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World Year of PHYSICS 2005

SMR.1670 - 33

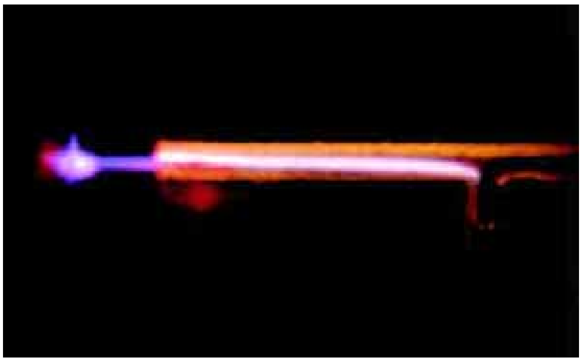
INTRODUCTION TO MICROFLUIDICS

8 - 26 August 2005

Chip-based MS

H. Gardeniers
University of Twente, Enschede, The Netherlands

Chip-based MS



Han Gardeniers

MESA+ Institute for Nanotechnology

University of Twente

Summer School in Microfluidics

ICTP, Trieste, Italy

Mass spectrometry principles

What is Mass Spectrometry (MS) ?

- Separation of molecular species according to their mass

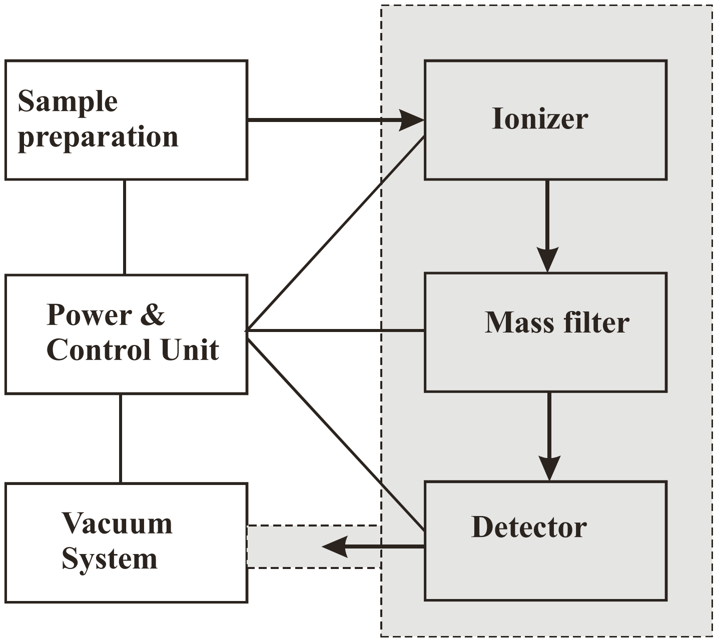
Why is MS useful ?

- The mass of a species can be used to identify a molecule
- Fragmentation under well-controlled conditions gives a fingerprint of a molecular species

How does MS work ?

- Species are ionized (sometimes fragmented) and accelerated in an electric field
- The trajectory of the species is altered by a second electric or a perpendicular magnetic field, the deviation of the path depends on the mass/charge ratio
- The trajectory deviation is monitored by detectors, this gives a "mass spectrum"

General set-up for mass spectrometry



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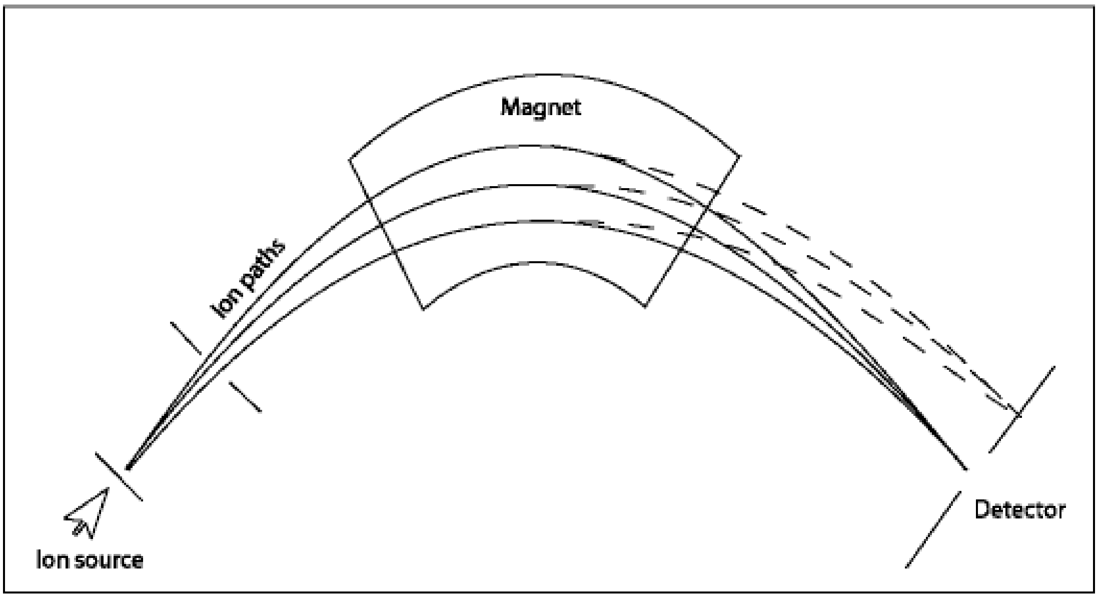
Example: magnetic sector MS



Lorentz force determines trajectory $$\frac{m_i}{z_i} = \frac{B^2 r^2}{2V_a}$$

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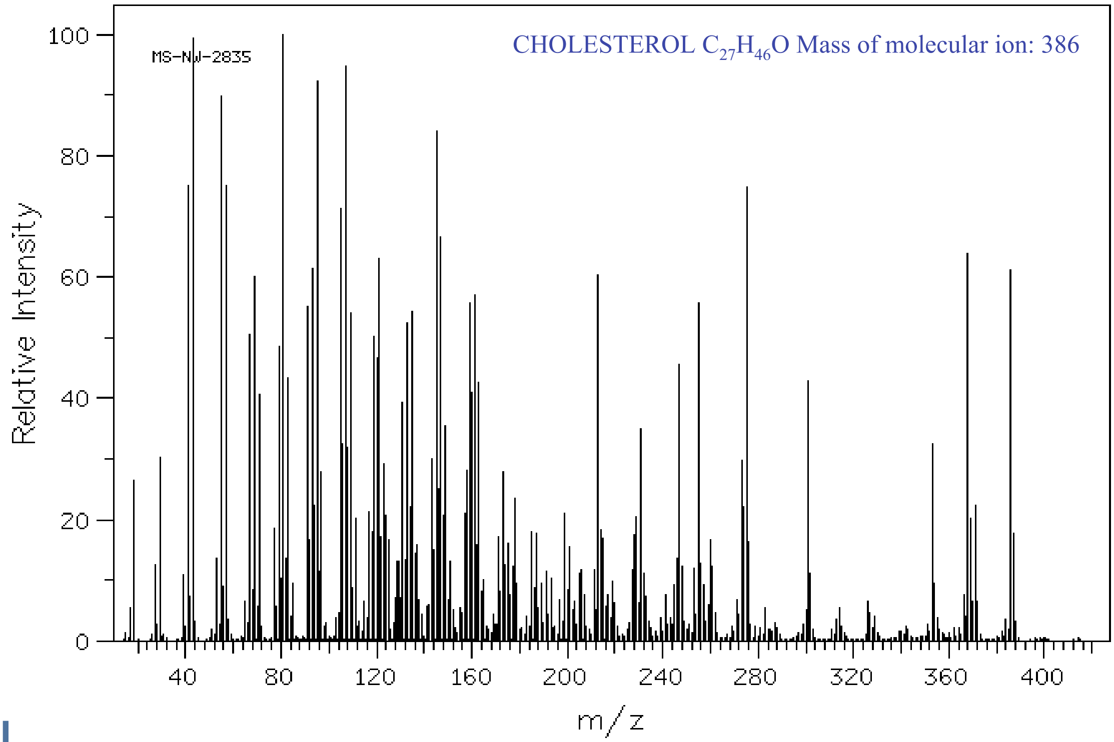
Typical mass spectrum

☞ choresterol structure



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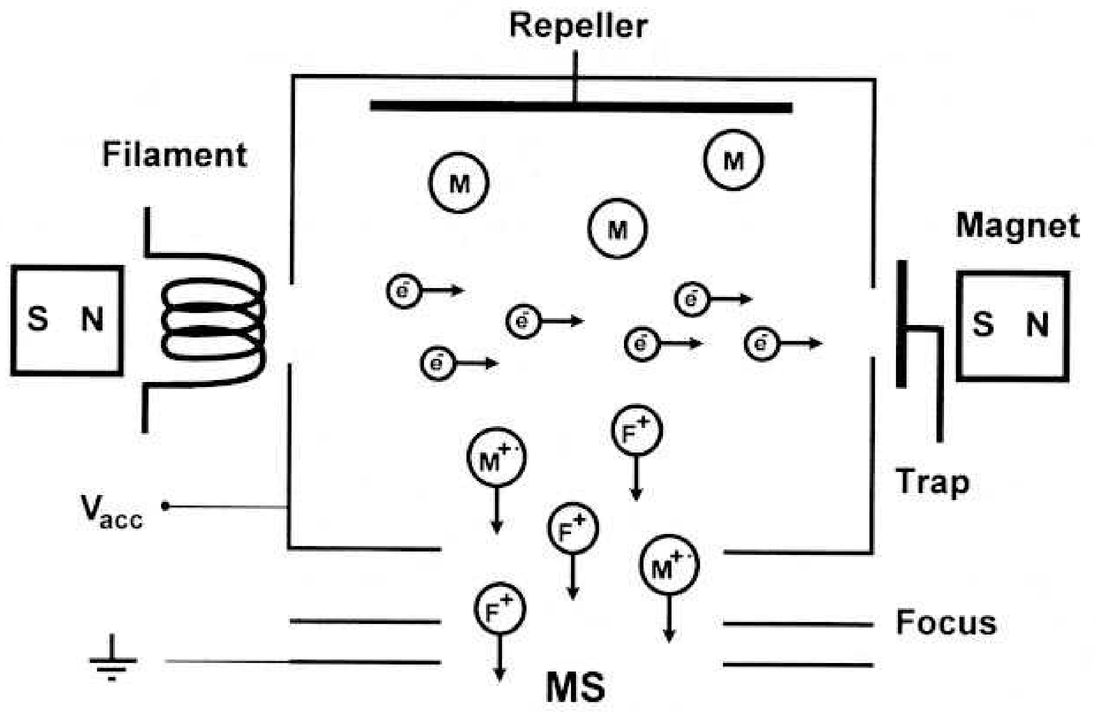
Ionization principles

Electron ionization

M^{+}= ionized molecule

F^{+}= ionized molecular fragment



Mechanisms of ion formation in electron ionization

Consider the ionization of the analyte species AB:

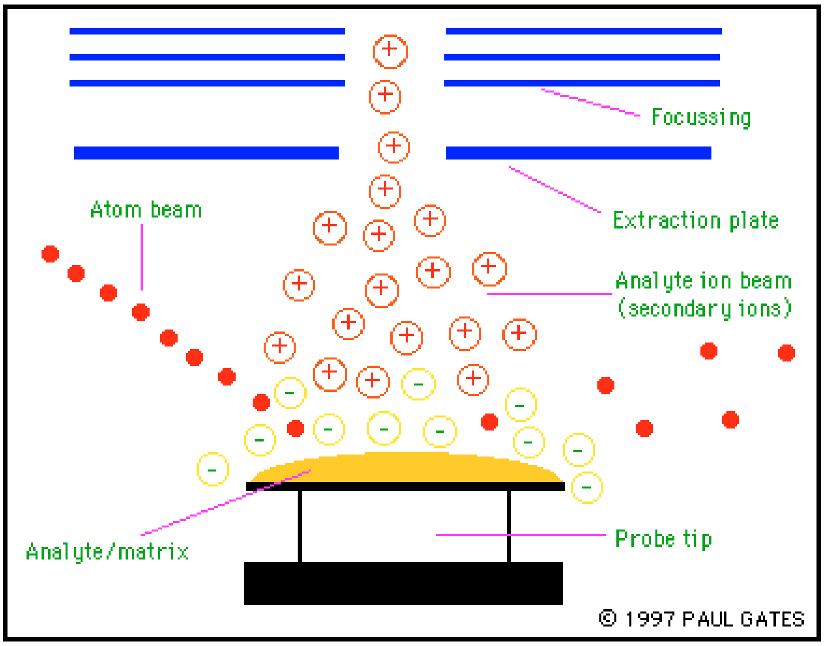
1. $AB + e^{-*} \Rightarrow A^{+} + B^{-} + e^{-}$
2. $AB + e^{-*} \Rightarrow A^{+} + B^{\circ} + 2e^{-}$
3. $AB + e^{-*} \Rightarrow [AB^{+\circ *}] + 2e^{-}$ *followed by* $[AB^{+\circ *}] \Rightarrow AB^{+\circ}$
4. $AB + e^{-*} \Rightarrow [AB^{2+*}]'' + 3e^{-}$ *followed by* $[AB^{2+*}]'' \Rightarrow A^{+} + B^{+}$ - very low abundance
5. $AH + e^{-*} \Rightarrow AH^{*} + e^{-}$ *followed by* $AH^{*} + AH \Rightarrow [AH+H]^{+} + A^{-}$ (self chemical ionization)

* = species in high energy state ° = radical " = short lived intermediate not seen in spectra

1 and 2: highest abundance; termed instantaneous fragmentation.
This is the reason why EI is considered a **hard ionization process**

3: fairly high abundance; process responsible for the molecular ion formation
(Unfortunately the highly energetic radical intermediate $[AB^{+\circ *}]$ tends to undergo fragmentation or rearrangement as a stabilizing process, this is responsible for the lower mass fragment ions present in the spectra)

Fast Atom Bombardment



FAB is a soft ionization method, i.e. little fragmentation occurs

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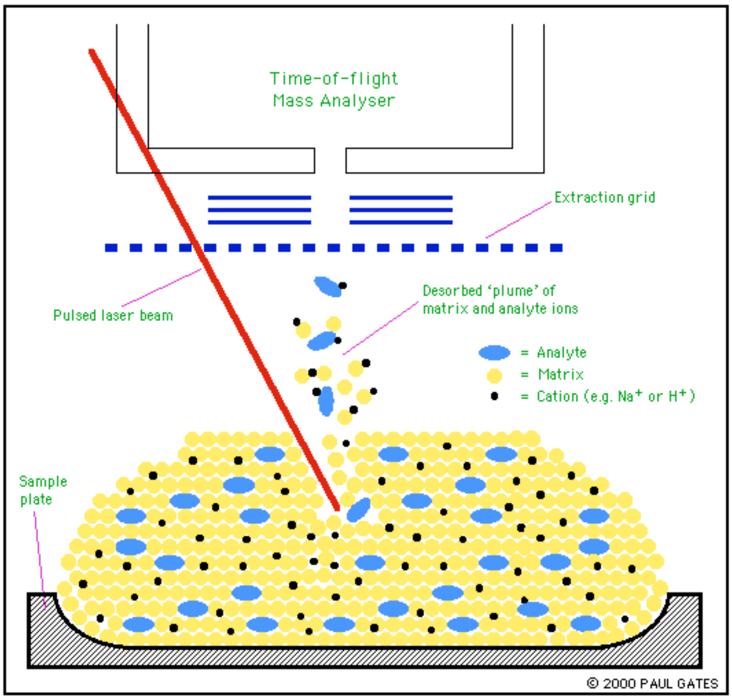
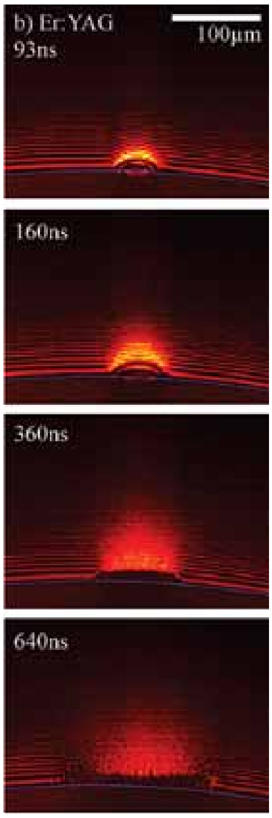
Matrix-Assisted Laser Desorption/Ionization

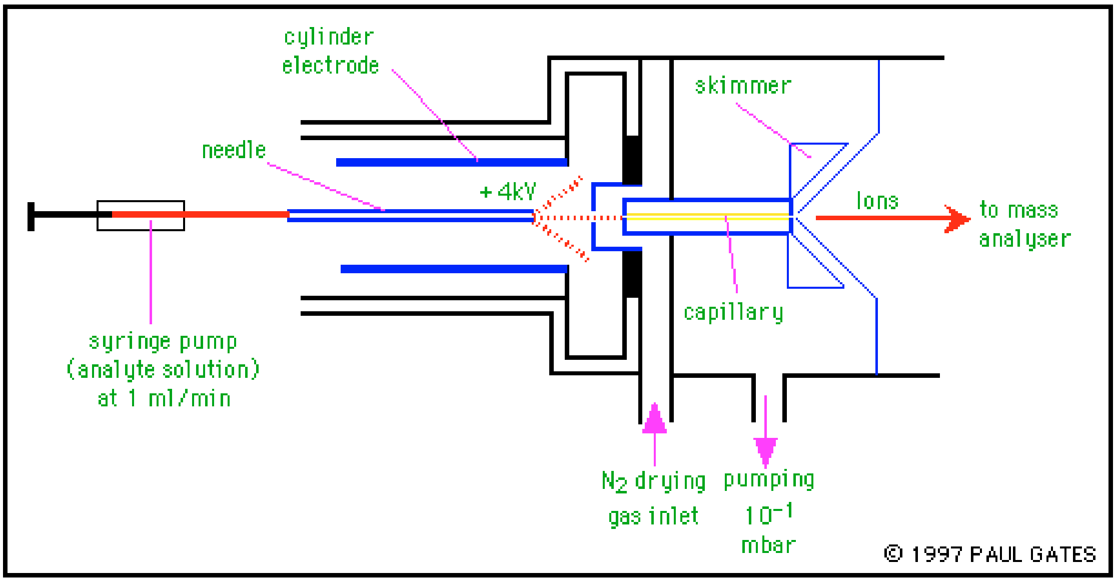




MALDI is a soft ionization method - gives ion burst which is compatible with TOF (Time-Of-Flight)

MESA+ Visualisation pictures from: Leisner e.a. J.Phys.Chem.B 109, 11661-11666 (2005) University of Twente The Netherlands

Electrospray Ionization (ESI)



ESI is a soft ionization method

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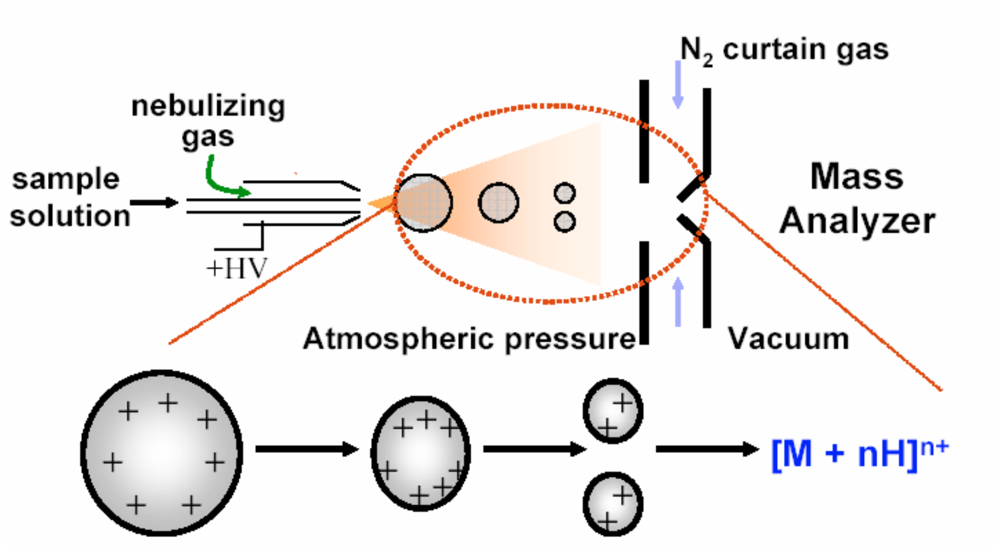
Principle of ESI



1. Solvent evaporation
2. Coulombic repulsion

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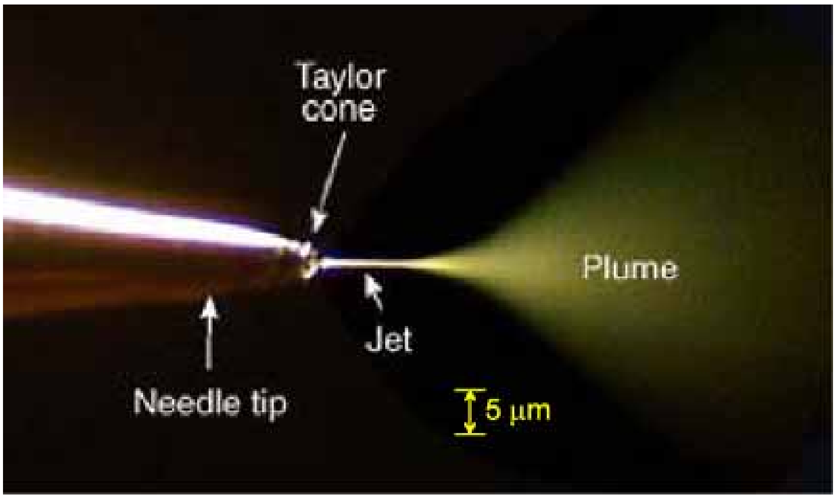
ESI: The Taylor cone



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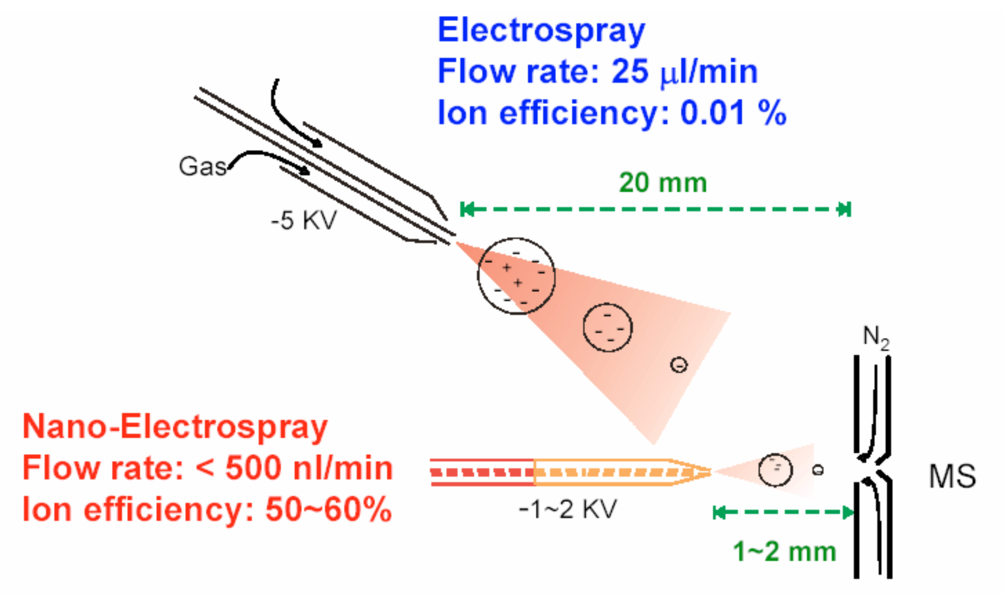
Miniaturization of ESI



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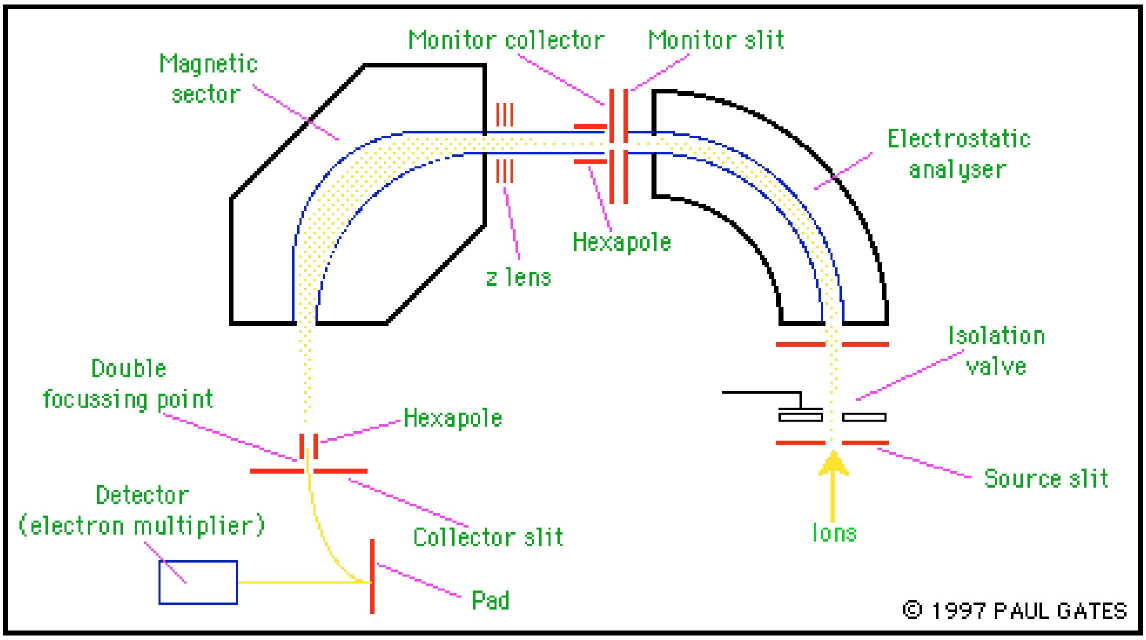
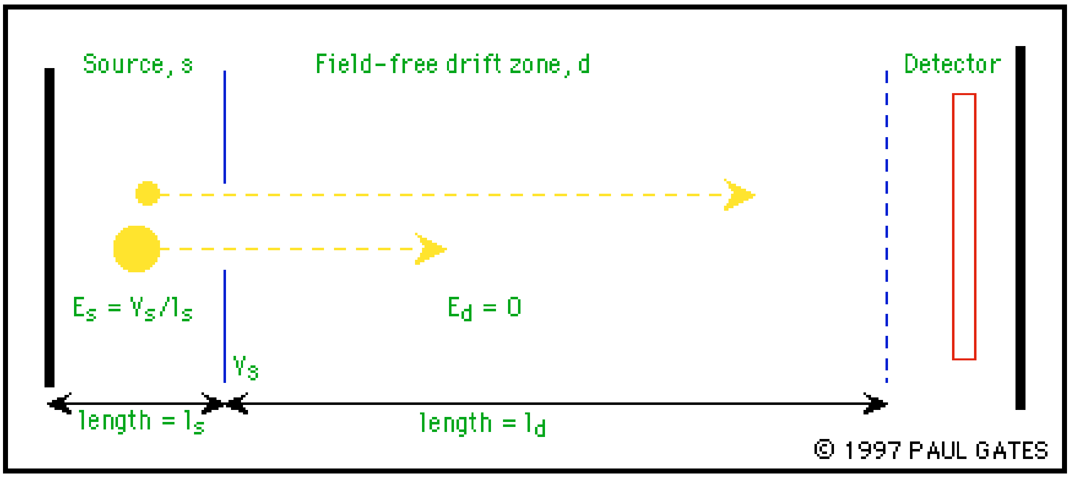
Mass analysis methods

Double Focussing (Sector) Analysis



Time-of-flight (TOF)



The larger the ion, the slower its velocity and thus the longer it takes to traverse the field-free drift zone. The field in the field-free zone, E_d, is zero at all times

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TOF basic equation

$$\frac{m_i}{z_i} = 2eEl_s\left(\frac{t_i}{l_d}\right)^2$$

Where:

m_i = mass of analyte ion

z_i = charge on analyte ion

E = extraction field

t_i = time-of-flight of ion

l_s = length of the source

l_d = length of the field-free drift region

e = electronic charge (1.6022×10^{-19} C)

Kinetic energy charge in E-field: $E_{kinetic} = \frac{1}{2}mv^2 = qV$

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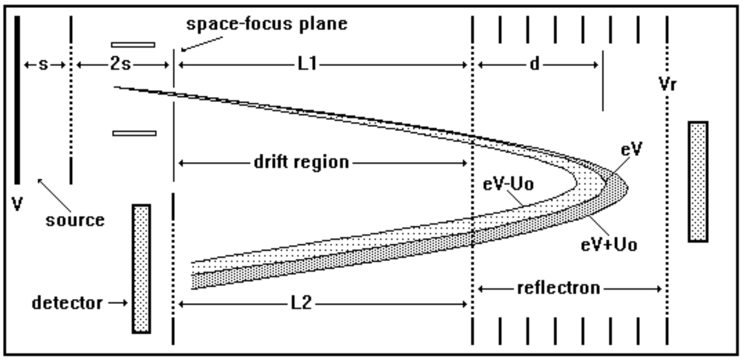
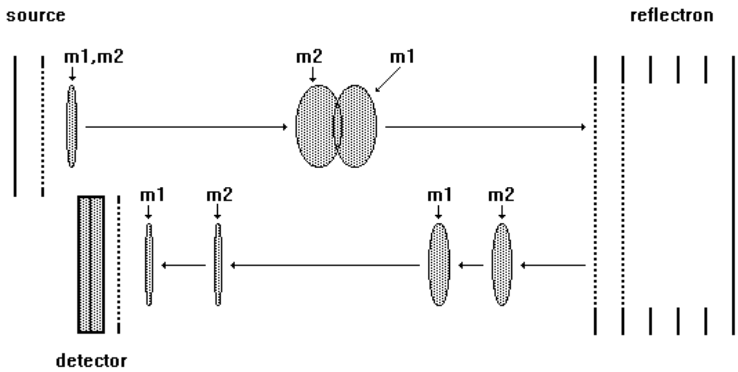
TOF with reflectron





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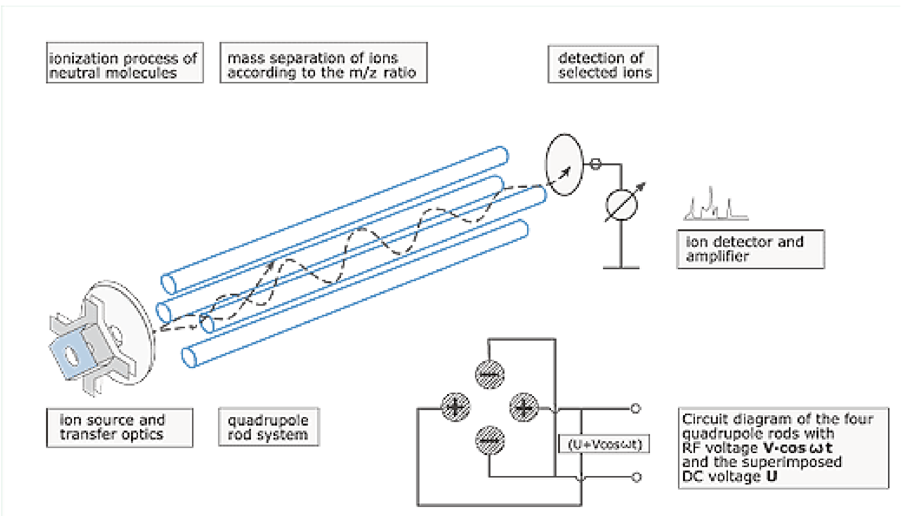
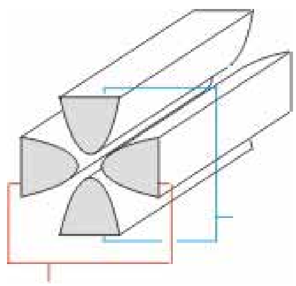
Quadrupole Mass Analyser





The four rods are shown as being circular in the diagram but in practice they have a hyperbolic cross-section

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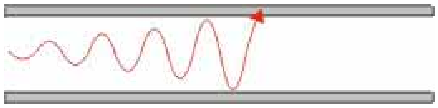
QMS principle

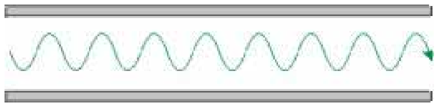
Alternating electric field makes ions go off into spirals as they pass down the quadrupole.
The constant voltage drags them in one constant direction, towards one pair of electrodes.

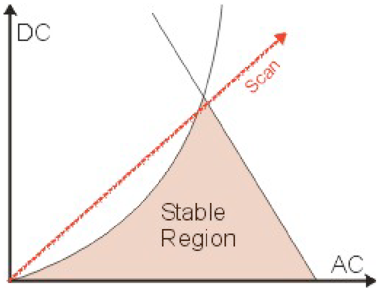
Small ion is dragged large distance by AC field, going into stronger and stronger field regions => collides with electrode and disappears



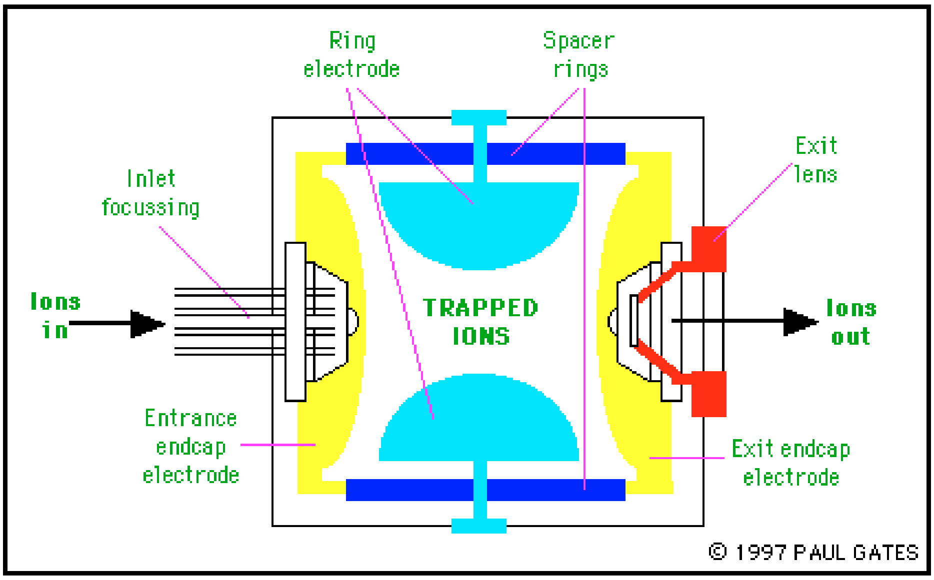
Large ion is not affected by AC field, but drifts in DC field => collides with electrode and disappears

Ion with correct size drifts slightly in DC field, but is always dragged back by AC field => stable trajectory to outlet of quadrupole and detector





Ion Trap Analysis



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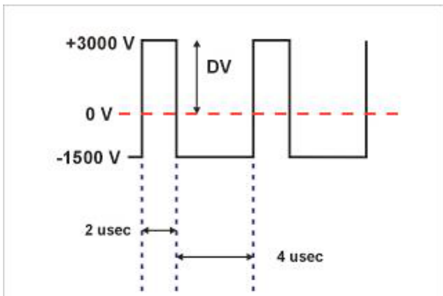
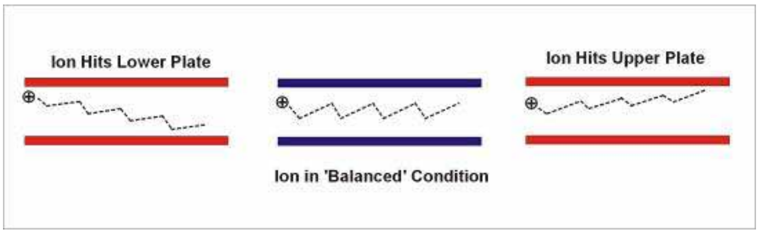
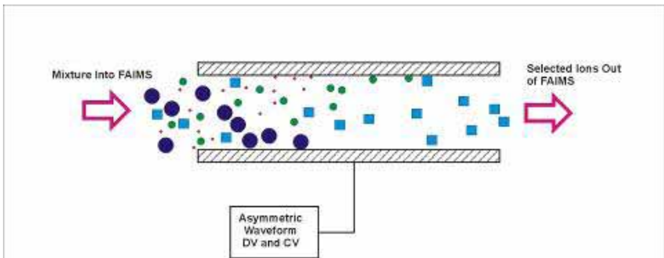
Field-Asymmetric Ion Mobility Spectrometer



asymmetric waveform





CV = compensation voltage

www.faims.com

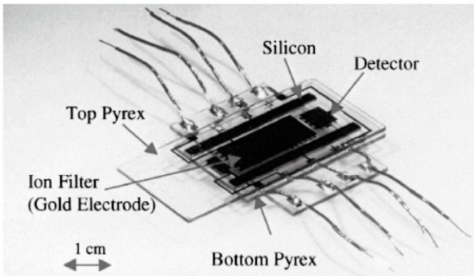


Fig. 3. Photograph of a micromachined field asymmetric ion mobility spectrometer.

Sensors and Actuators B 67 2000 300–306

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Coupling microfluidics to MS

ESI from a chip

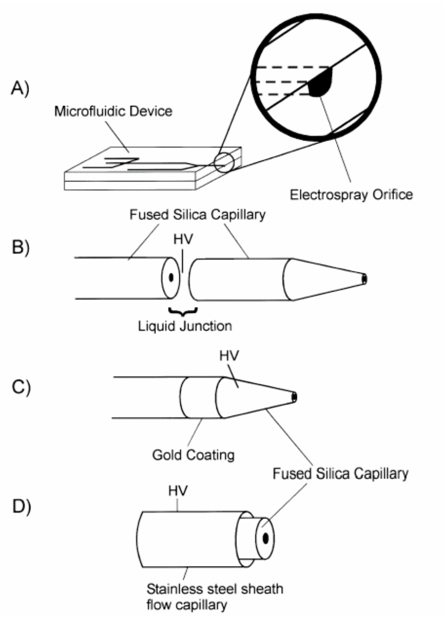
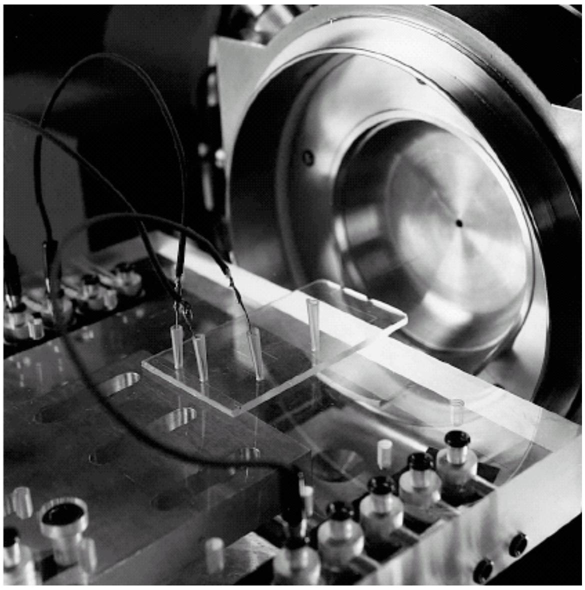


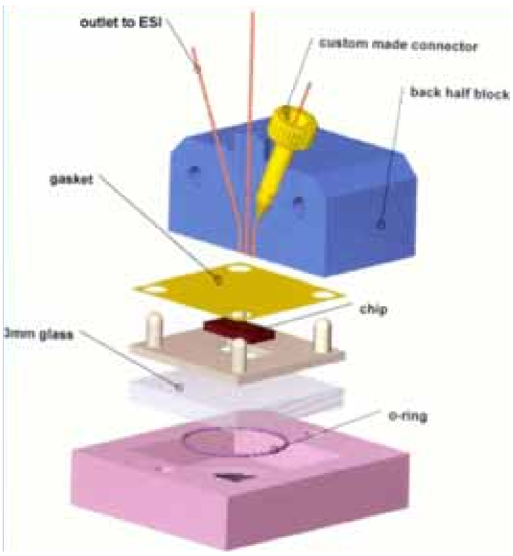
Fig. 2. Schematic diagram of different electrospray interfaces that have been developed for chip-ESI-MS: (A) spraying directly from an exposed channel at the edge of a chip; (B) liquid junction capillary interface; (C) gold-coated capillary interface; and (D) coaxial sheath flow configuration. HV denotes points to which the electrospray voltage is applied.

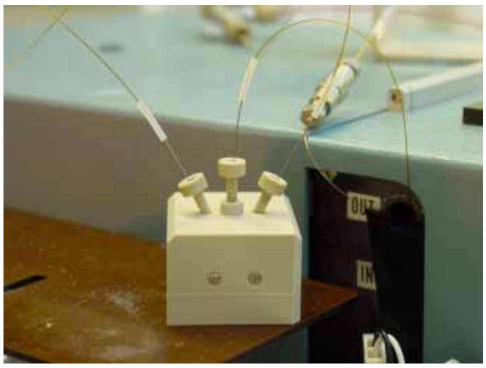


chip with capillary interface

Oleschuk & Harrison, Tr. Anal. Chem. vol. 19, no. 6, 2000, 379-388

ESI from chip via capillary (1)



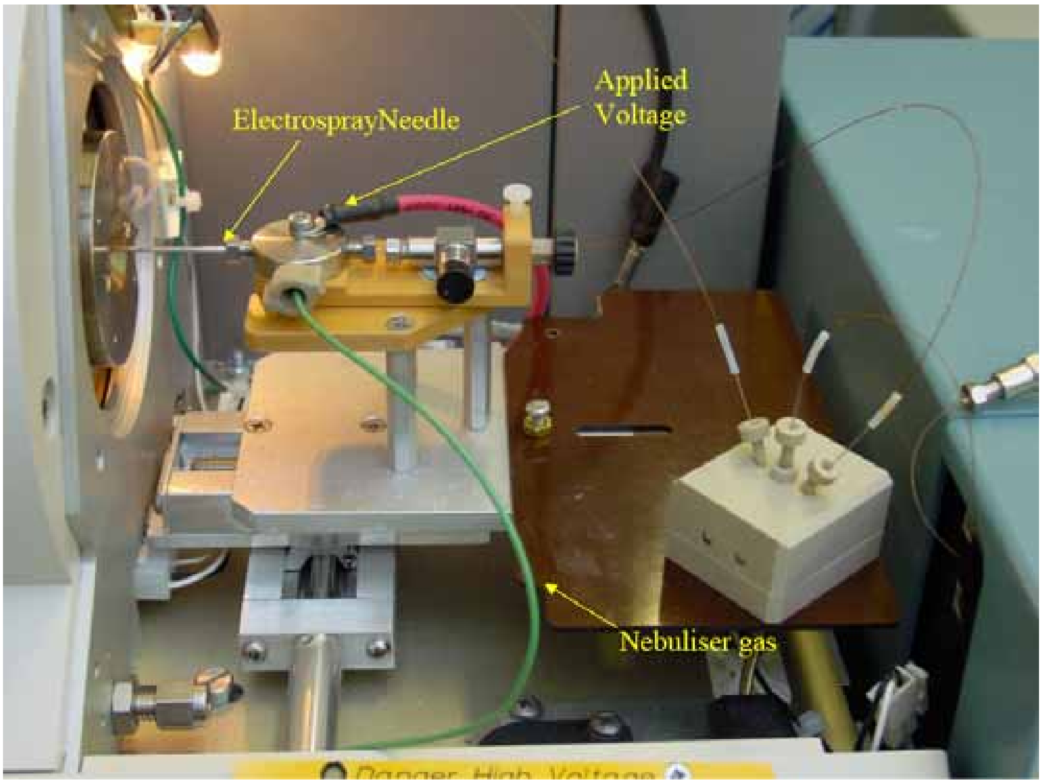


Derivatization
after LC
before MS
using micromixer-reactor

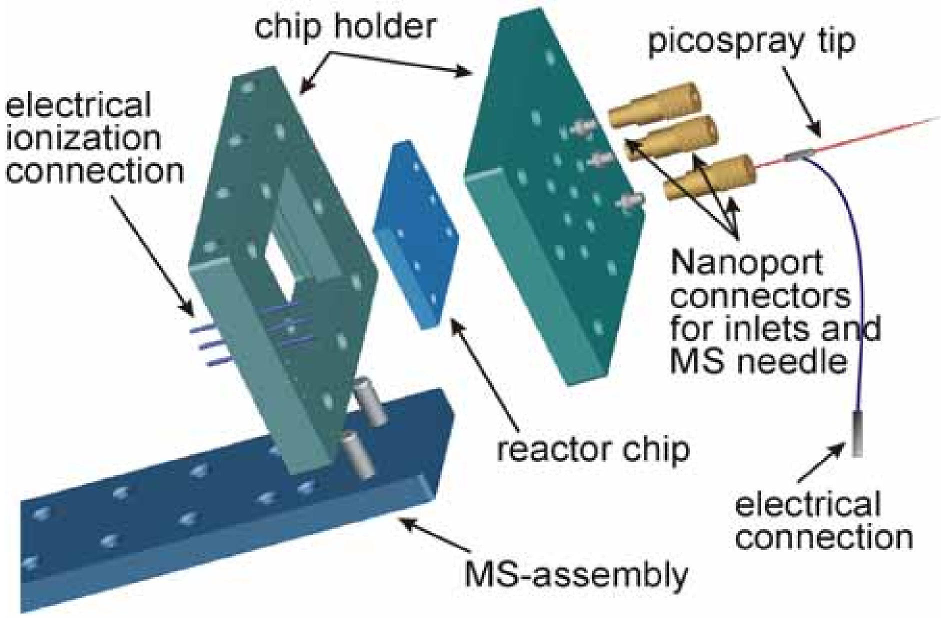
micromixer A. Manz

Bill Leavens, Glaxo Smithkline UK

ESI from chip via capillary (2)

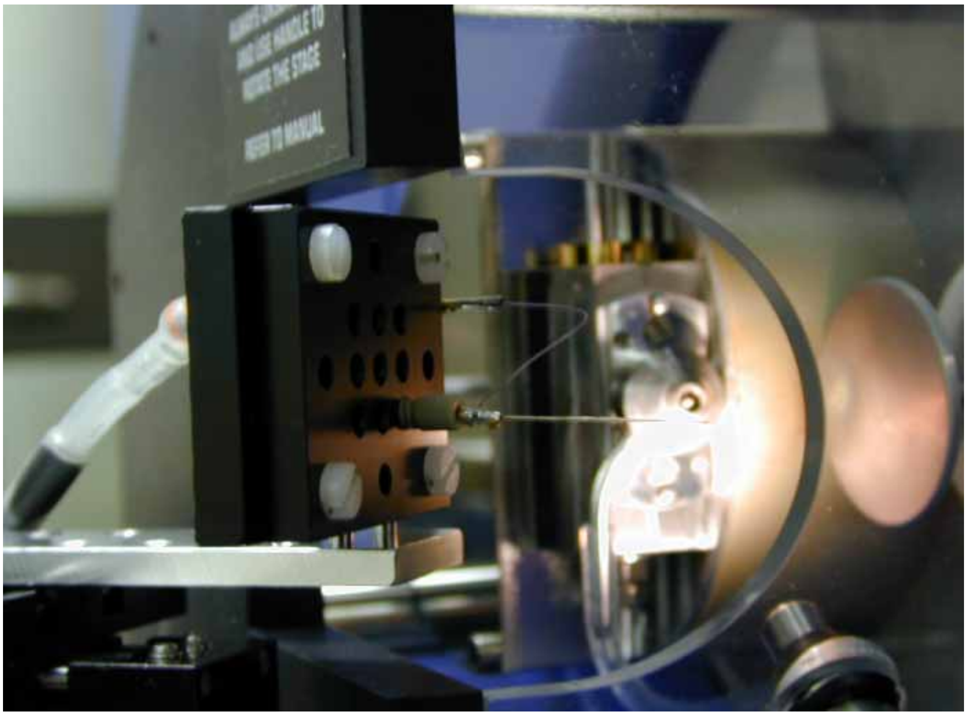


Nano-ESI interface



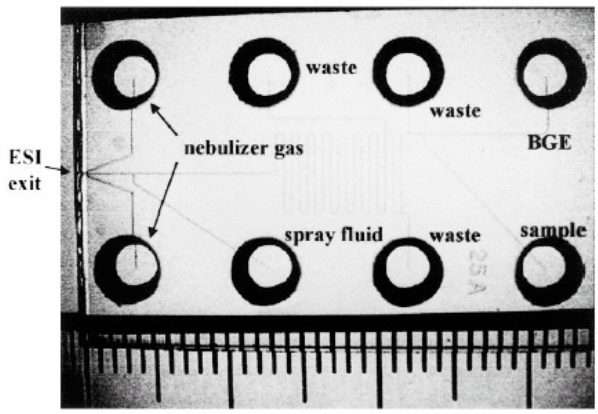
Oosterbroek, Brivio e.a., to be published

Nano-ESI interface

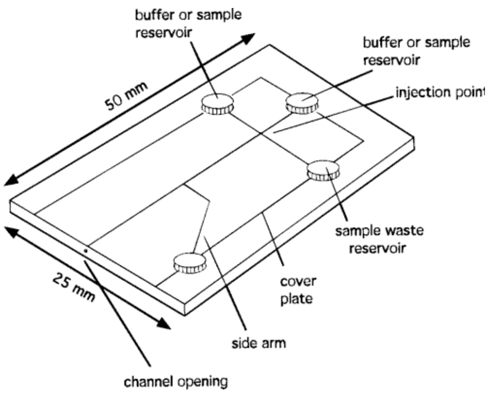


Oosterbroek, Brivio e.a., to be published

ESI directly from a chip outlet

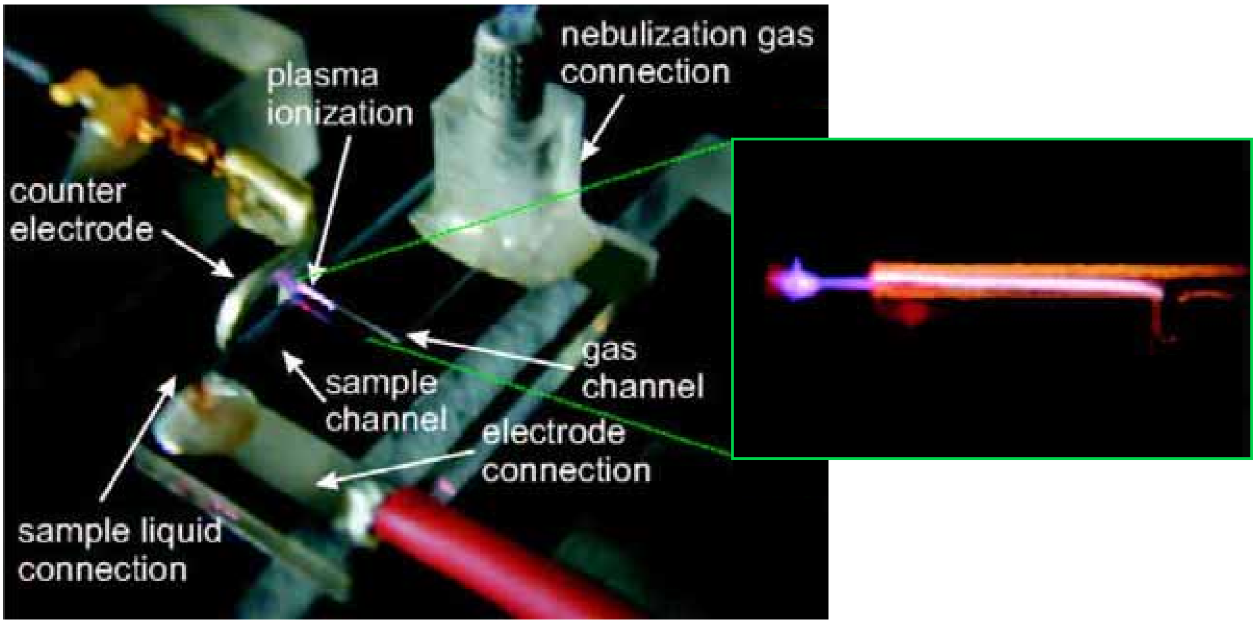


Anal. Chem. 71, 3258 (1999)



Anal. Chem. 69, 1174 -1178 (1997)

Atmospheric plasma generation



Stable plasma at ca. 2 kV/cm at 1 atm

Oosterbroek, University of Twente, 2002, unpublished

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ESI from chip with micromachined nozzle

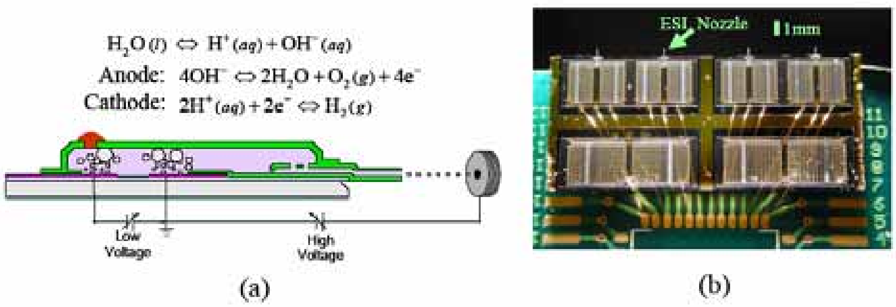

Figure 1. (a) Operation principle of the integrated system. (b) Fabricated device with electrical connections.

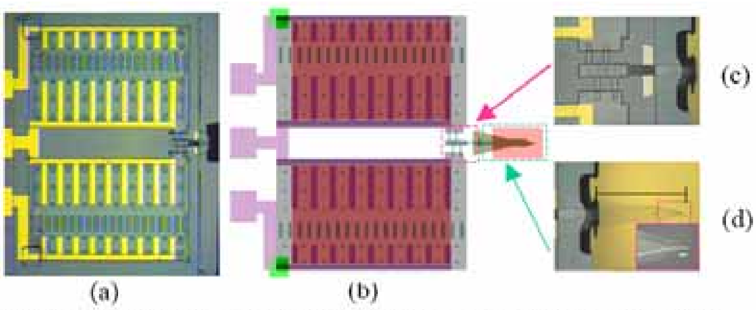

Figure 3. Detailed pictures of integrated system. (a) two pumping chambers, (b) design layout, (c) micro passive mixer and (d) ESI nozzle.

Jun Xie e.a.,
Proc. µTAS 2002,
p. 709-711

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Chip with micromachined nozzles -fabrication process

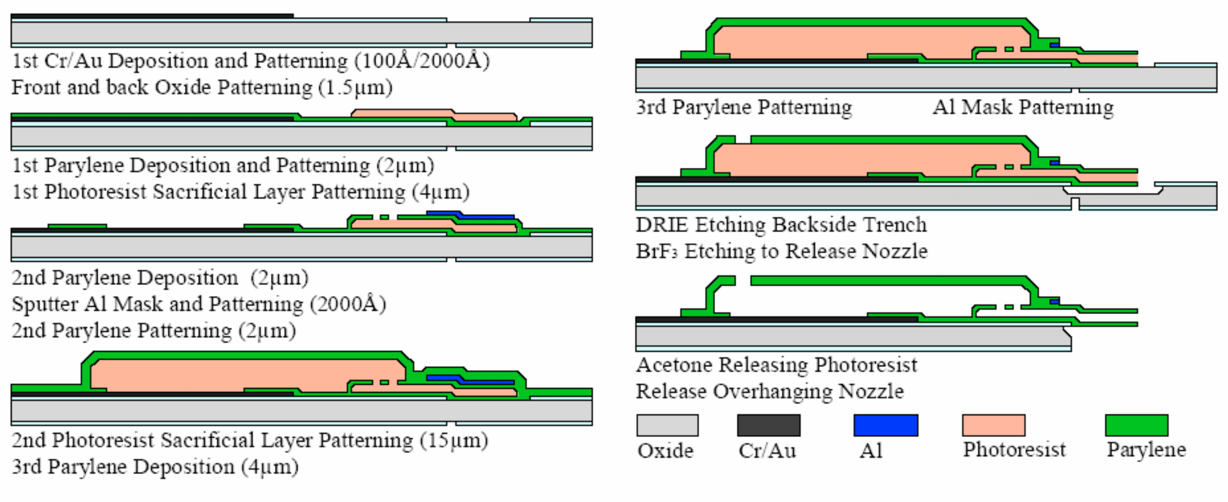

Figure 2. Fabrication process flow.

Jun Xie e.a., Proc. µTAS 2002, p. 709-711

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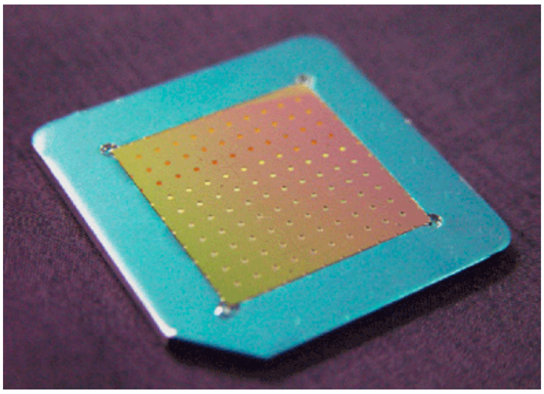
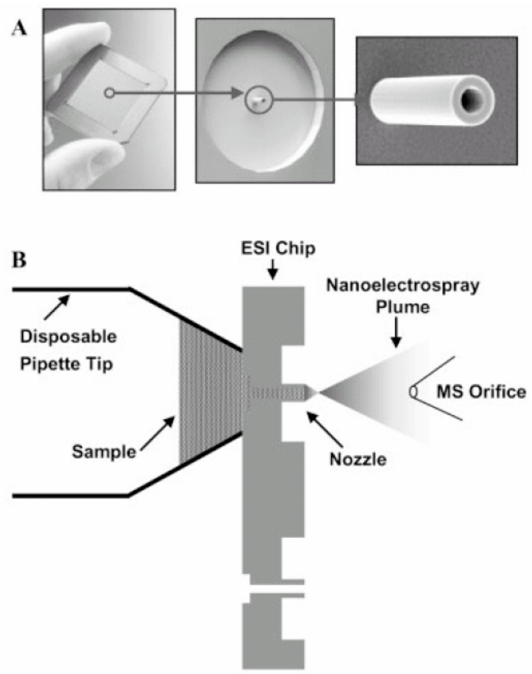
Advion silicon ESI chip





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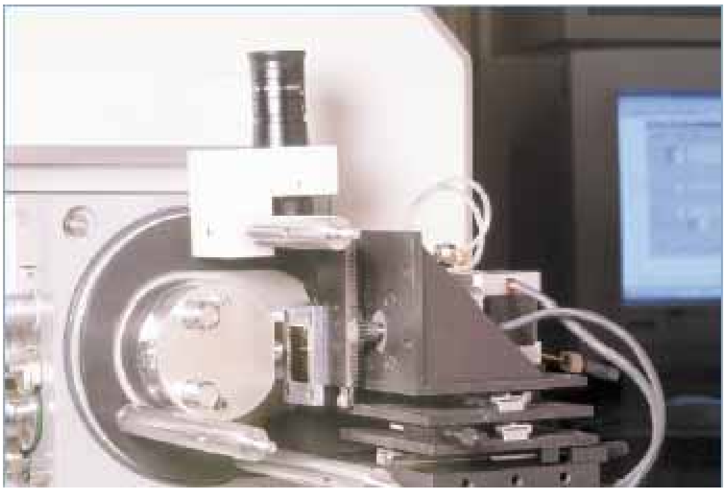
Advion ESI nozzle silicon chip



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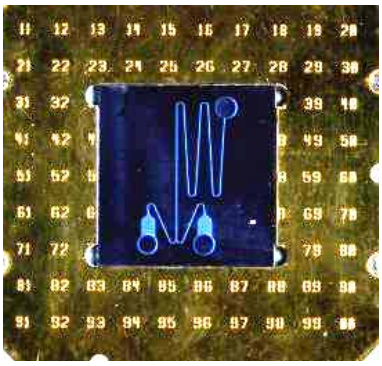
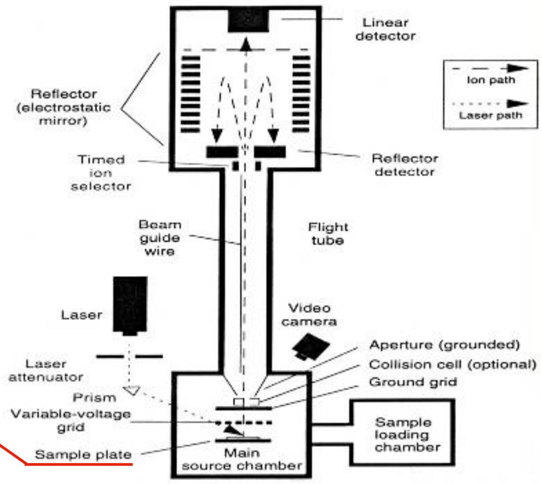
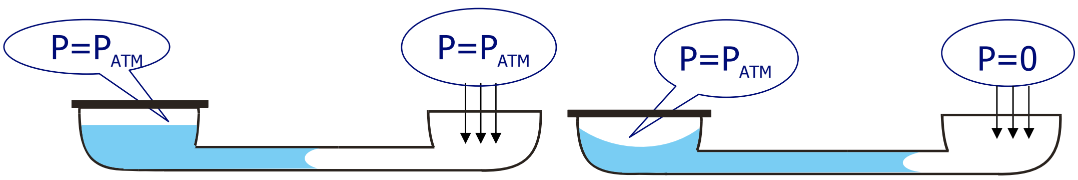
Microreactor and MALDI-TOF-MS





Liquid flow driven by vacuum of MALDI chamber:



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Brivio e.a. Anal. Chem. 74, 3972-3976 (2002)

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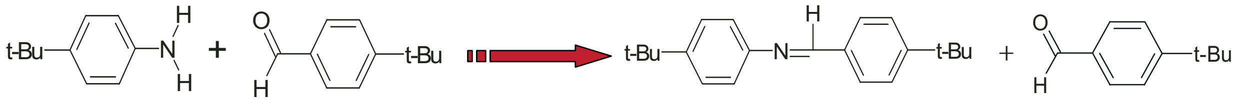
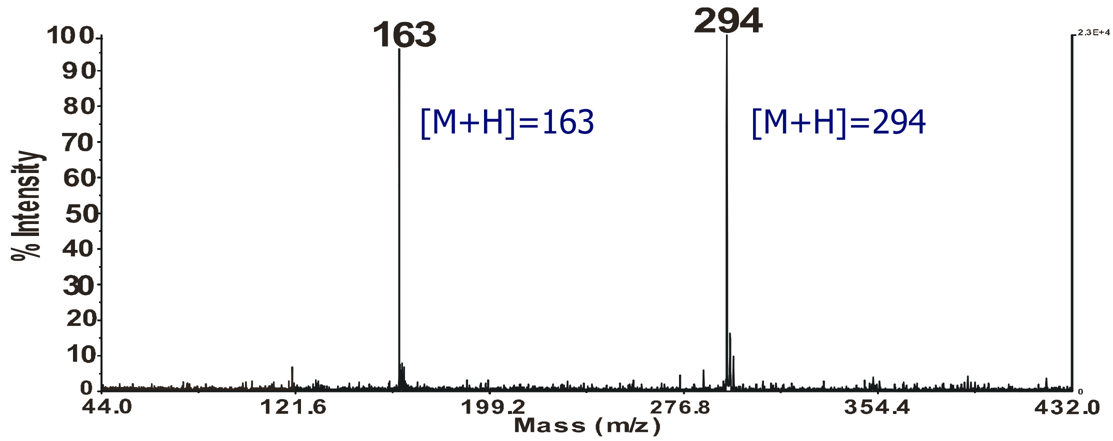
Example: Schiff-base reaction



Molar ratio 1:2 Mass=293 Mass=162



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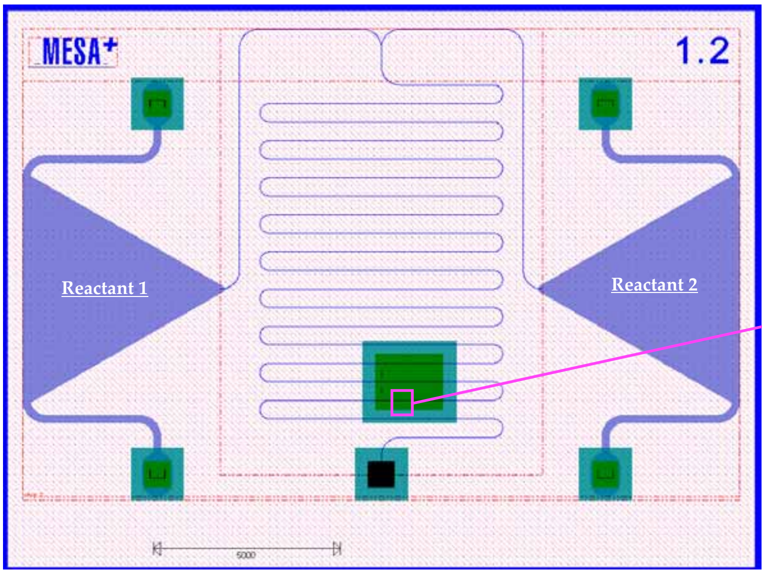
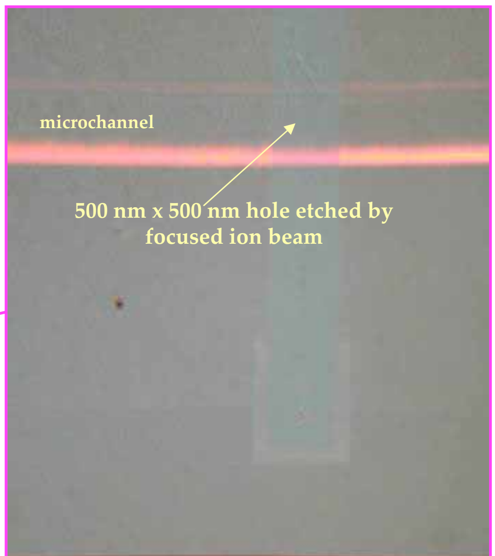
Chip re-design to increase reaction times



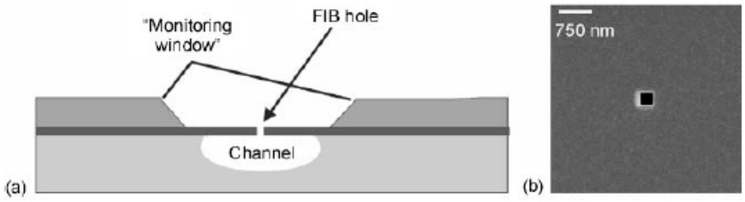
Design of chip with perforated membrane for MALDI



Microscope picture of microchannel underneath perforated membrane

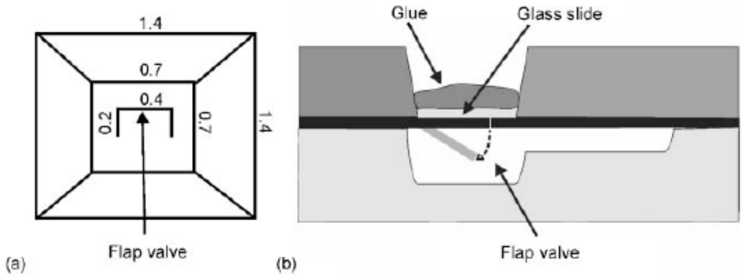
MESA+ Brivio e.a. Lab Chip 5, 378-381 (2005) University of Twente The Netherlands

MALDI-chip with monitoring window



$$\Delta p = R\phi_V$$

$$R = \frac{4\mu L}{ab^3}\left\{\frac{16}{3} - 3.36\frac{b}{a}\left(1 - \frac{b^4}{12a^4}\right)\right\}^{-1}$$



b,a: half of channel width,depth
L: channel length
μ: liquid viscosity (water)
φ_V: volumetric flow
Δp: pressure drop
$t_{(r)}$: residence time at 1 atm
γ: surface tension, 0.07 N/m
P_c: capillary pressure
h: channel height (=a or b)
θ_c: contact angle, 25°

$$t_{(r)} = \frac{LabR}{\Delta p} = 190ms \qquad P_c = \frac{2\gamma\cos\theta_c}{h} = 0.13atm$$

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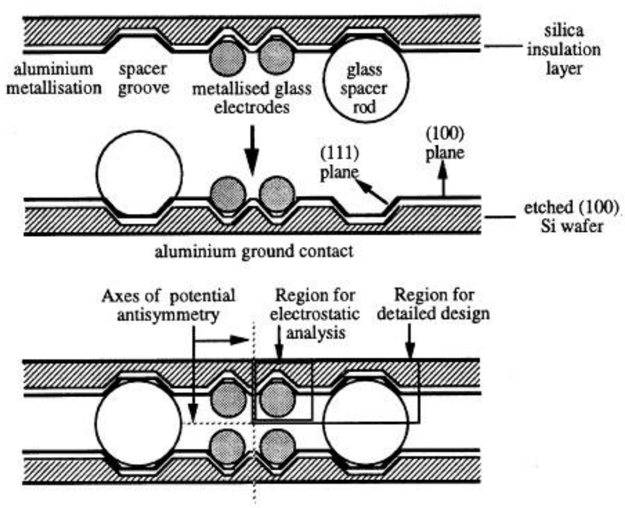
Miniaturised and micromachined MS

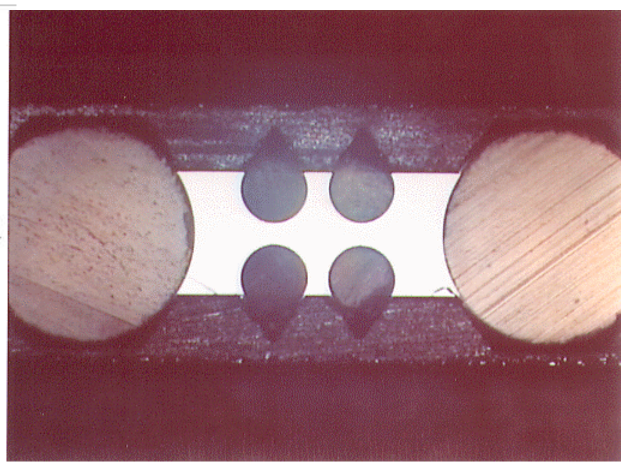
Space needs more space

Volatile Organic Analyzer-Risk Mitigation Experiment (VOA-RME) on Shuttle

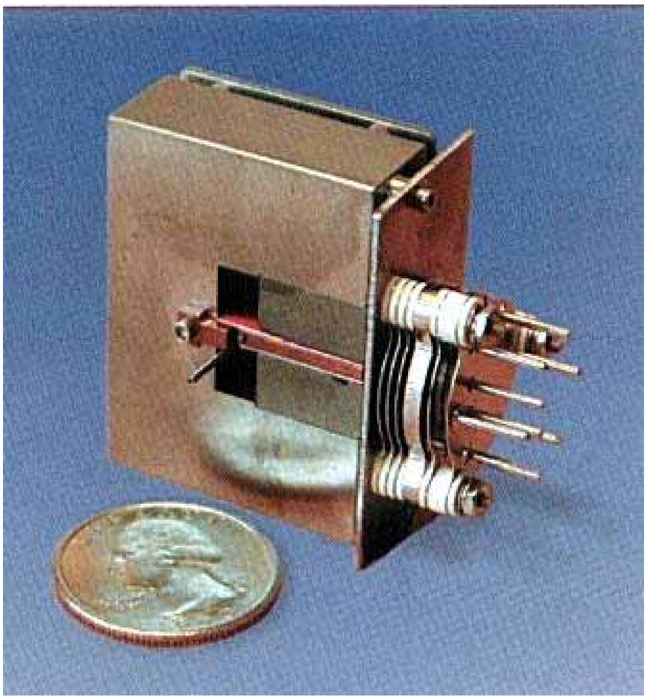
Palmer & Limero "Mass Spectrometry in the U.S. Space Program: Past, Present, and Future" J.Am.Soc. Mass Spectr. 12, 656-675 (2001)

Miniaturized quadrupole MS





Miniature magnetic sector MS



Mass Sensors Inc, St Louis

Double focussing magnetic sector MS,

ILD-50: Golf ball sized

Range: 0-50 amu

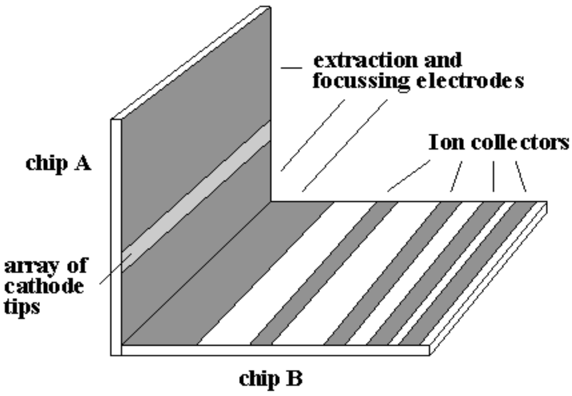
m/Δm = 40

Weight = 153g

Operating pressure 10^{-4} Torr

cells include a 32 bit RISC processor, optional wireless communications interface, and time profiling software

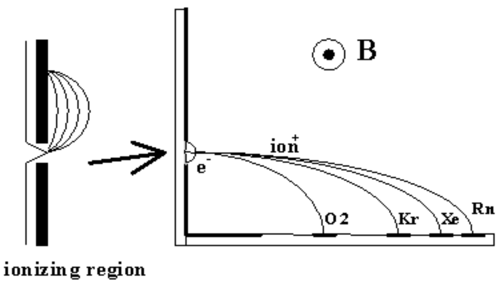
Microengineered magnetic sector MS

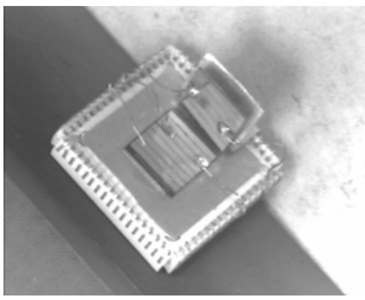


Field emission micro-tip array as an electron source

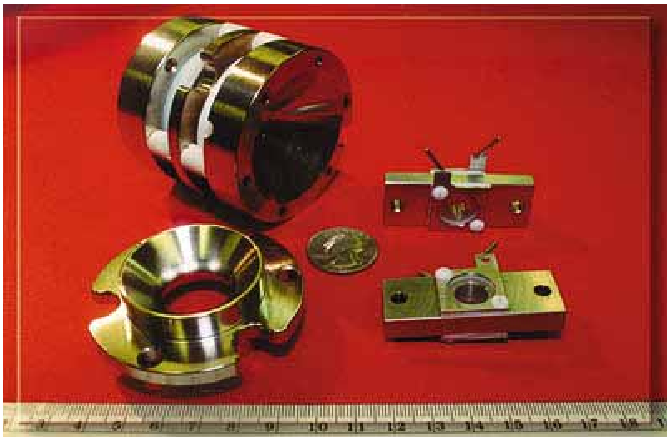
$$m/e = B^2 r^2 / 2V_z$$

Masses separated by magnetic field and detected at collection electrodes





Miniature cylindrical ion trap MS



Cooks e.a. Purdue University

stainless steel, inner radius 2.5mm, (1/4 full size. 1/64 volume)

Mass range to 600 amu

Ramsey and Whitten at ORNL

inner radius 0.5mm, half height 0.55mm (1/1000 volume)

mass range 40-400amu

MESA+ http://pubs.acs.org/hotartcl/ac/99/apr/shrink.html University of Twente The Netherlands

Scaling issues

Comparison of mass analyzers and the consequence on the free variable for mass analysis of m/z 300 with $V = 10$ V and the length scale r or $L = 1$ µm

Technique	Governing equation	Consequence on free variable
Magnetic deflection	$m/z = B^2r^2/2V$	$B = 7880$ T
Time of flight	$m/z = 2Vt^2/L^2$	$t = 0.39 \pm 0.12$ ns for $\delta E_i = \pm 0.1$ eV
Linear quadrupole	$m/z = 7 \times 10^6 V_{rf}/f^2 r_0^2$	$f = 470$ MHz (length of rod is mm)
Quadrupole ion trap	$m/z = 8\ V_{rf}/q_z (r_0^2 + 2z_0^2)\Omega^2$	$f = 590$ MHz

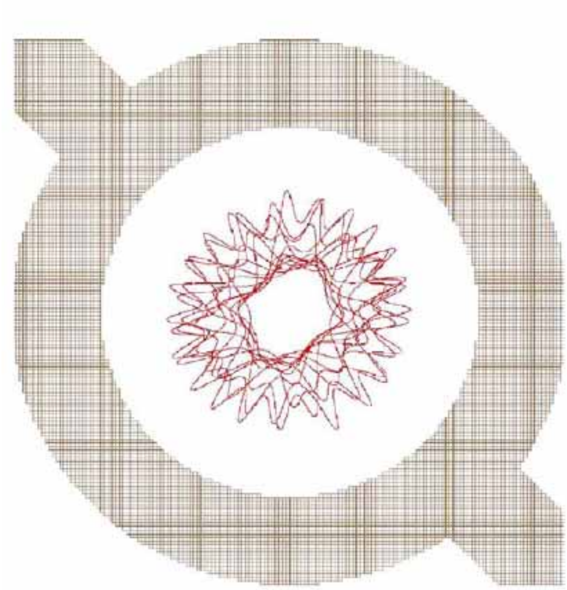
Quadrupole techniques are most appropriate for scaling down:

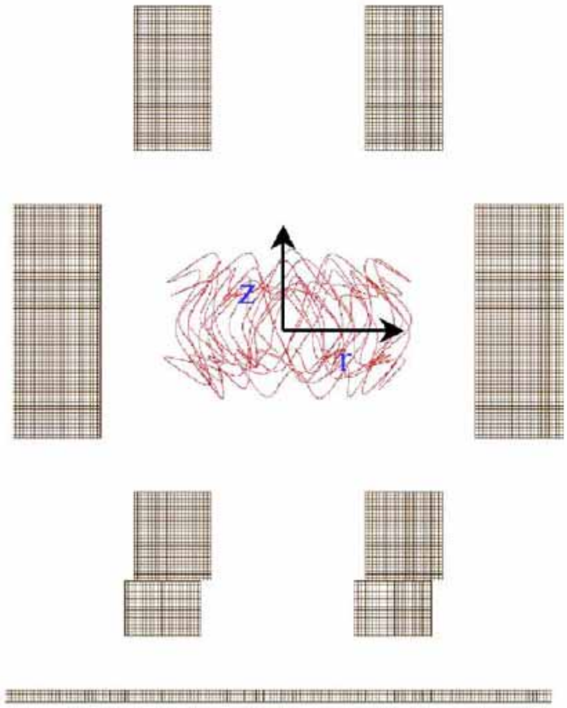
mass ranges for quadrupole techniques scale inversely with square of the characteristic length (L) of the analyzer. TOF also scales with L^{-2}, but resulting flight times are so short that mass resolution suffers severely.

Ion trap is appealing for miniaturization because of its high sensitivity, its ability to operate at higher pressure (~10^{-3} Torr), and most significantly its ability to perform MS/MS, viz. multiple stages of mass analysis using a single-analyzer

MESA+ Table and text from: Blain e.a. Int.J.Mass Spectr. 236, 91–104 (2004) University of Twente The Netherlands

Trajectories in ion trap: micro-Lissajous





Ion trajectory simulation result for a single trapped ion in a radius = 1.0 µm CIT with *m*/*z* = 93, 8V, 1.2 GHz. Trajectories follow typical Lissajous curves and encompass a large volume of the trap.

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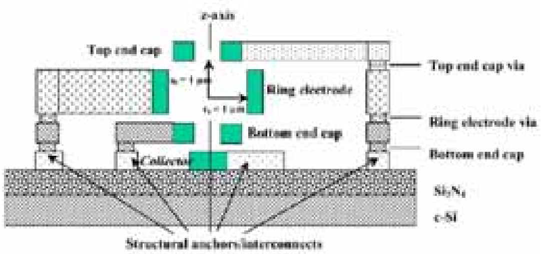
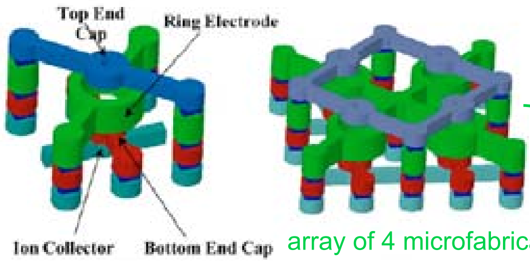
Blain e.a. Int.J.Mass Spectr. 236, 91–104 (2004)

University of Twente
The Netherlands

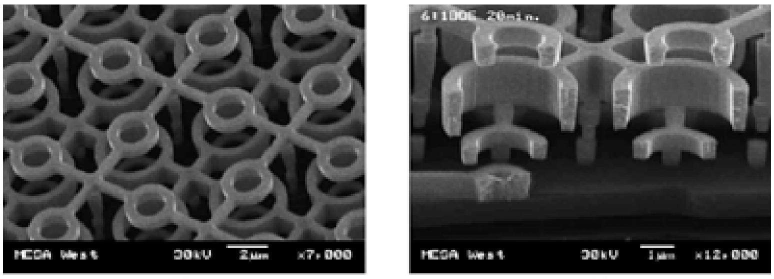
Surface-micromachined cylindrical ion trap





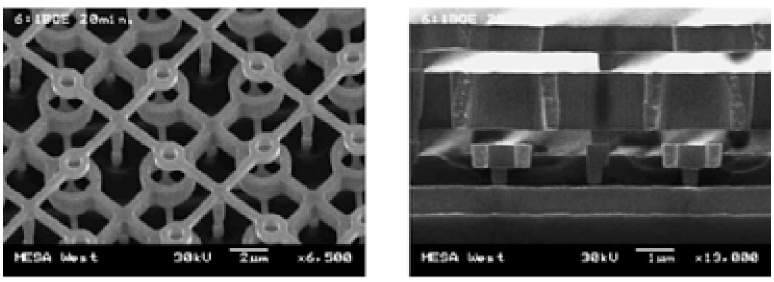
array of 4 microfabricated traps

0.25 cm² array of 10^6 one-micrometer CITs, incl. integrated ion detectors, constructed in tungsten on silicon



(A) (B)

Blain e.a.
Int.J.Mass Spectr.
236, 91–104 (2004)



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