z$$

$q_{eject} = 0.908$

$$a_z = \frac{-8eU_{DC}}{mr_0^2\Omega^2}$$

$$q_z = \frac{4eV_{RF}}{mr_0^2\Omega^2}$$

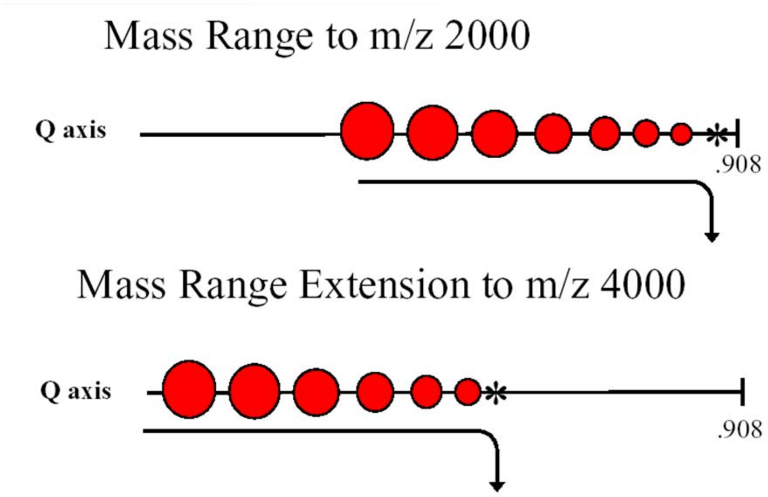


Ion Trapping

Ions can either be injected and created within the interior of the ion trap. They are confined by application of appropriate RF voltage and their position is maintained near the center of the ion trap.

Ion Trap Ejection Mode

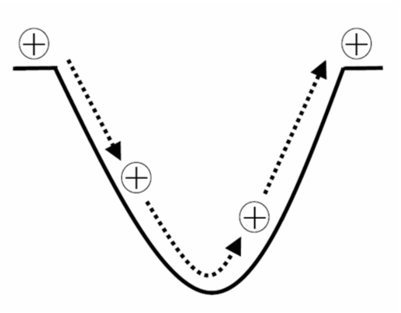
Mass range extension using resonance ejection



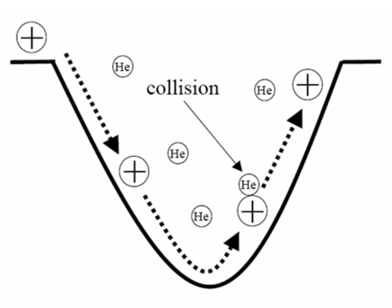
Quadrupole Ion Trap – Collisions with Background Gas

Trapping injected ions

Without Helium

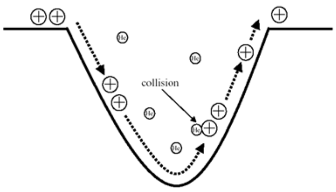


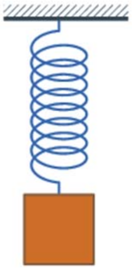
With Helium



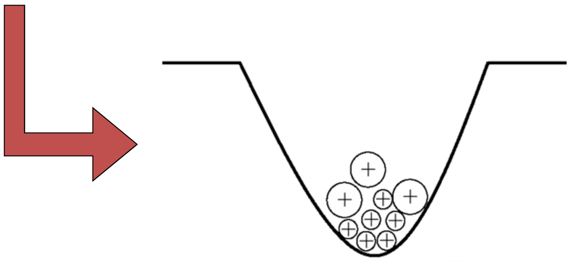
Quadrupole Ion Trap

KE Damping

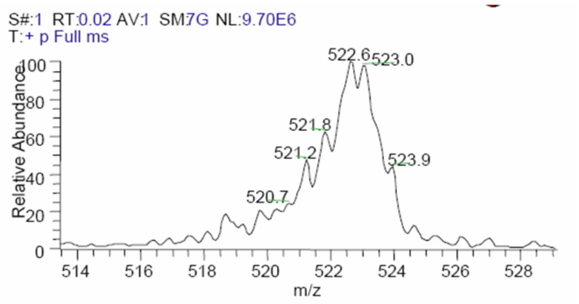




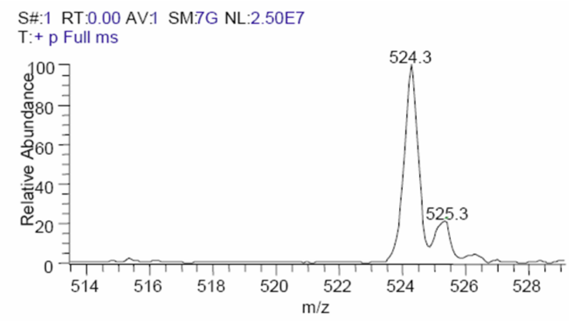
Collisions!!



Without He



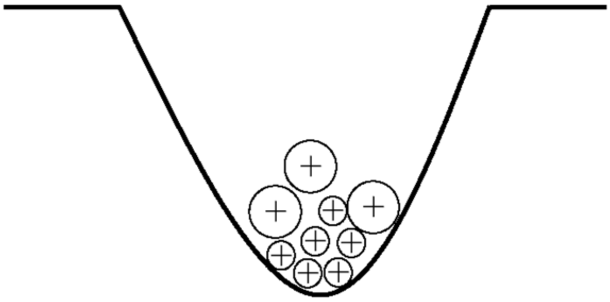
With He



Quadrupole Ion Trap

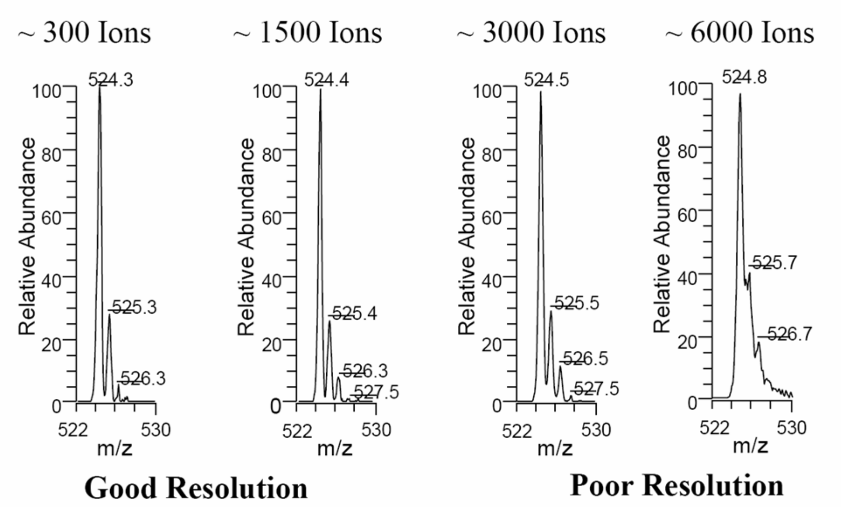
Trapping capacity vs. space charge

$$D_z = 2D_r = \frac{q_z V}{8}$$

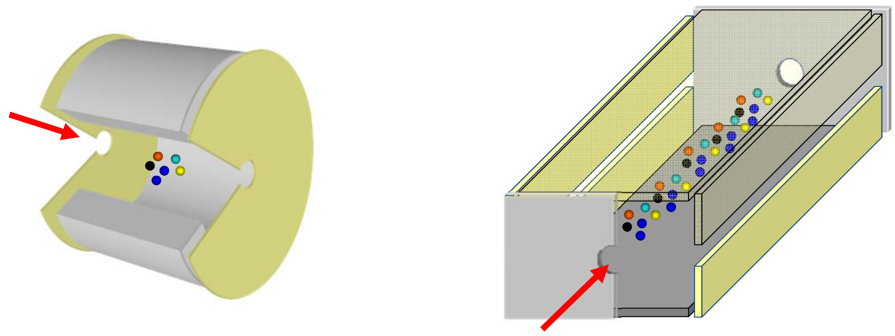


Quadrupole Ion Trap

Trapping capacity vs. space charge – 3D Trap



Why Linear Ion Trap?



5%

Trapping Efficiency
for external ion injection

~100 %

Theory of Quadrupole Ion Trap

Equations of motions

Acceleration of Ion expressed as a Second Order Differential Equation:

$$\frac{d^2z}{dt^2} = \frac{4e}{m(r_0^2 + 2z_0^2)} [U - V(t) \cos\Omega t] z$$

Quadrupole Field

$$+ \quad \frac{e}{2mz_0} V_{aux}(t) \cos\Omega_{aux}(t)\, t$$

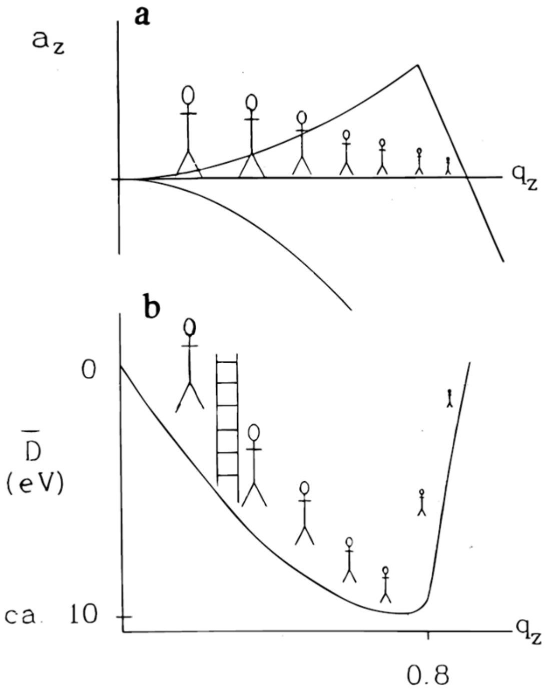
Dipole Field

$$+ \quad 1 - 1 \left(1 - \sqrt{1 - \frac{4m_b}{m_i}} \, R(t) \, L(t) \right)$$

Collision Term

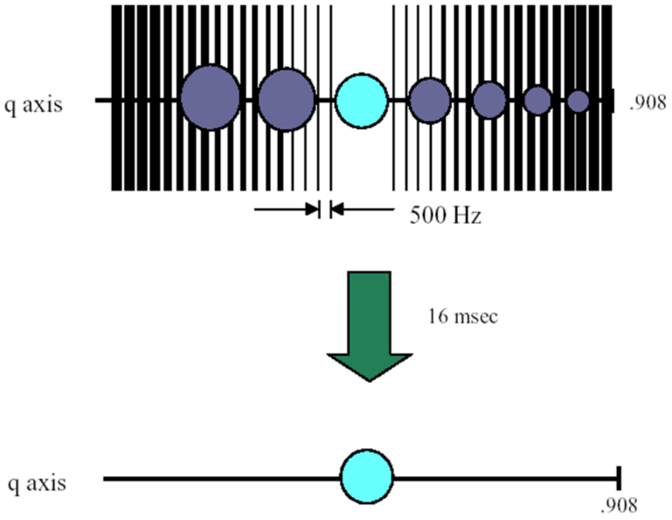
$$+ \quad \frac{e}{4\pi\varepsilon_0 m \sum_i \frac{1}{r - r_i{}^2}}$$

Coulombic Term



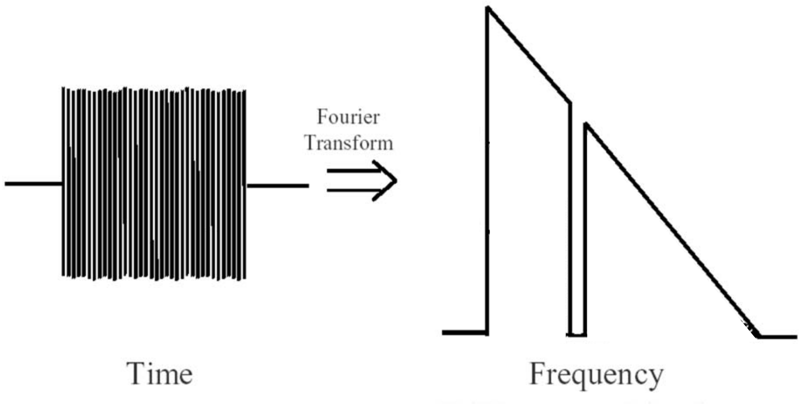
Theory of Quadrupole Ion Trap

Isolation waveforms



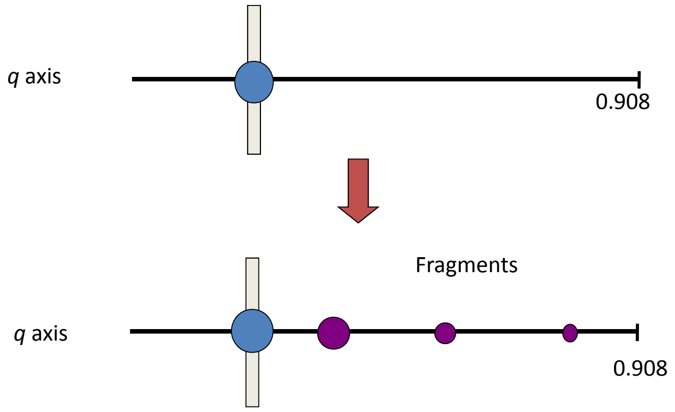
Theory of Quadrupole Ion Trap

Isolation waveform



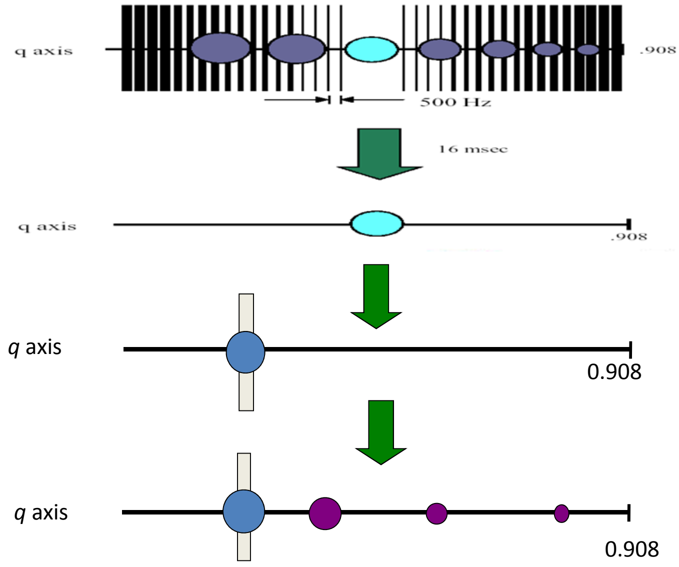
Theory of Quadrupole Ion Trap

Resonance excitation



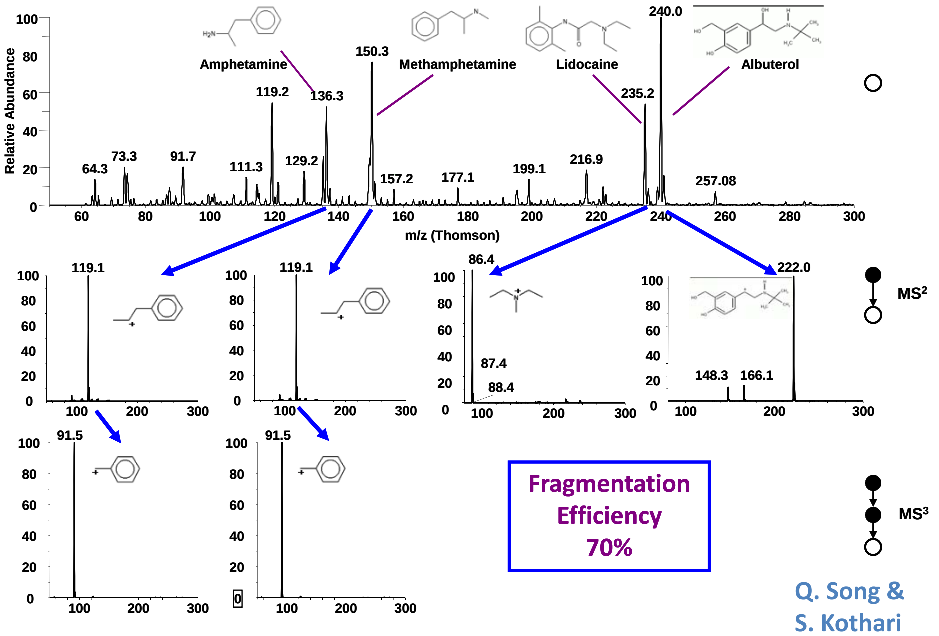
Theory of Quadrupole Ion Trap

MS/MS



ESI-RIT Instrument – MS^n analysis to mixtures

ALMA mixture (100pg/ul)



Fragmentation Efficiency 70%

Q. Song & S. Kothari

Performance of Quadrupole Ion Trap

- R= 10^3-10^4
- 50-100 ppm accuracy
- m/z range <100,000 (typ. 4000)
- LDR: 10^2-10^5

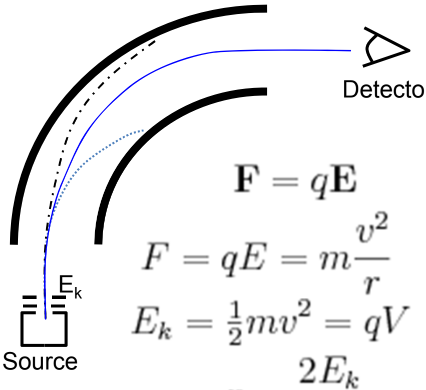
- Efficiency: <1-95%
- Speed: 1-30 Hz

- Ionizer: pulsed and continuous
- Cost: low to moderate
- Size: benchtop

Very common mass analyzer

Sectors

Separation in space
Electric Sector Mass Analyzer



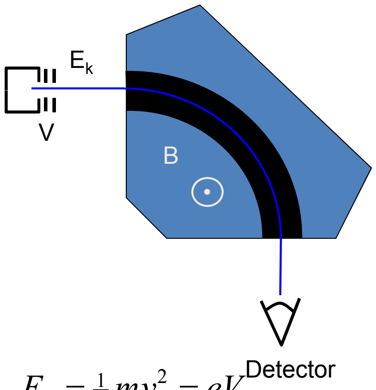
$$\mathbf{F} = q\mathbf{E}$$

$$F = qE = m\frac{v^2}{r}$$

$$E_k = \tfrac{1}{2}mv^2 = qV$$

$$r = \frac{2E_k}{qE}$$

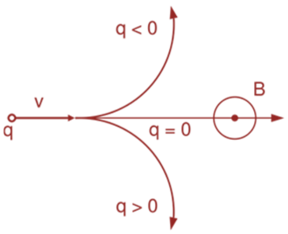
Separation in space
Magnetic Sector Mass Analyzer

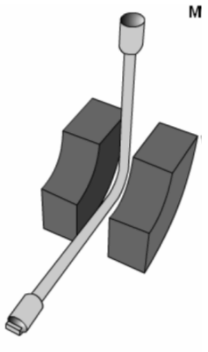


$$E_k = \tfrac{1}{2}mv^2 = eV$$

$$F = \frac{mv^2}{r} = Bev$$

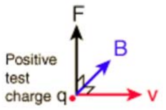
$$\frac{m}{e} = \frac{B^2r^2}{2V}$$





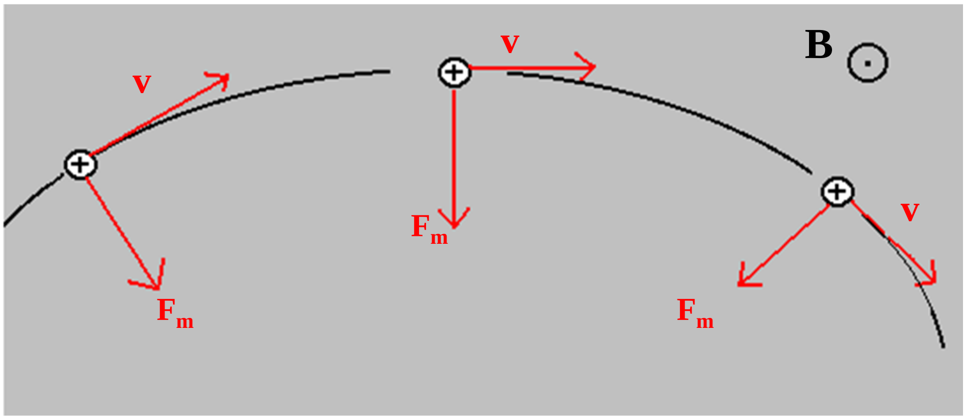
Lorentz Force

$$\vec{F} = q\vec{v} \ x \ \vec{B}$$



Magnetic Sector Mass Analyzer

+ ion moving through magnetic field with strength B



F_m = magnetic force always acts perpendicular to direction of motion

*Use right hand,
Cross v into B with fingers
Thumb points in dir. of F_m

Uniform circular motion w/ radius r_m when:

$$F_m = Bzev = \frac{mv^2}{r_m}$$

Rearrange to get: $$\frac{mv}{z} = Br_m e$$

So B sector is a momentum/charge analyzer, <u>not a mass analyzer</u>

Include KE from source:

$$KE = \frac{1}{2}mv^2 = zeV \quad \Rightarrow \quad v = \sqrt{\frac{2zeV}{m}}$$

$$\frac{m}{z} = \frac{B^2 r_m{}^2}{2V}$$

How do we get a m/z spectrum?

$$\frac{m}{z} = \frac{B^2 r_m^{\ 2}}{2V}$$

Scan either:

B (vary mag. field: slow)
V (vary acc. voltage: faster) AND / OR
r_m (array detector)

Performance of Sector magnets

The sector magnet is lighter and hence more convenient, than the 180^0 magnet. It shares the property of bringing a divergent beam of ions to focus (to first order) — i.e. it is a direction focusing device. Ions entering normal to a magnetic field experience a force which depends upon the field strength, the magnitude of the charge and the velocity. Since the three vectors (B, r, v) are mutually orthogonal, no change in velocity occurs and a circular path results.

Barber's rule states that for normal entry and egress, object, image and apex are collinear. The law is true for all sector angles and for both symmetrical and unsymmetrical arrangements of object and image.

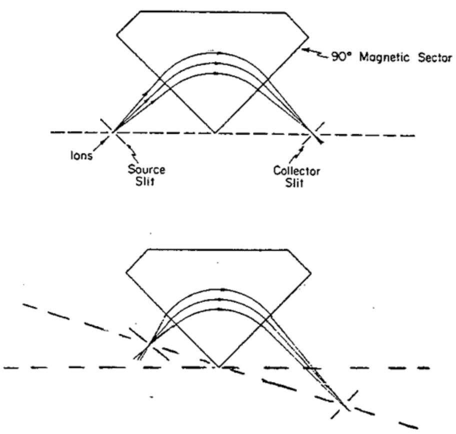


Fig. 4. Focusing action of a wedge-shaped (sector) magnetic field on a mono-energetic beam of ions, all of the same mass-to-charge ratio.

In fact, one desires both velocity and direction focusing. This is termed double focusing and is achieved with a suitable combination of a sector magnet and an electric sector. Each of these devices independently focuses for direction and together they give equal and opposite dispersions for velocity, i.e. they yield velocity focusing. Such double focusing instruments give high resolution. The fields may be arranged so that all masses are simultaneously subject to double focusing or, this may be true for just one mass/charge ratio at a time. They will be discussed later. However, it is important to recognize that there exist degrees of success in achieving both velocity and direction focusing. If focusing is to first order then the beam position is independent of the first power of velocity (5) or direction (a), but dependent on the square terms. Focusing to second order means that a dependence exists on the third power of the parameters, etc.

There are two important geometries of double-focusing instruments from which all other designs have been developed, the *Nier-Johnson* geometry uses an electric sector (E) followed by a magnetic sector (B), the image of the electric sector being the object point of the magnetic sector, i.e. there is a point of intermediate focus. Along a plane normal to the ion beam and running through this focal point the beam is dispersed approximately linearly in terms of translational energy; the j3—slit located at this point must be quite wide for high sensitivity. It is along this plane that the velocity dispersions due to the two sectors are equal and opposite for ions of the same m/z ratio. The final slit is located at the point at which a and 5 disappear to first order ie double—focussing is achieved.

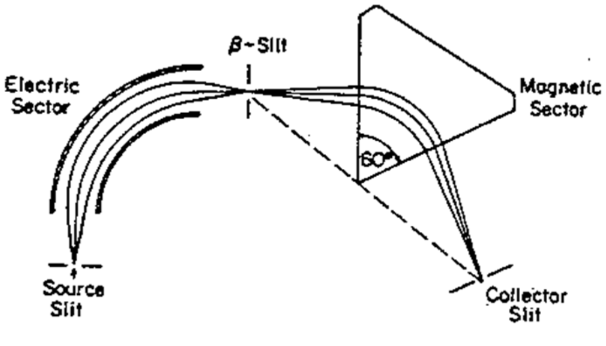


Fig. 8. Arrangement of the electric and magnetic fields for a double-focusing mass spectrometer of Nier—Johnson type geometry.

The *Mattauch-Herzog* geometry differs from the Nier-Johnson in many ways: (i) there is no point of intermediate focus, in fact the beam is approximately parallel between the sectors (ii) there is a plane of final focus, rather than a point and this allows imaging detectors to be used (note however, that the resolution is not the same at all points along the plane and is highest at the end which corresponds to maximizing the area of the sector covered by the ion beam).

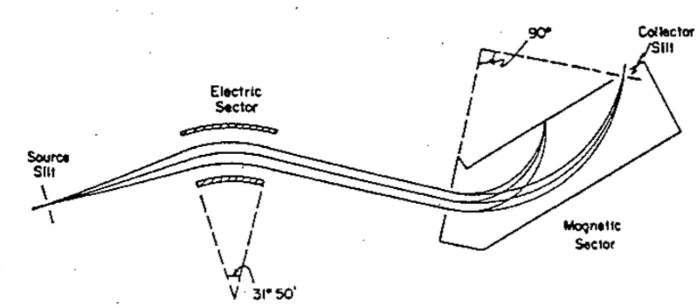
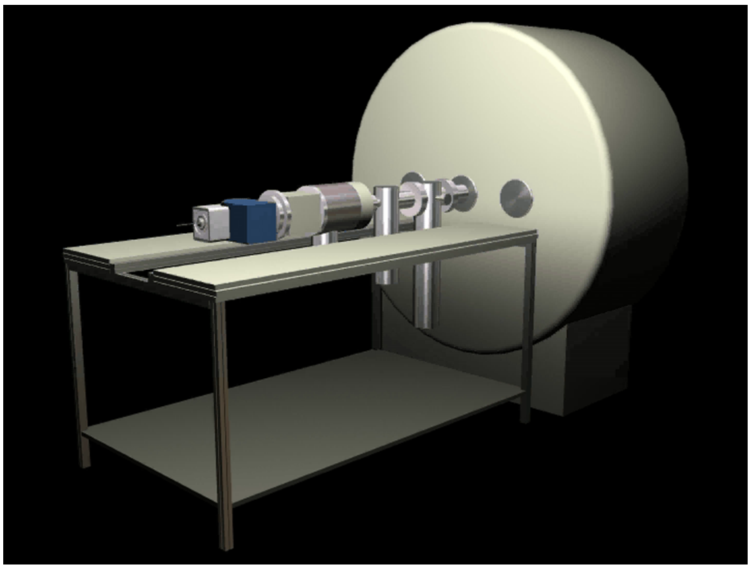


Fig. 9. Arrangement of the electric and magnetic fields for a double-focusing mass spectrometer of Mattauch—Herzog geometry.

1. FT-ICR



Ion excitation for m/z analysis

Add power to excite ion packet to larger radii

*ions do not hit detector plates

(use dipolar excitation pulse)

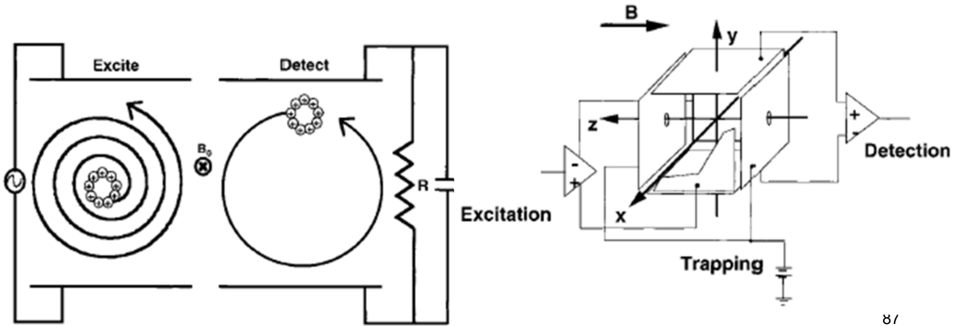
$$r = \frac{V_{pp} T_{excite}}{2dB}$$

[s]

[m]

[T]

Coherent ion packet oscillates at cyclotron freq



87

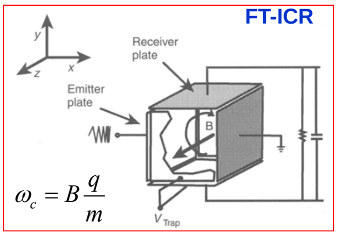
Mass Spectrom. Rev., *17*, 1-35 (1998).

2. The Orbitrap Mass Analyzer

- **Employs orbital trapping in an electrostatic field with potential distribution:**

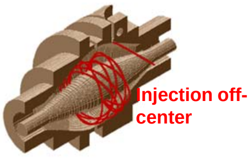
$$U(r,z)=\frac{k}{2}\left(z^2-\frac{r^2}{2}\right)+\frac{k}{2}(R_m)^2\ln\left[\frac{r}{R_m}\right]+C$$

No cross terms in *r* and *z*. Thus the potential in the *z*-direction is exclusively quadratic and independent of *r*, ϕ motion.



***r-y* plane**

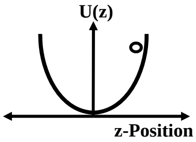
3-D View



General features:

- **High mass resolution (up to ~150,000)**
- **Increased space charge capacity at higher masses**
- **High mass accuracy (0.2-5ppm), dynamic range (10^3- 10^4) and upper mass limit (*m/z* 6000)**
- **Small size and relatively low cost**

Axial Harmonic Oscillator

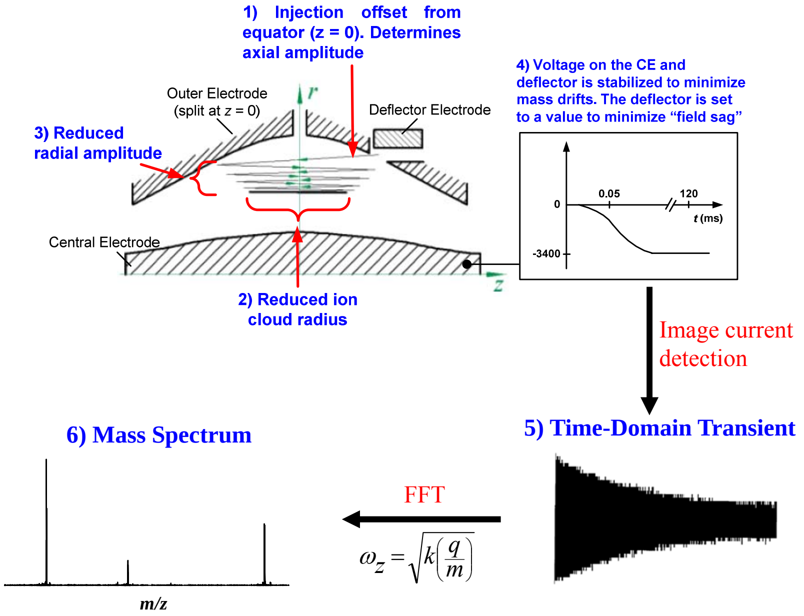


$$\omega_z = \sqrt{k\left(\frac{q}{m}\right)}$$

ω is independent of the energy and spatial spread of the ions

1. Qizhi Hu, Robert J. Noll, Hongyan Li, Alexander Makarov, Mark Hardman and R. Graham Cooks, *J. Mass Spectrom.*, 2005, *40*, 430; 2. Alexander Makarov, *Anal. Chem.*, 2000, *72*, 1156. 3. Oksman, P., *Int. J. Mass Spectrom. Ion Processes*, 1995, *141*, 67

Ion Capture, Squeezing and Detection



1) Injection offset from equator (z = 0). Determines axial amplitude

4) Voltage on the CE and deflector is stabilized to minimize mass drifts. The deflector is set to a value to minimize "field sag"

3) Reduced radial amplitude

2) Reduced ion cloud radius

Image current detection

5) Time-Domain Transient

6) Mass Spectrum

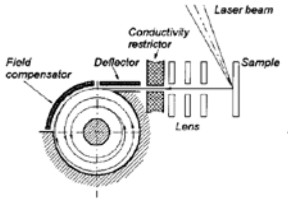
FFT

$$\omega_z = \sqrt{k\left(\frac{q}{m}\right)}$$

1. Qizhi Hu, Robert J. Noll, Hongyan Li, Alexander Makarov, Mark Hardman and R. Graham Cooks, *J. Mass Spectrom*., 2005, *40*, 430; 2. Alexander Makarov, *Anal. Chem*., 2000, *72*, 1156.

Instrumentation

Orbitrap Prototypes

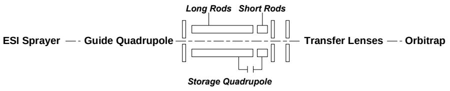


Disadvantages of FT-ICR:
- **Small space charge capacity**
- **High complexity and cost.**

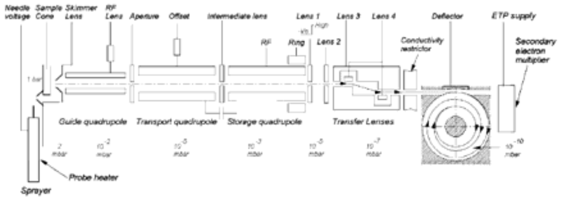
Disadvantages of the Paul Trap:
- **Unit resolution**
- **Insufficient mass accuracy (10 ppm at best)**
- **Small space charge capacity.**

- **The Orbitrap is a complementary alternative to these methods**
- **It employs dynamic ion trapping in an electrostatic field.**

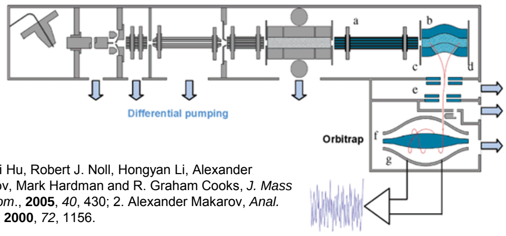
(a) First API-Orbitrap Prototype Instrument



(b) Second API-Orbitrap Prototype Instrument



Commercial LTQ-Orbitrap

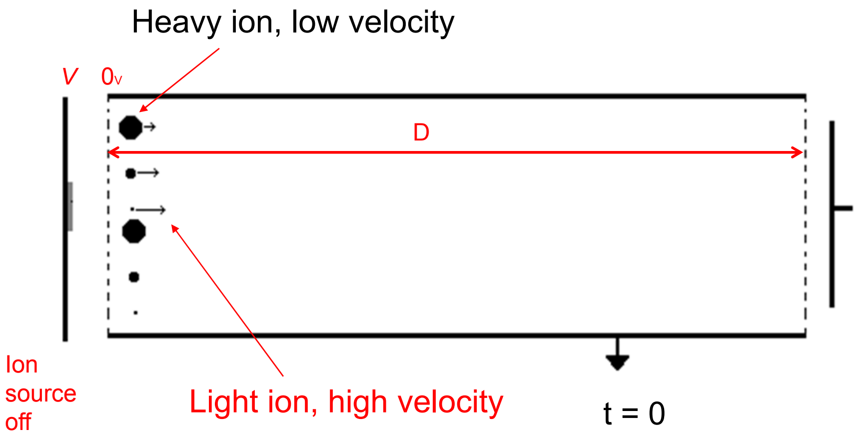


1. Qizhi Hu, Robert J. Noll, Hongyan Li, Alexander Makarov, Mark Hardman and R. Graham Cooks, *J. Mass Spectrom*., **2005**, *40*, 430; 2. Alexander Makarov, *Anal. Chem*., **2000**, *72*, 1156.

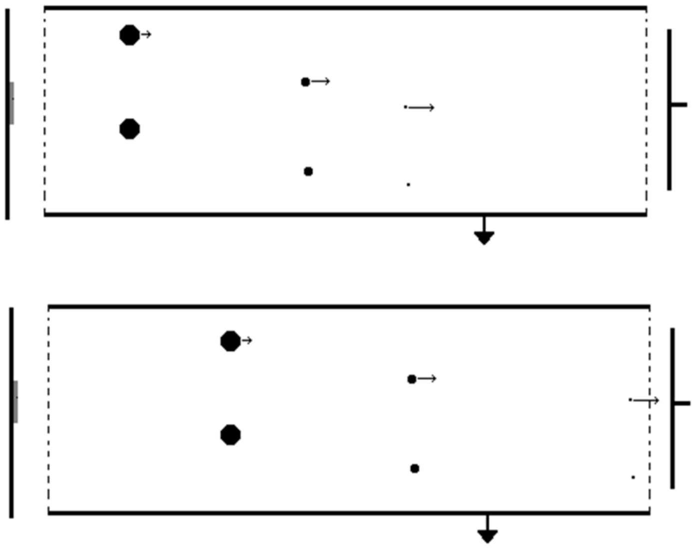
TOF

$$KE = qV = \frac{1}{2}mv^2 \qquad v = \sqrt{\frac{2qV}{m}}$$

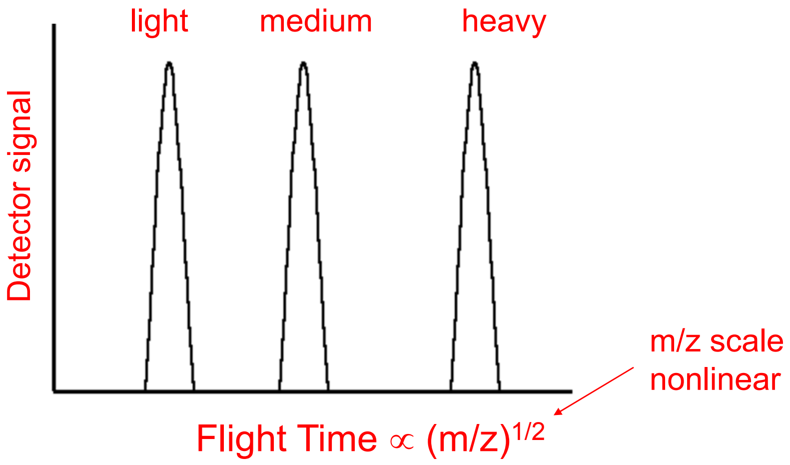
$$t = \frac{D}{v} = \frac{D\sqrt{m}}{\sqrt{2zeV}} \qquad \frac{m}{z} = \frac{2eVt^2}{D^2}$$



t_1, ions drift apart as fly down tube



t_2, light ions near detector, heavy ions still in tube



Detect “all” ions that entered flight tube

Full m/z range but *no scanning*

Evolution of TOF from 1950 to 2000

- **1946** Stephens presented concept of linear TOF MS
- **1953** Woff and Stephens published design and spectra from linear TOFMS
- **1955** First commercial linear TOF based on Wiley and McLaren 's design
- **1973** Reflectron-TOF by Mamyrin
- **1986** TOF/TOF by Brucat
- **1988** MALDI source by Karas, Hillenkamp, then MALDI-TOF
- **1989** Dawson and Guilhaus described EI+orthogonal TOF
  ESI+orthogonal TOF by Dodonove
- **90's** QqTOF

Factors Contributing to TOF-MS Renaissance

High mass

- The need to measure the mass of biological molecules
- Discover MALDI ionization by Karas and Hillenkamp
- Quadrupoles and sectors have fundamental high mass limit

Digital electronics

- Advances in the speed and data handling of computers
- Progress in high speed timing electronics
- nanosecond digitizers, focal plane detector, affordable laser

Speed

- Detect ions quasi-simultaneous
- Well in the time-frame of chromatography

Gilhaus et al. *Rapid Conmmun. Mass Spectrom.* **1997**,11, 951-962

Reduced Eqn for TOF

Volts μs

$$\frac{m}{z} = 1.92\frac{Vt^2}{L^2}$$

cm

- m/z scale non-linear
- time scale shrinks at higher m/z

To observe very high m/z, just wait longer

No (theoretical) limit to mass range
-detector response poor
-peaks very close in time

L = 1 m V = 2700 volts

m/z	t (μs)	Δt (ns) ~ time resolution needed
$^{14}N^+$	5.20	180
$^{15}N^+$	5.38	
$^{207}Pb^+$	20.00	50
$^{208}Pb^+$	20.05	
500	31.09	30
501	31.12	
20,000	196.623	5
20,001	196.628	

Create ion pulse<5 ns

Time constants of electronics need to be faster than 5 ns

Effect of Instrument Parameters on Resolution

$$m/z = m = \frac{2\,V\,t^2}{L^2} = 2\,V\,t^2\,L^{-2}$$

$$dm = \frac{2\,t^2}{L^2}\,dV + \frac{2\,V}{L^2}\,(2t)\,dt + 2\,V\,t^2\,(-2L^{-3})\,dL$$

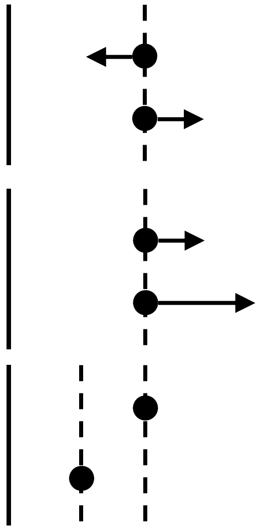
$$\frac{dm}{m} = \frac{dV}{V} + \frac{2dt}{t} + \frac{2dL}{L}$$

Small dL
All ions same tube length
Long tube

Small KE spread
Large KE, high V
(2 – 10 kV)

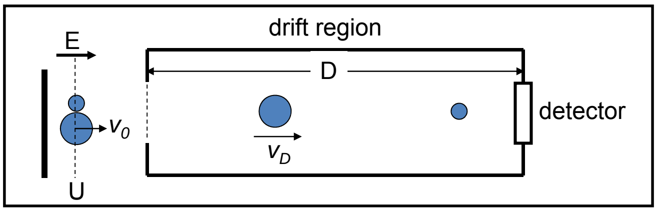
Fast time response
Long flight time, long tube

What causes poor resolution (time spread)?



- Direction spread
- Velocity spread
- Position spread

TOF Mass Spectrometer– Theory of Work

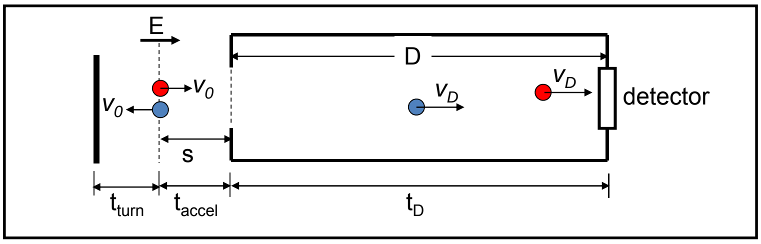


$$TOF = t_{delay} + t_{accel} + t_D + t_{detect}$$

$$qU = \frac{1}{2} m v_D^2 \qquad t_D = \frac{D}{\sqrt{2U}} \boxed{\left(\frac{m}{q}\right)^{1/2}}$$

t_{delay}	any delays between ionization and acceleration	
t_{accel}	time to reach full velocity before enter drift region	$t_{accel} = \frac{v_D - v_0}{E}\left(\frac{m}{q}\right)$
t_D	drift time in the 100 μs time frame	$t_D = \frac{D}{\sqrt{2U}}\left(\frac{m}{q}\right)^{1/2}$
t_{detect}	detector response time (1-5 ns)	

Direction Spread: the Turn-Around Problem



If U_0 = initial kinetic energy, then $t_{turn} = \frac{2\sqrt{2mU_0}}{Eq}$

- t_{turn} can be decreased by increasing E or decrease U_0

$$t_D = \sqrt{\frac{2m(EqS + U_0)}{Eq}}$$

- Relative contribution of t_{turn} can be decreased by increasing D

$$t = \frac{(2m)^{1/2}\left[\left(U_0 + qES\right)^{1/2} \pm U_0^{1/2}\right]}{qE} + \frac{(2m)^{1/2} D}{2\left(U_0 + qES\right)^{1/2}}$$

Resolving Power of TOF

$$m \propto t^2 \Rightarrow \frac{dm}{m} = \frac{2dt}{t} \qquad \text{or} \qquad \frac{m}{\Delta m} = \frac{t}{2\Delta t}$$

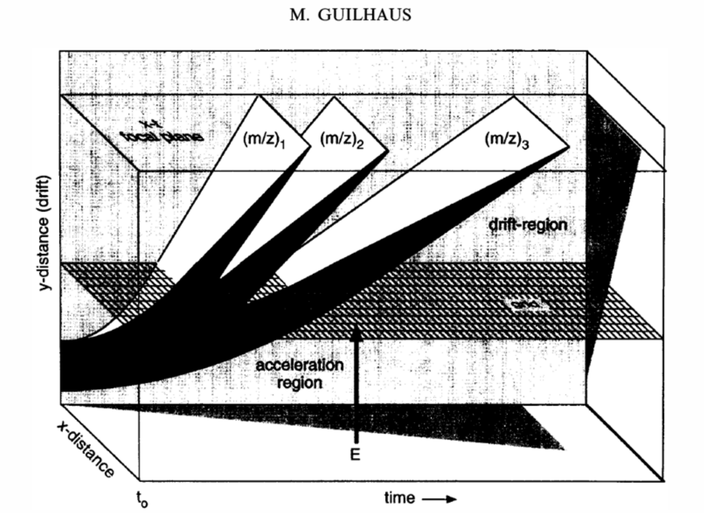
Δt: the full-width at the maximum height of the peak (FWHM)

$$TOF = t_{delay} + t_{accel} + t_D + t_{\det ect}$$

Contributions to Δt:

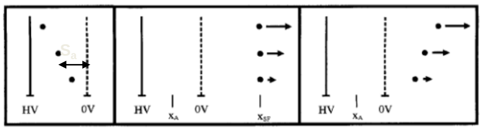
1. timing/duration of gating and detection interval
2. position spread
3. direction spread (turn around time)
4. initial velocity spread

$$t = \frac{(2m)^{1/2}\left[\left(U_0 + qES\right)^{1/2} \pm U_0^{1/2}\right]}{qE} + \frac{(2m)^{1/2} D}{2\left(U_0 + qES\right)^{1/2}}$$



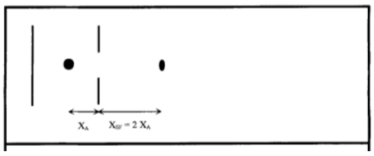
Mass-dispersed space-time trajectories

Initial Position Spread and Spatial Focusing



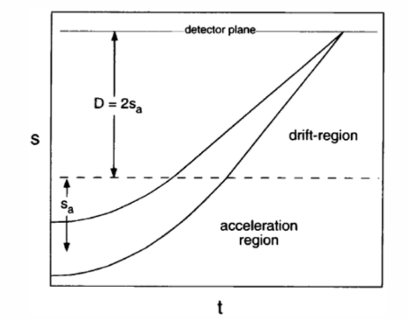
$$\frac{dt}{ds_a}(U_0 = 0) = \sqrt{\frac{m}{2qEs_a}} \times \left(1 - \frac{D}{2s_a}\right)$$

$$\frac{dt}{ds_a} = 0 \Rightarrow D = 2S_a$$

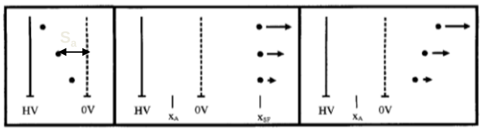


One stage acceleration

Spatial focus at D=2S$_a$

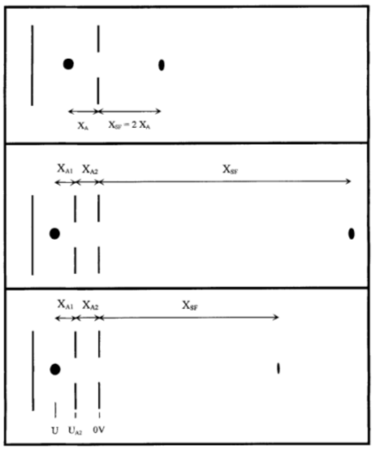


Initial Position Spread and Spatial Focusing



$$\frac{dt}{ds_a}(U) = \sqrt{\frac{m}{2qEs_a}} \times \left(1 - \frac{D}{2s_a}\right)$$

$$\frac{dt}{ds_a} = 0 \Rightarrow D = 2S_a$$



One stage acceleration

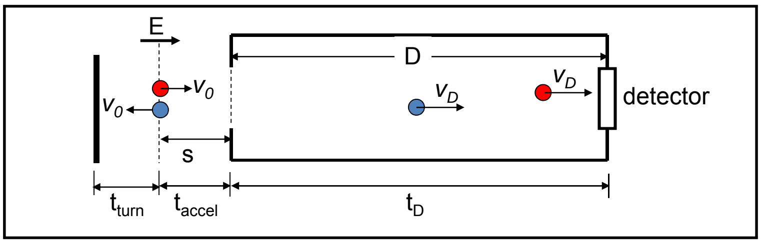
Spatial focus at D=2S$_a$

double stage acceleration

Double stage acceleration with second order space focus

Bosel et al. *Int. J. Mass Spectrom. Ion Processes* **1992**, 112, 121

Direction Spread: the Turn-Around Problem



If U_0 = initial kinetic energy, then $t_{turn} = \frac{2\sqrt{2mU_0}}{Eq}$

- t_{turn} can be decreased by increasing E or decrease U_0

$$t_D = \sqrt{\frac{2m(EqS + U_0)}{Eq}}$$

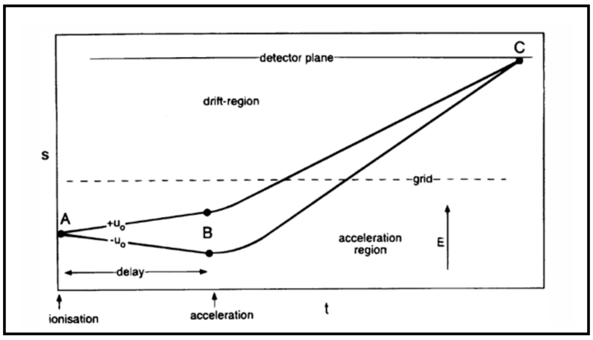
- Relative contribution of t_{turn} can be decreased by increasing D

$$t = \frac{(2m)^{1/2}\left[\left(U_0 + qES\right)^{1/2}\right) \pm U_0^{1/2}\right]}{qE} + \frac{(2m)^{1/2} D}{2(U_0 + qES)^{1/2}}$$

Initial Velocity Distribution and Time-lag Focusing

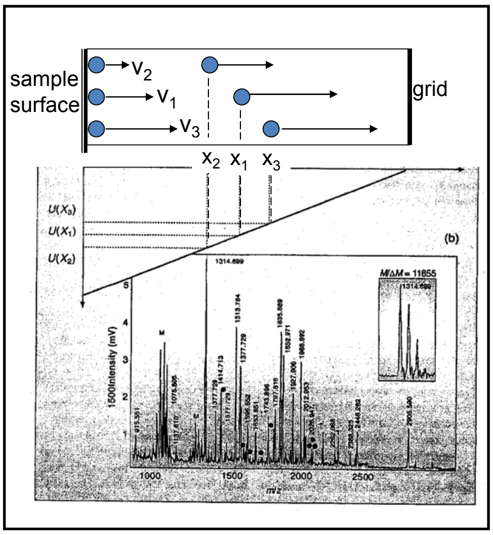
Time-lag focusing: delay between ion ionization and extraction (Wiley & McLaren)

Convert velocity distribution to spatial distribution, then use spatial focusing



- Focus is m/z dependent
- enhanced resolving power for a limited mass range
- Dose not solve turn-around problem

Initial Velocity Distribution & Delayed Extraction for MALDI/TOF



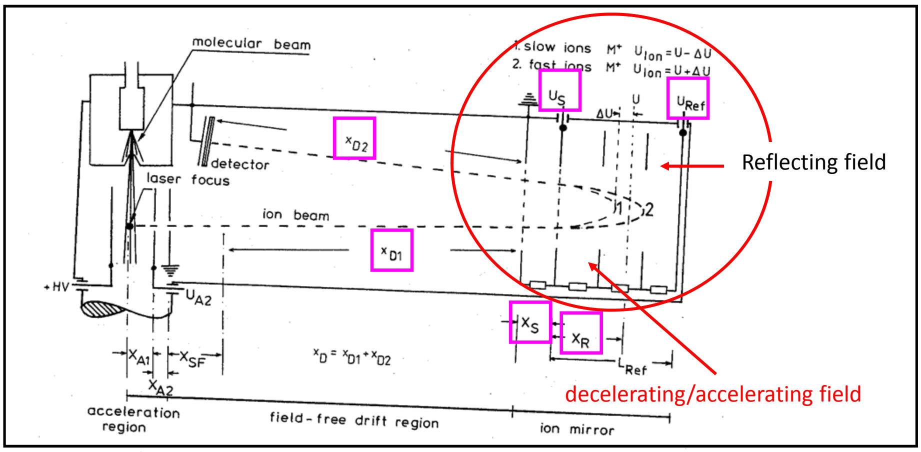
Correlated space and energy distributions
- Ions with larger initial velocity acquires less energy from the field

Difference between time-lag focusing
- In time-lag focusing: no correlation between energy and space

- Focus is still m/z dependent
- No turn-around problem for MALDI

Colby et al. *Rapid Conmmun. Mass Spectrom.* **1994**, 8, 865-868

Energy Correction by Reflectron (Mamyrin et al.)



- ✓ Reflectron consists two fields (three electrodes)
- ✓ By properly choose parameters (in box), energy distribution (5%) can be corrected
- ✓ Increase fly length without increase size, resolution can reach 20,000
- ✓ Can not solve turn-around problem (works well with ions generate from surface)

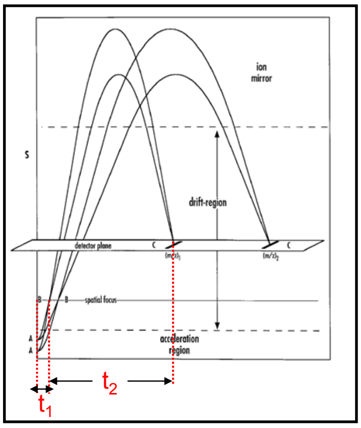
Bosel et al. *Int. J. Mass Spectrom. Ion Processes* **1992**, 112, 121

Reflectron Continued…

for energy compensation ion mirror:
second-order focus ion source

$$t = \left(\frac{m_1}{2eV}\right)^{1/2}\left[L_1 + L_2 + 4d\right]$$

L_1: drift region before reflection
L_2: drift region after reflection
d: penetration depth in the reflectron
V: acceleration voltage
Optimal focusing when L1+L2 = 4d



Resolution for a reflectron:

$$\frac{\Delta t}{t} = \underbrace{\frac{1}{4}\left(\frac{\Delta U}{U}\right)^2 \frac{t_1}{t}}_{\text{“second-order term of ion source”}} + \underbrace{\frac{3}{16}\left(\frac{\Delta U}{U}\right)^3 \frac{t_2}{t}}_{\text{“third-order term of ref”}} \pm \underbrace{\frac{x_{A1}}{U_{A1}}\left(MU_i\right)^{1/2}\frac{1}{t}}_{\text{“turn around time”}} + \underbrace{\frac{\Delta t_{fix}}{t}}_{\text{“laser pulse width”}}$$

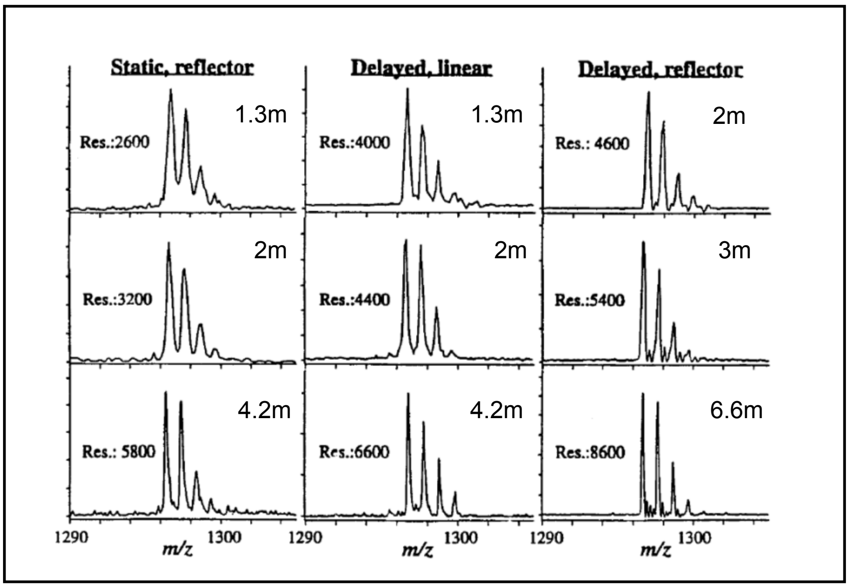
Bosel et al. *Int. J. Mass Spectrom. Ion Processes* **1992**, 112, 121

Table 1 Limiting factors for mass resolution of reflectron TOF with a laser ionization source. The values of Δt are determined for ions with M=106, an ion energy of 700eV and a flight time of 60 μs.

Limitations for mass resolution (R<3000)		
Δt (laser pulse width)	5-8 ns	commercial dye laser
Δt (detector rise time)	1.4 ns	
Δt (turn around time)	5 ns	T=300 K
Δt (Re-TOF third-order term)	< 1 ns	
Δt (Re-TOF geometry)	5 ns	Reflector with grids
Δt (space charge)	12 ns	10^4 ions, focus r=0.05 mm, l=1mm
Optimization for high mass resolution (R> 10 000)		
Δt (laser pulse width)	1.5 ns	Pulse cutting
Δt (turn around time)	< 1 ns	Supersonic jet cooling
Δt (space charge)	< 1 ns	Optimized focus size
Δt (Re-TOF grid)	0 ns	Gridless reflector
Result: for M=106 (*p*-xylene): Δt_{FWHM}=3.2 ns, Δt_{unit}=310 ns		
$R_{50\%}$=M Δt_{unit}/ Δt_{FWHM}=10270		

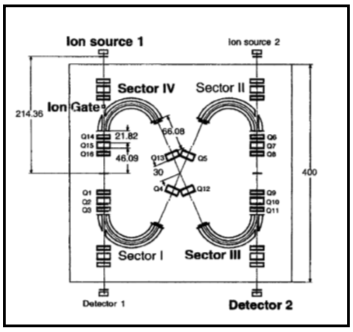
Bosel et al. *Int. J. Mass Spectrom. Ion Processes* **1992**, 112, 121

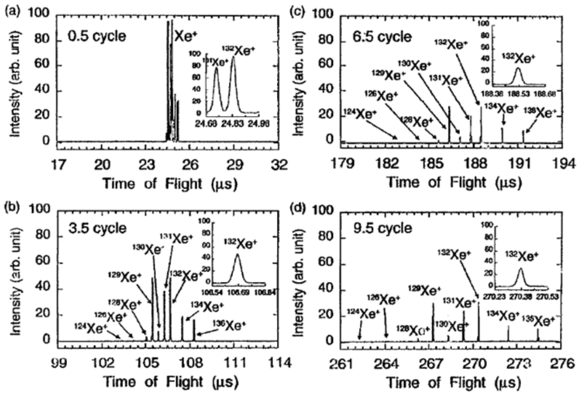
Comparison of the Resolution and S/N for Angiotensin I

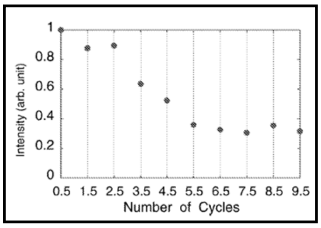


Vestal et al. *Rapid Conmmun. Mass Spectrom.* **1995**, 9, 1044

Multiturn TOF for High Resolution







- Four cylindrical E-sectors
- Eight quadrupole lenses for space focus
- Linear TOF for ion detection
- Resolution increases as ion path increases
- Most ion loss in the first 5.5 cycles

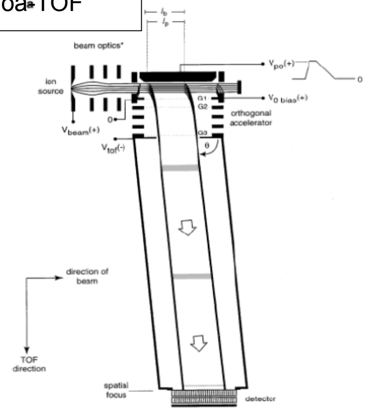
Toyoda et al. *J. Mass Spectrom.* **2000**, 35, 163

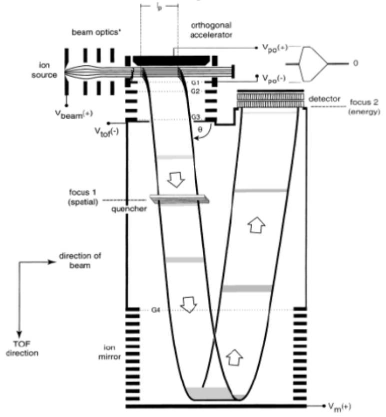
Orthogonal Acceleration TOF- Solutions for Continuous Ionization

~ 1989 Guihaus' group and Dodonov's group

Linear oa-TOF

reflectron oa-TOF

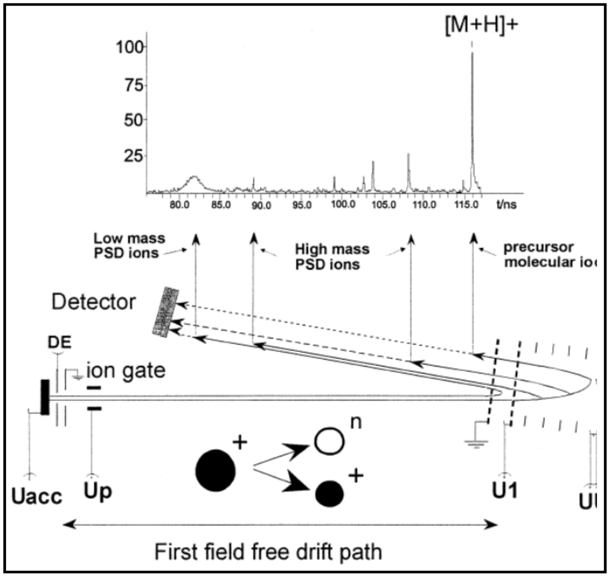




Guihaus et al., *Mass Spectrom. Rev.,* **2000**, 19, 65-107

MS^n Capabilities of TOF – Post Source Decay

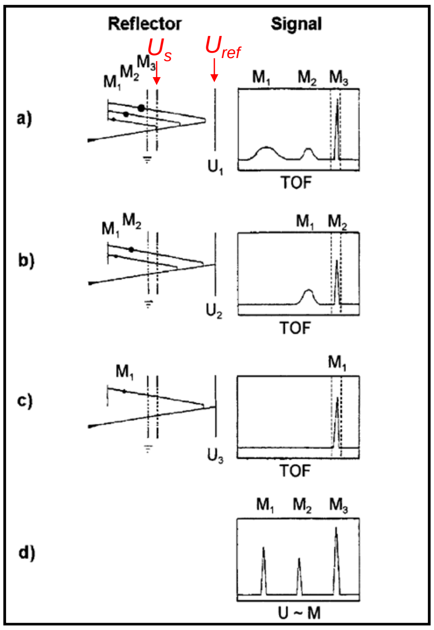
(Kaufmann et al.,1996)



- PSD: parent ions acquired sufficient internal energy during the desorption process, fragmented in first field free region.
- Fragment ions have the same velocity as their precursor ions but have different kinetic energy as function of their mass. (can not use linear TOF)
- Lighter ions reach earlier than heavier ions in ref-TOF
- For linear field reflectron, best focus when L=4d.
- Bad resolution with one reflectron voltage.

Chaurand et al. *J. Am. Soc. Mass Sepctrom.* **1999**, 10, 91

Scan Method for Secondary Mass Spectra



Weinkauf et al., 1989

- Scan U_{ref} and keep U_{ref}/U_s constant as parent ion.
- Fragment ions penetrate same distance in reflectron, thus have same resolution as parent ion.
- Lose major advantage of TOF: detect all masses quasi-simultaneously

Bosel et al. *Int. J. Mass Spectrom. Ion Processes* **1992**, 112, 121

Curved-Field Reflectron for Secondary Mass Spectra

Cotter et al., 1993

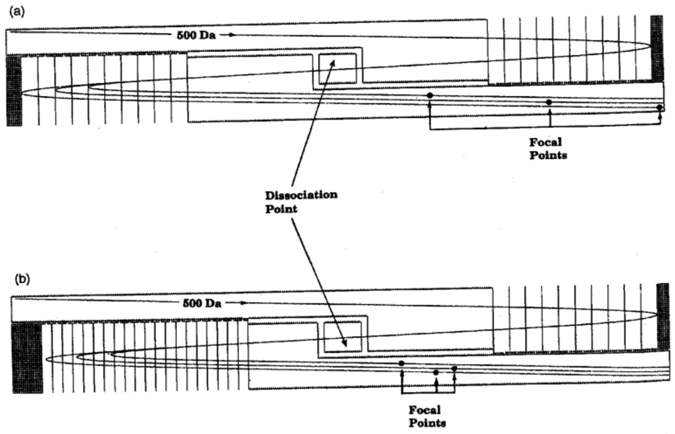
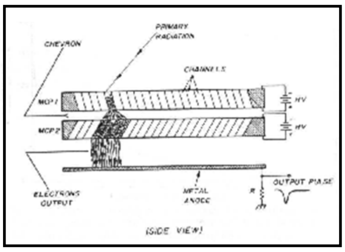


Figure 2. SIMION trajectory plots modeling the CID fragmentation of 500 Da ions. The energy focusing points of *m/z* 400 and 300 Da product ions through (a) the linear-field and (b) the curved-field reflectrons are shown.

Cotter et al. *Rapid Commun. Mass Spectrom.***1993**, 7, 1037-1040

Detection in TOF



- multi-channel plate in "Chevron" arrangement 10-25 µM channels inclined @ 8-12°
- Single ion impact → 1-5 ns pulse width
- detect single ion impact (problem at high m/z)
- Flat conversion surface
- Large area, detect large ion packets
- Better use smallest channel diameter (time spread)

Digitizers in TOF

Time-to-digital converter (TDC)

- for low ion currents (ESI)
- Register events of pulses
- Good S/N
- Good time resolution (<0.3 ns)
- Limited dynamic range due to dead time
- Can only register one ion at a time

Integrating Transient Recorder (ITR)

- For high ion currents (MALDI, ICP)
- Analog systems digitize ion current from MCP.
- Expensive
- Inherent background noise
- Low repeat rates

Feature of Merit -- TOF vs. QIT

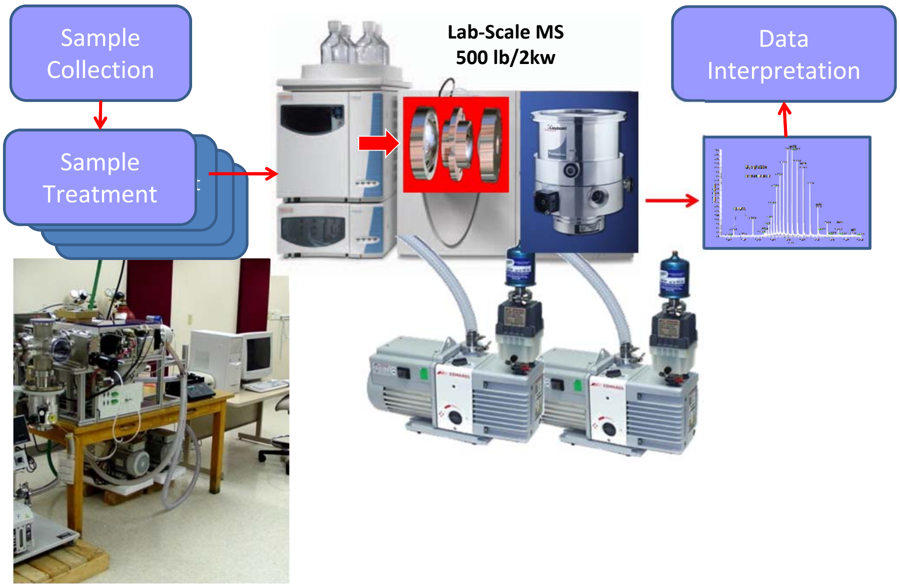
	TOF	Ion-trap
Mass resolving power	10^3-10^4	10^3-10^4
Mass accuracy	5-50 ppm	50-100 ppm
Mass range	>10^5	1.5 x 10^5
Linear dynamic range	10^2-10^6	10^2 -10^5
precision	0.1-1%	0.2 -5%
Abundance sensitivity	Up to 10^6	10^3
Efficiency (transmission x duty cycle)	1-100%	<1- 95%
speed	10-10^4 Hz	1-30 Hz
Compatibility with ionizer	Pulsed and continuous	Pulsed and continuous
cost	Moderate-high	Low to moderate
Size/weight/utility requirements	benchtop	benchtop

McLuckey et al. *Chem. Rev.* **2001**, 101, 571-606

Suggested Reading

- Weickhardt et al., *Mass Spectrom. Rev.,* **1996**, 15, 139-162, “Time-of-flight mass spectrometry: state-of-art in chemical analysis and molecular science
- Bosel et al., *Int. J. Mass Spectrom. Ion Processes,* **1992**, 112, 121-166, “Reflectron time-of-flight mass spectrometry and laser excitation for analysis of neutrals, ionized molecules and secondary fragments”
- Guihaus et al., *Mass Spectrom. Rev.,* **2000**, 19, 65-107, “Orthogonal acceleration time-of-flight mass spectrometry”
- Chernushevich et al., *J. Mass Spectrom.,* **2001**, 36, 849-865, “An introduction to quadrupole-time-of-flight mass spectrometry”
- McLuckey et al., *Chem. Rev.,* **2001**, 101, 571-606 “Mass Analysis at the Advent of the 21st Century”

MS Instrumentation and Miniaturization



Sample Collection

Sample Treatment

Lab-Scale MS
500 lb/2kw

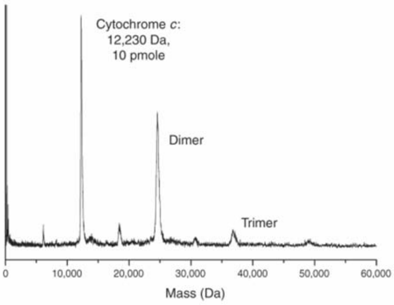
Data Interpretation

Tiny TOF

Cotter, Johns Hopkins

Higher Order KE Focusing
5 cm Endcap Reflection

m/z 70,000, R = 70



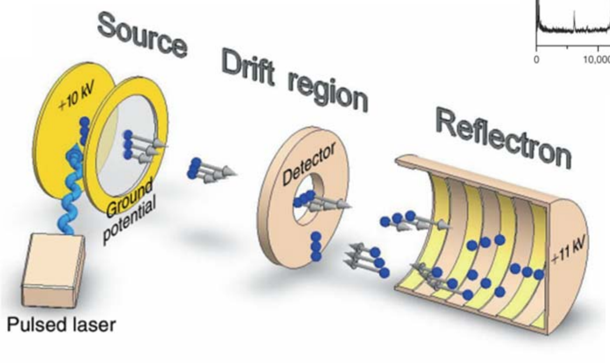
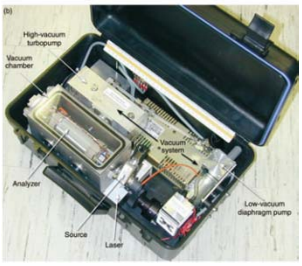


Figure 3

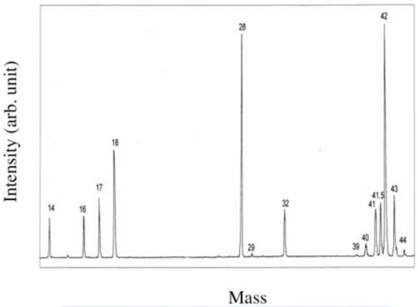


Double Focusing

Sinha, JPL

Mattauch-Herzog
Light B Sector

m/z 300, R = 300



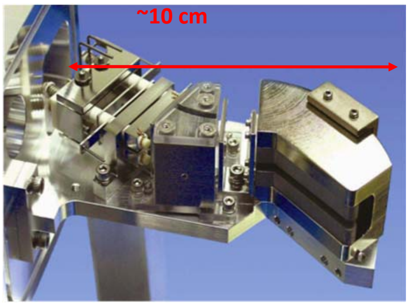
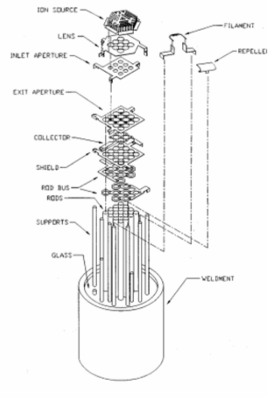


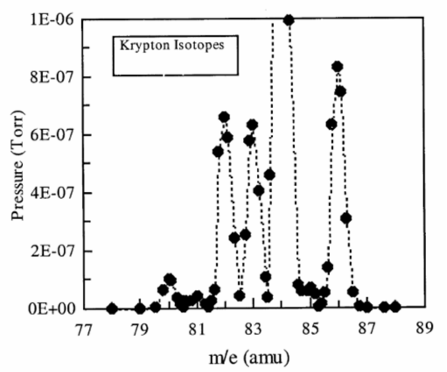
Figure 3

Quadrupole Filter Array

Ferran

0.5 ID Rod

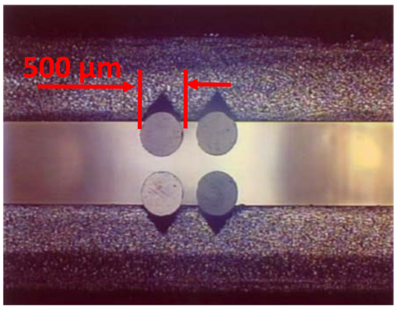


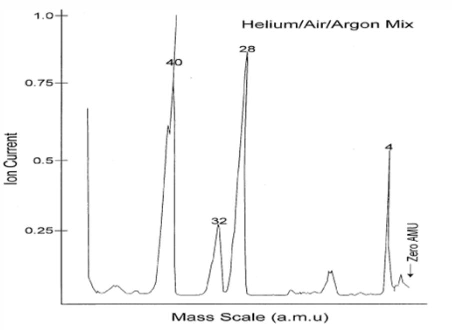


Micro-fabricated Mass Analyzer

Syms, Imerial

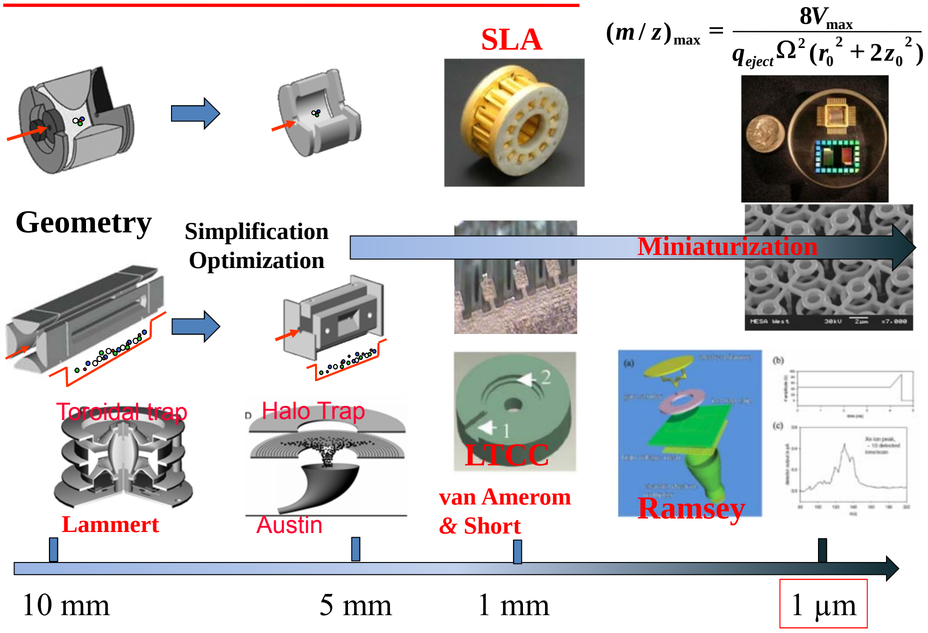
V-Groov Filter



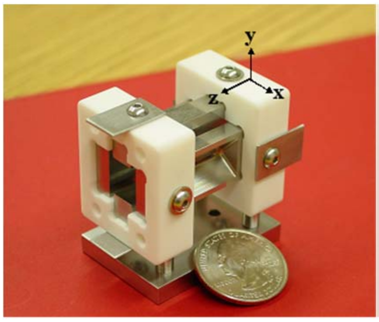


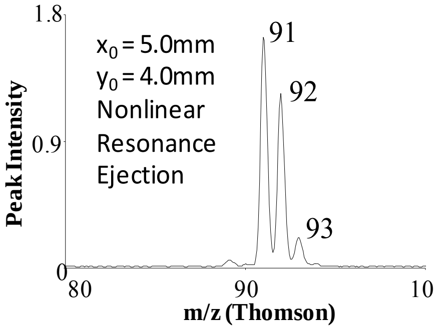
Miniaturization of Ion Trap Mass Analyzer

$$(m/z)_{max} = \frac{8V_{max}}{q_{eject}\Omega^2(r_0{}^2+2z_0{}^2)}$$

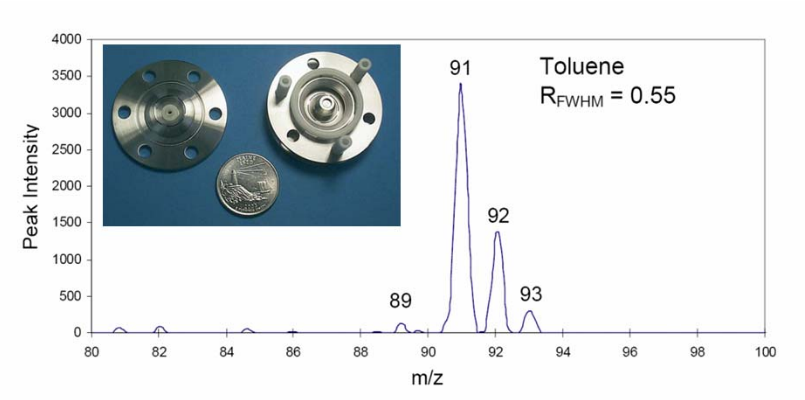


Rectilinear Ion Trap

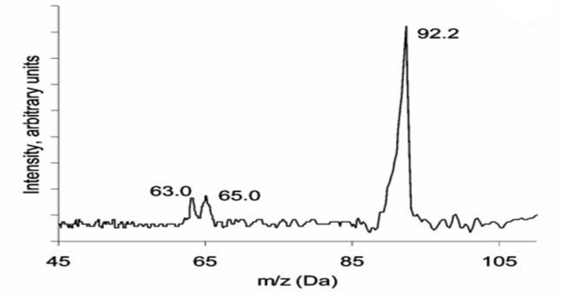


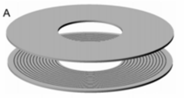


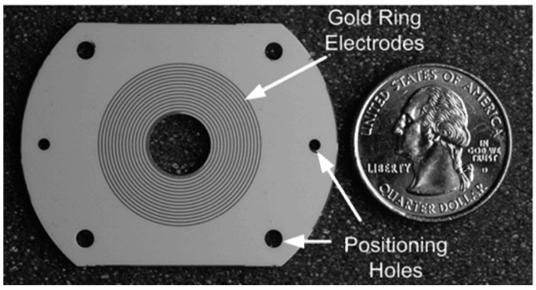
Toroidal Ion Trap



Halo Trap







Tradeoff and Balance

Low Scan Voltage - V_{RF} vs. D - Deep Trapping Potential Well

$$V_{RF} \propto \frac{m}{z} * r^2 * \Omega_{RF}^2 \qquad D \propto V_{RF}$$

r: r_0, for 3D or
x_0, for 2D linear

Ω_{RF}: RF frequency

Trapping Efficiency

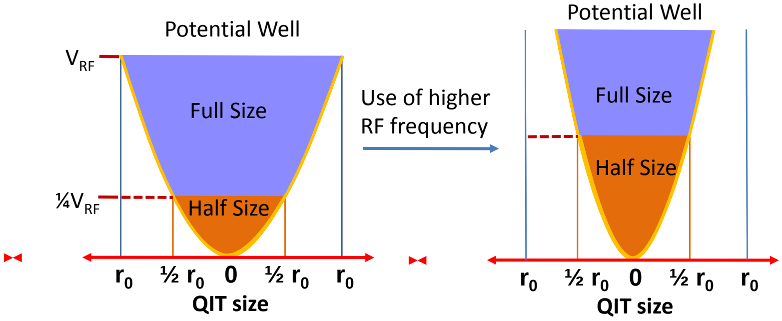


Figure 7

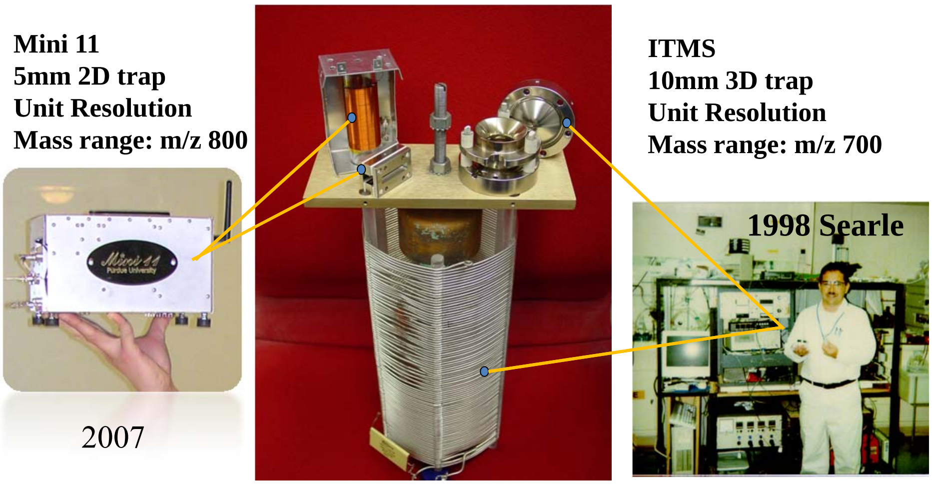
Impact of Trap Size

RF Voltage and Power?

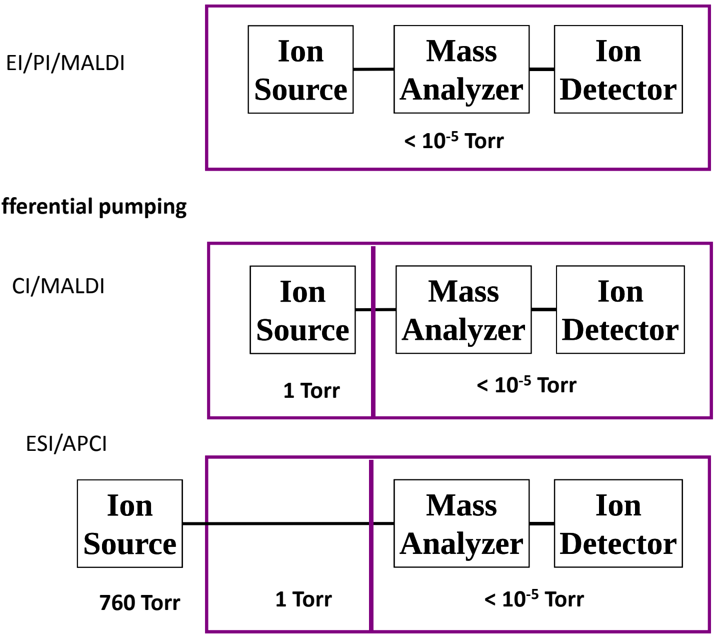
$$(m/z)_{max} = \frac{8V_{max}}{q_{eject}\Omega^2(r_0^2+2z_0^2)}$$

Mini 11
5mm 2D trap
Unit Resolution
Mass range: m/z 800

ITMS
10mm 3D trap
Unit Resolution
Mass range: m/z 700



Pressure matching between the ion source and the mass analyzer



EI/PI/MALDI

Ion Source — Mass Analyzer — Ion Detector

< 10^{-5} Torr

Differential pumping

CI/MALDI

Ion Source | Mass Analyzer — Ion Detector

1 Torr

< 10^{-5} Torr

ESI/APCI

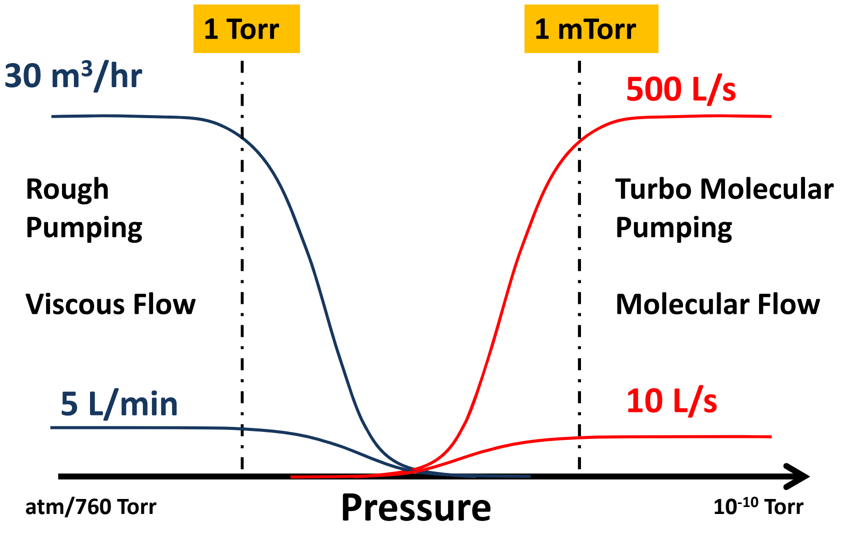
Ion Source | Mass Analyzer — Ion Detector

760 Torr

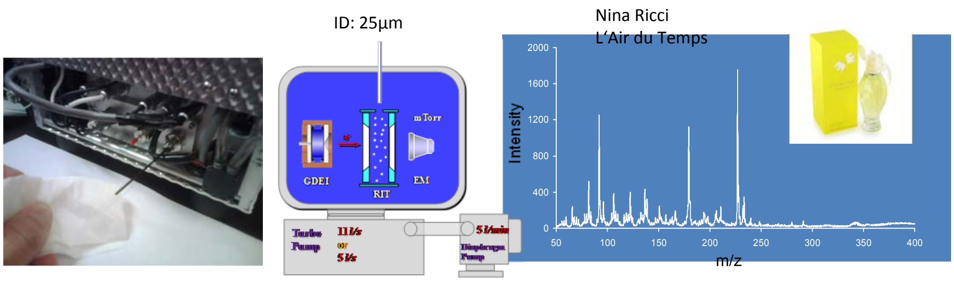
1 Torr

< 10^{-5} Torr

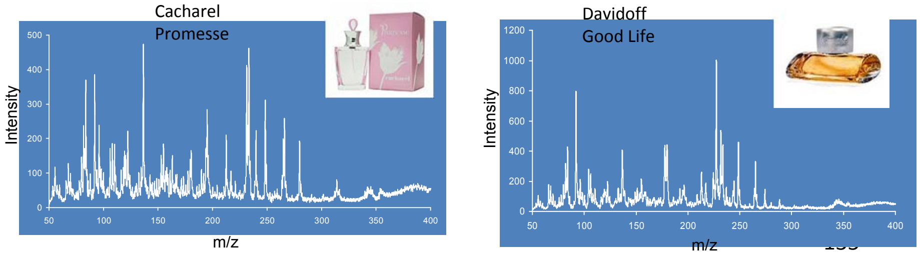
Pumping



Direct Leak



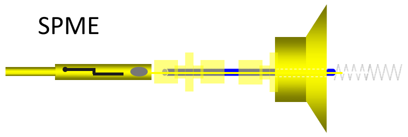
Nina Ricci
L'Air du Temps



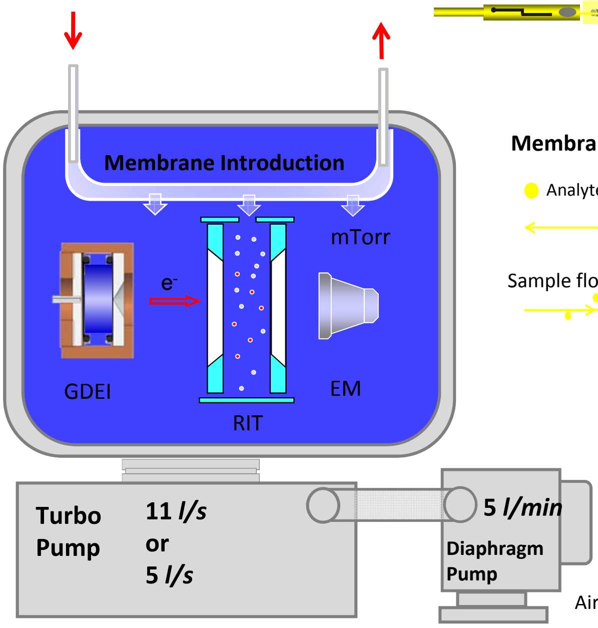
Cacharel
Promesse

Davidoff
Good Life

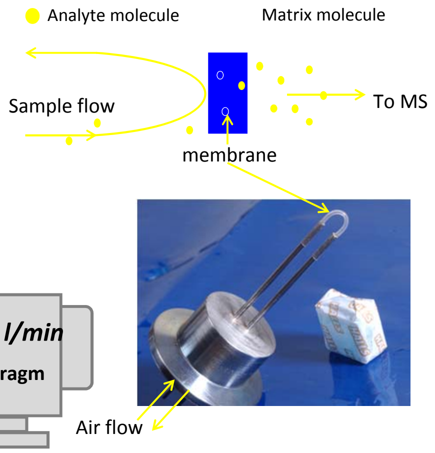
Sampling and Pumping



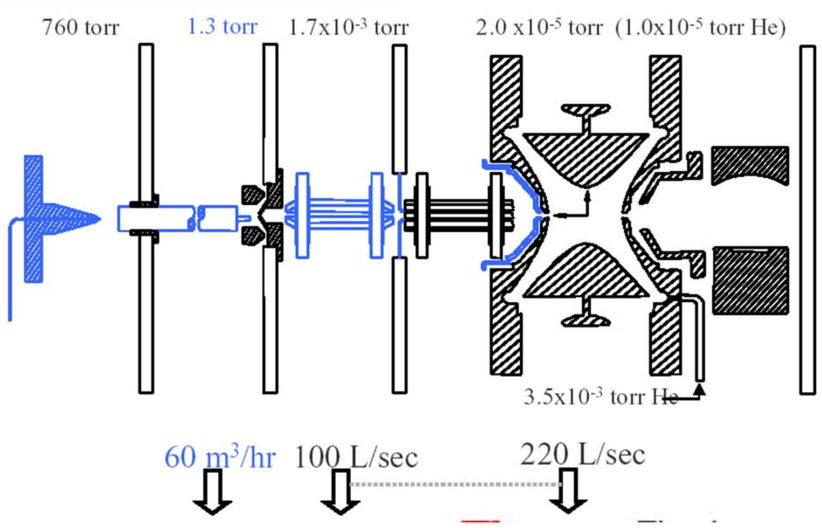
SPME



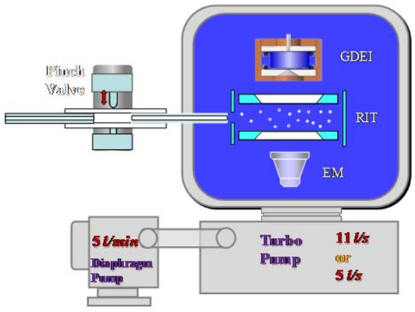
Membrane Introduction

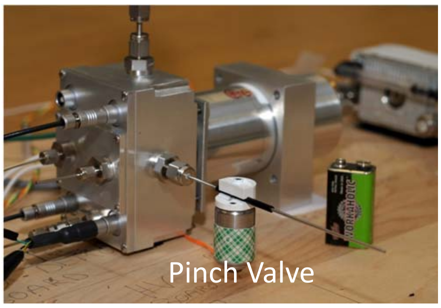


Gas and Ions

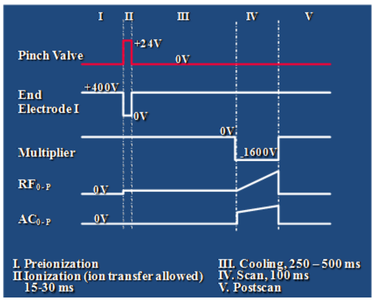


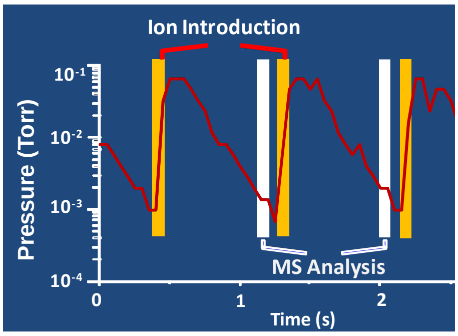
Discontinuous Atmospheric Pressure Interface (DAPI)





Scan Function





Systems	Self-Sustainable Portable Systems						Portable Systems without Rough Pumping	
	Mini 10/ Mini 11 (3, 4)	ChemCube (119)	Guardion-7 (5)	Suitcase TOF (9)	Griffin 600 (120)	Ion-Camera (121)	Palm-Portable MS (52)	HAPSITE (75)
Developer	Purdue University	Microsaic Systems	Torion Technologies	Johns Hopkins Applied Physics Lab	Griffin Analytical	O-I-Analytical	Sam Yang Chemical	Inficon
Weight	10 kg /4 kg	14 kg	11 kg	N/A	15 kg	18 kg	1.5 kg	18 kg
power	70 W/30w	50 W	75 W	N/A	N/A	75 W	5 W	< 150 W
Mass Analyzer	Rectilinear ion trap	Quadruple mass filter	Toroidal ion trap	Time of flight	Cylindrical ion trap	Mattauch-Herzog sector	Cylindrical ion trap	Quadrupole mass filter
MS/MS	Yes	No	Yes	No	Yes	No	No	No
Sampling /Ionization	MIMS, direct leak, GDEI, APCI, ESI, DESI, LTP	SPME EI	SPME, Mini GC EI	MALDI	SPME,MIMS EI	Direct gas leak EI	Pulsed gas leak EI	GC EI
Mass range /Resolution	m/z 550, R= 550; m/z 2000, R = 100	m/z 400, R = 100	m/z 500, R = 500	m/z 70,000, R = 70	m/z 425, R = 400	m/z 300, R=300	m/z 300, R = 150	m/z 300, R = 300
System Photo