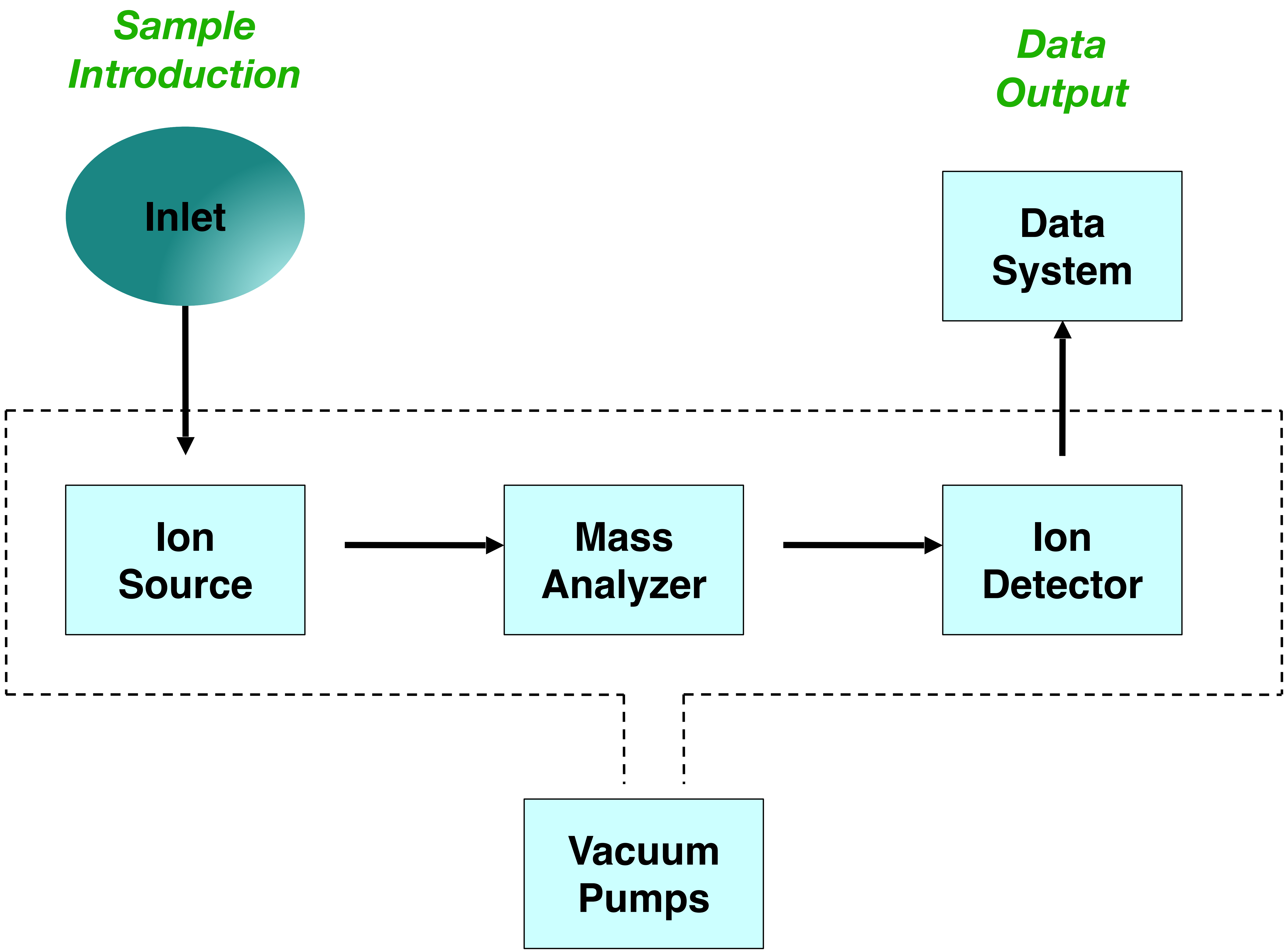
Mass spectrometry instrumentation

Elements of a mass spectrometer



Sample Introduction

Data Output

Inlet

Data System

Ion Source

Mass Analyzer

Ion Detector

Vacuum Pumps

Mass spectrometry instrumentation

Understanding instrumentation basics:

Ionization methods

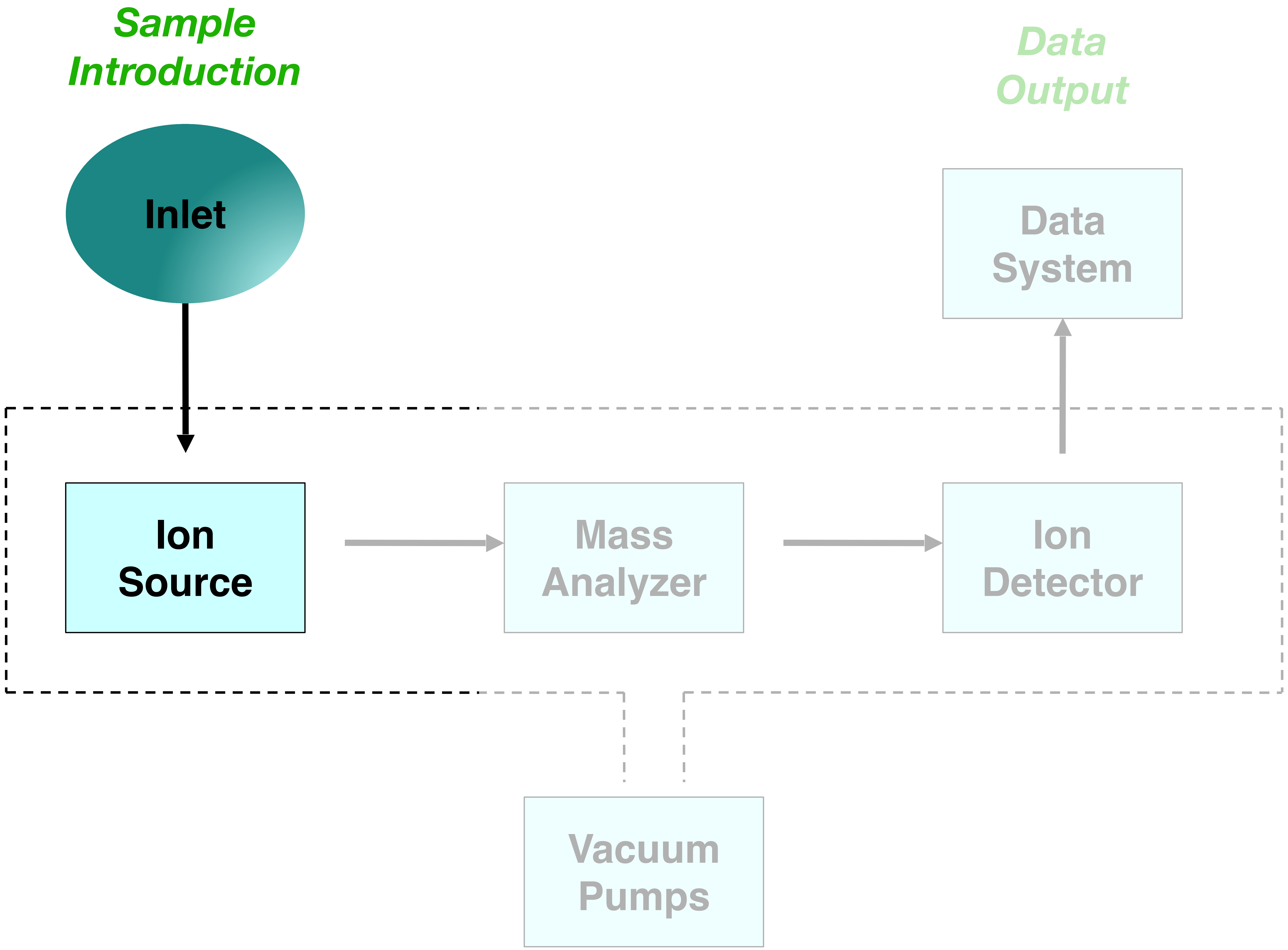
- Different techniques, advantages and disadvantages

Mass analyzers:

- Basic working principles of the most widely used MS
- Comparative analytical characteristics of different MS

Ion detectors

Ionization methods



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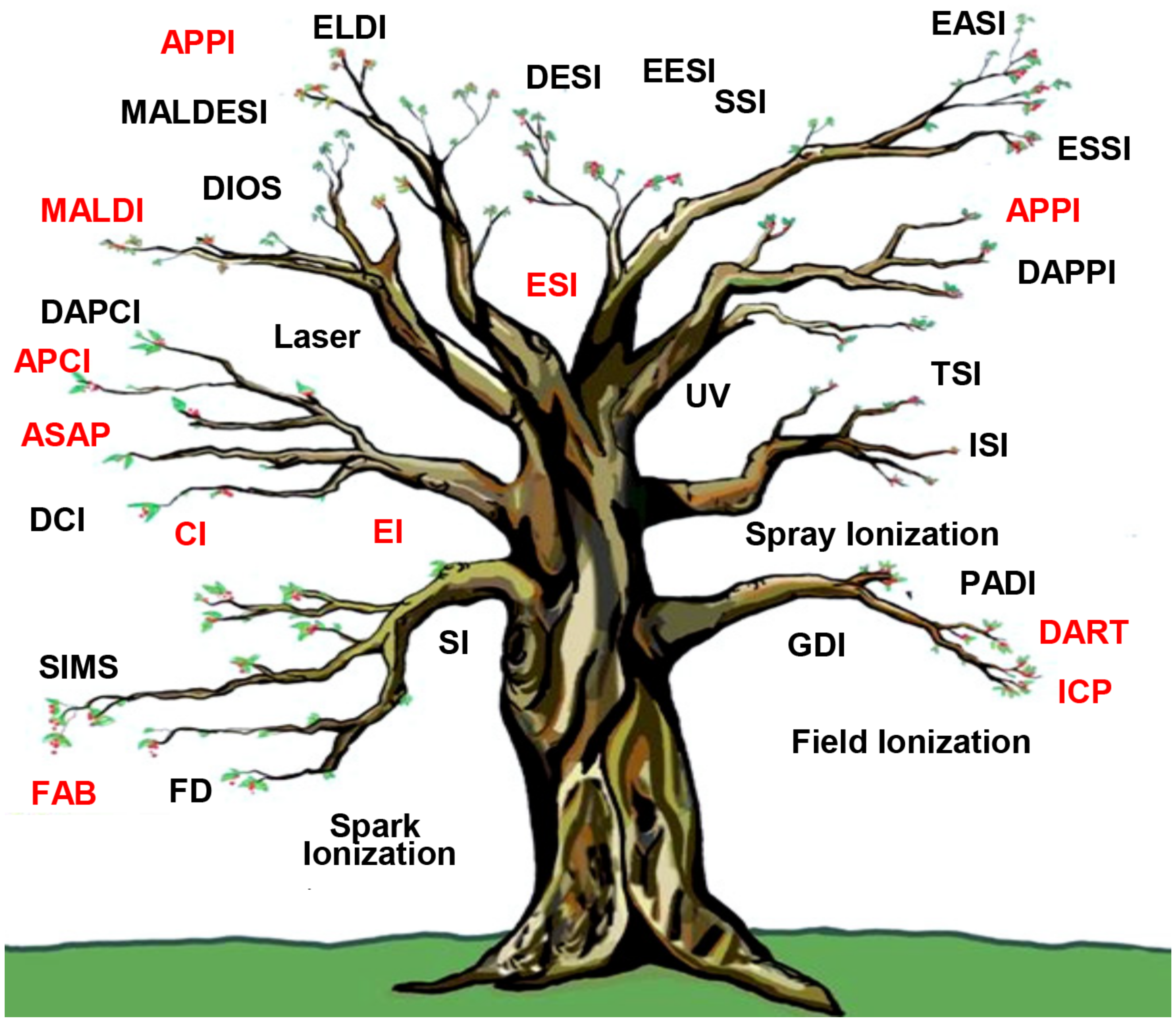
Ionization methods



Ionization techniques for molecular analysis

What do we want to achieve?

Desired characteristic	*Characteristics usually achieved*
High ion current	10^{-10} A (10^9 ions/sec)
High ionization efficiency (neutrals⟶ions)	0.1%
Bipolarity (positive and negative ions)	Except for EI
High molecular weight compounds	Approximately 10^5 Da
All sample states	All physical states are compatible with MS
Control of fragmentation	By control of energy deposited in the ion

Not every method exhibits all these characteristics.

Ionization methods

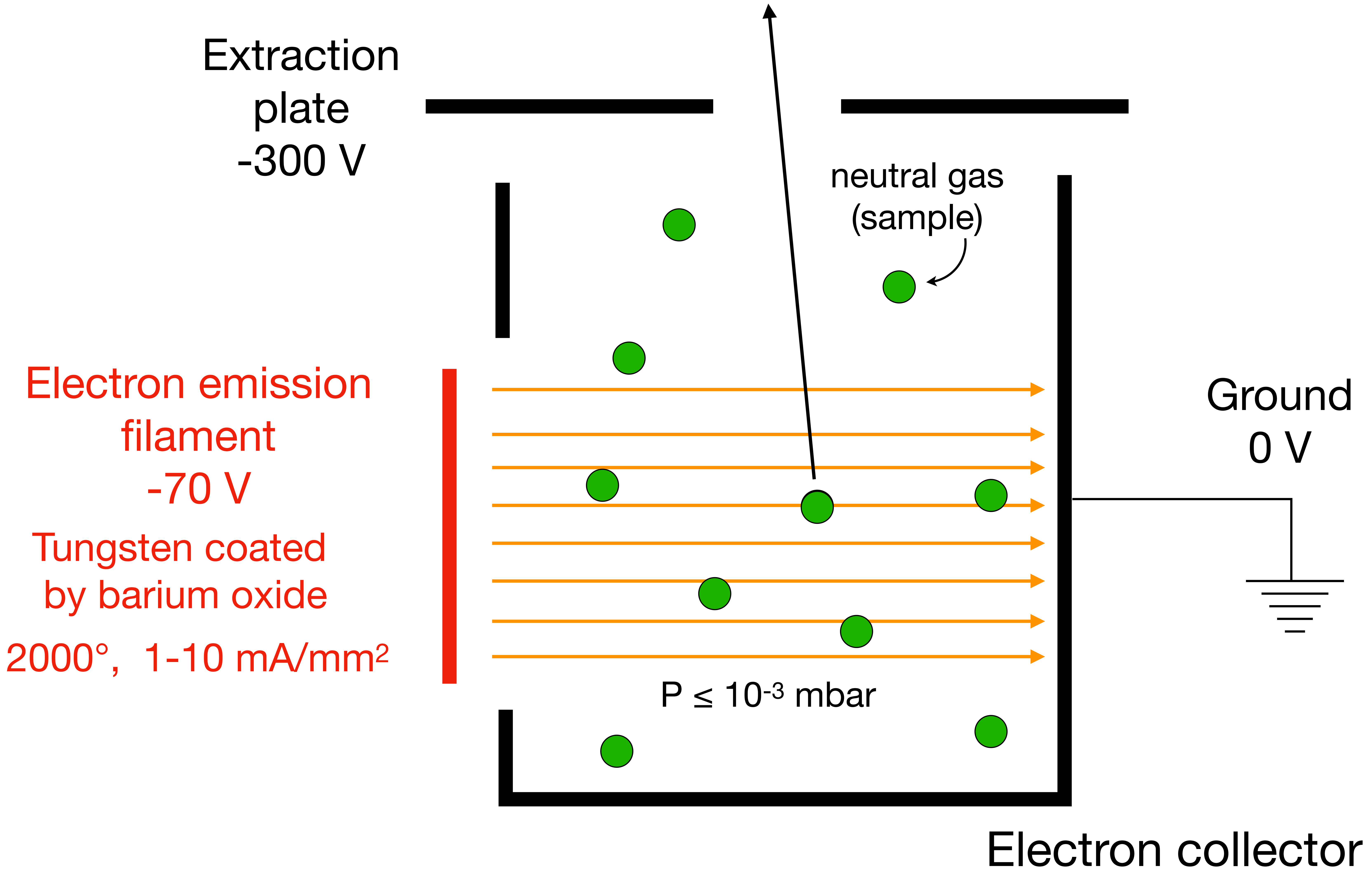
Molecular Analysis

- Electron impact ionizaton (EI)
- Chemical ionization (CI)
- Photoionization (PI)
- Electrospray ionization (ESI)
- Matrix-assisted laser desorption/ ionization (MALDI)

Elemental Analysis

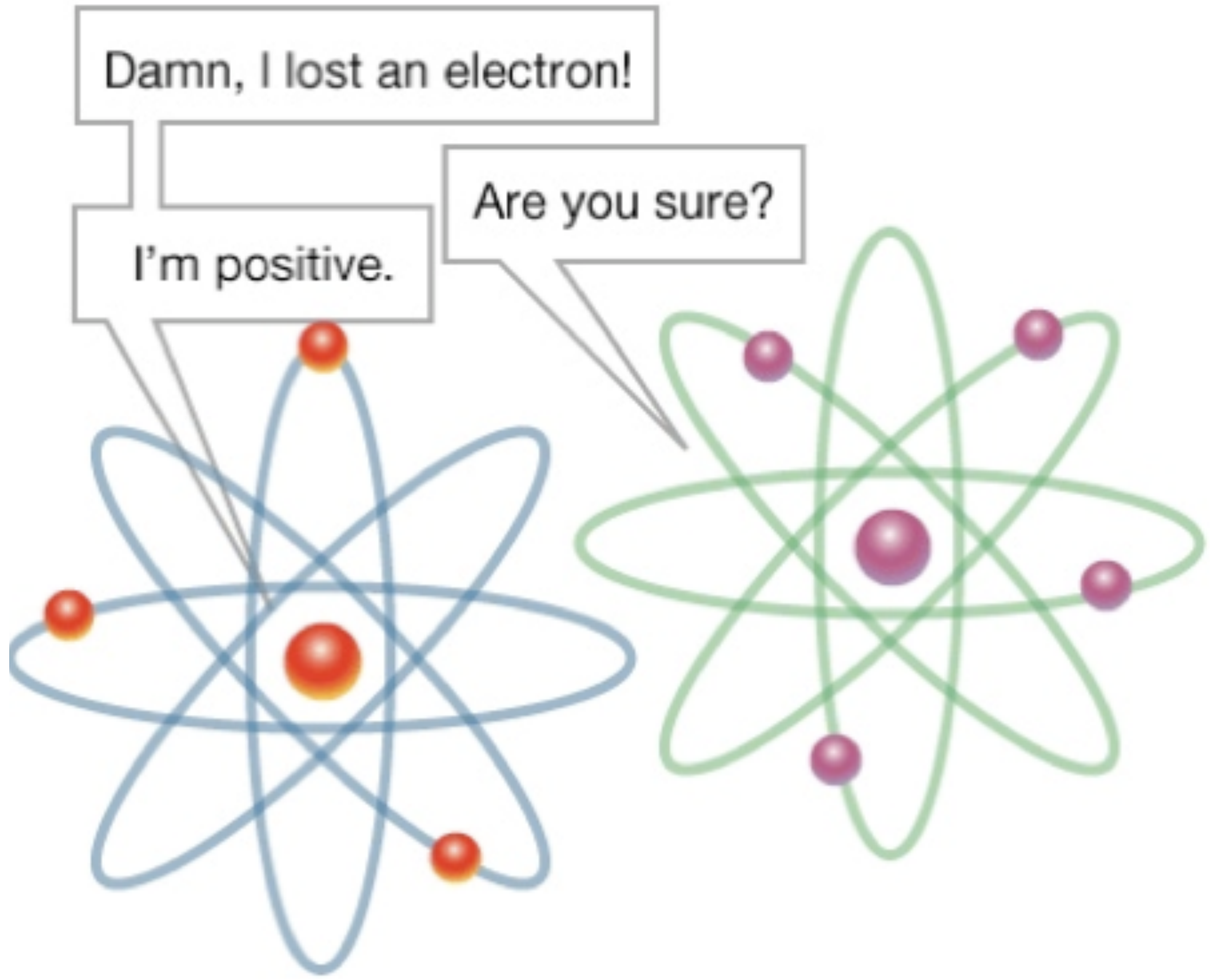
- Thermal desorption
- Spark ionization
- Inductively coupled plasma
- Glow discharge
- Secondary ion mass spectrometry (SIMS)

Electron impact ionization (EI)



Electron impact ionization (EI)

Ionization step: $\mathbf{M + e^- \longrightarrow M^{+\cdot} + 2e^-}$



Subsequent fragmentation:

Open shell ion $\mathbf{M^{+\cdot}}$

$$\mathbf{M^{+\cdot}} \longrightarrow \underset{\text{even ion}}{\mathbf{EE^{+}}} + \underset{\text{radical}}{\mathbf{R^{\cdot}}}$$

$$\mathbf{M^{+\cdot}} \longrightarrow \underset{\text{odd ion}}{\mathbf{OE^{+\cdot}}} + \underset{\text{molecule}}{\mathbf{N}}$$

Must determine the molecular ion:

- The MI must have the highest mass in the spectrum (except isotopes)
- The MI must be an odd electron ion, $M^{+\bullet}$
- The MI must be able to fragment to generate sensible high-mass, odd-electron fragments.

Electron impact ionization (EI)

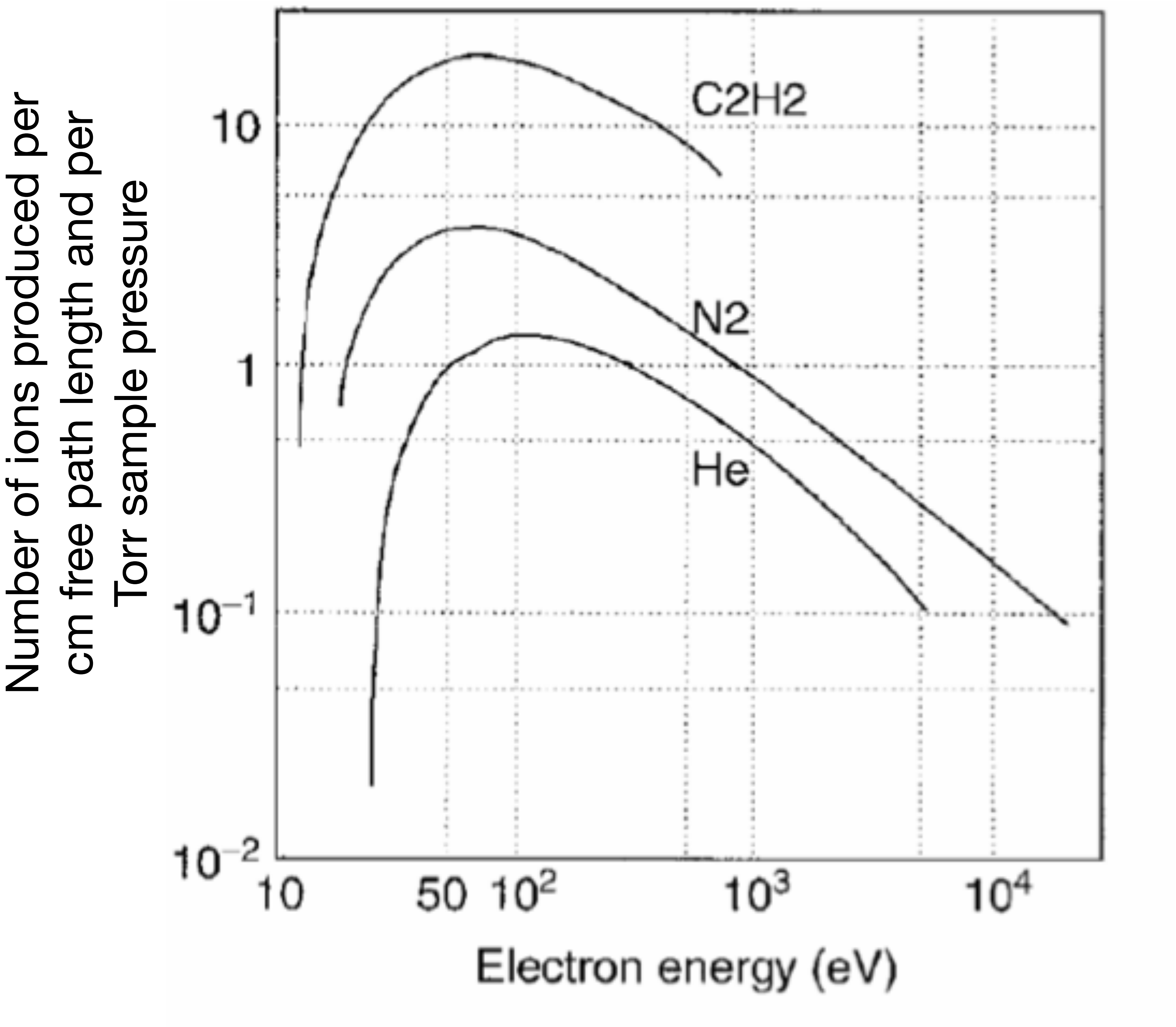
- The ionization potential is the electron energy that will produce a molecular ion. The appearance potential for a given fragment ion is the electron energy that will produce that fragment ion.
- Most mass spectrometers use electrons with an energy of 70 electron volts (eV) for EI.
- Decreasing the electron energy can reduce fragmentation, but it also reduces the number of ions formed.

Electron energy dependence

Number of ions produced as a function of the electron energy

$I = \alpha \cdot i \cdot p \cdot V$

i – filament current
p – pressure
V - volume



Note the wide maximum at around 70 eV

Clicker question

Why does the ionization cross section of molecules increase from 10 eV to 70 eV?

A. Valence electrons are typically bound by approximately 70 eV.
B. An electron of 70 eV is resonant with a transition to a particular excited electronic state.
C. The electron wavelength better matches the size of the molecule.
D. None of the above.

http://responseware.eu **Session ID: structure314**

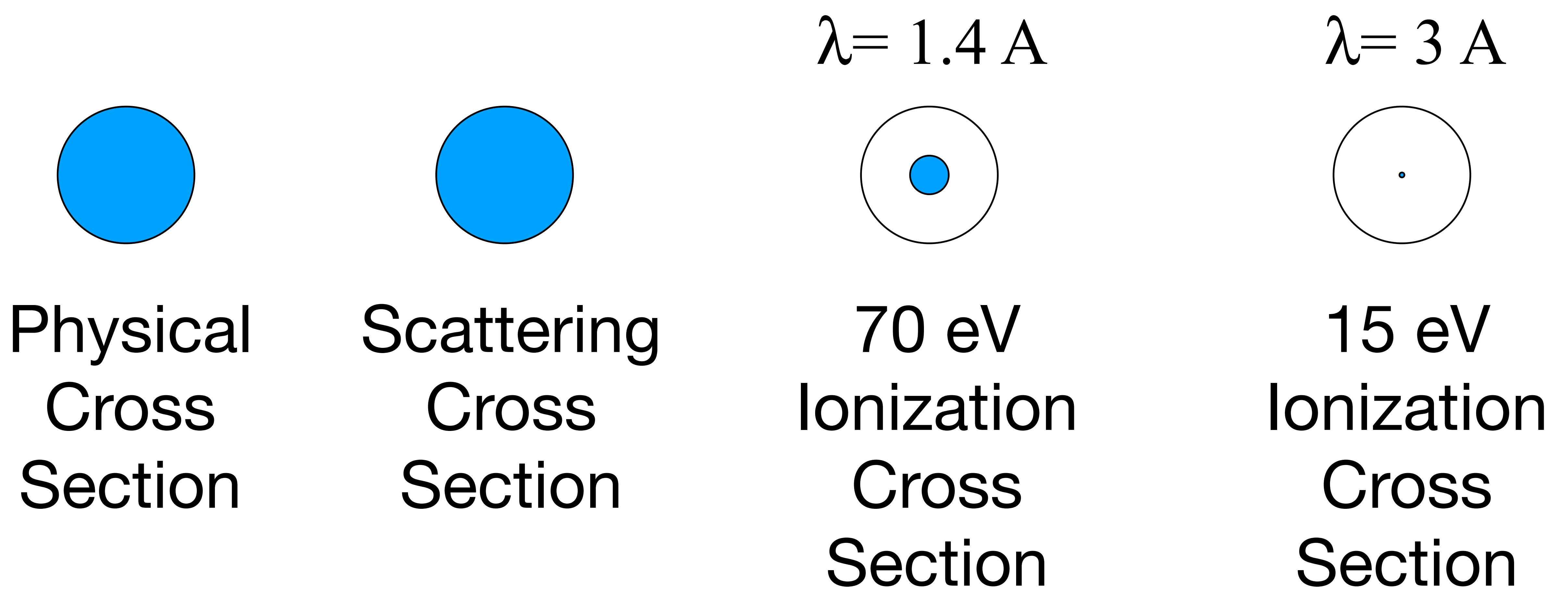
Clicker question

Why does the ionization cross section of molecules increase from 10 eV to 70 eV?

Ionization cross section

Consider electrons traveling perpendicular to the page

DeBroglie wavelength: λ = h/mv



λ has to be close to the diameter of the electron orbital

Electron impact ionization

Advantages

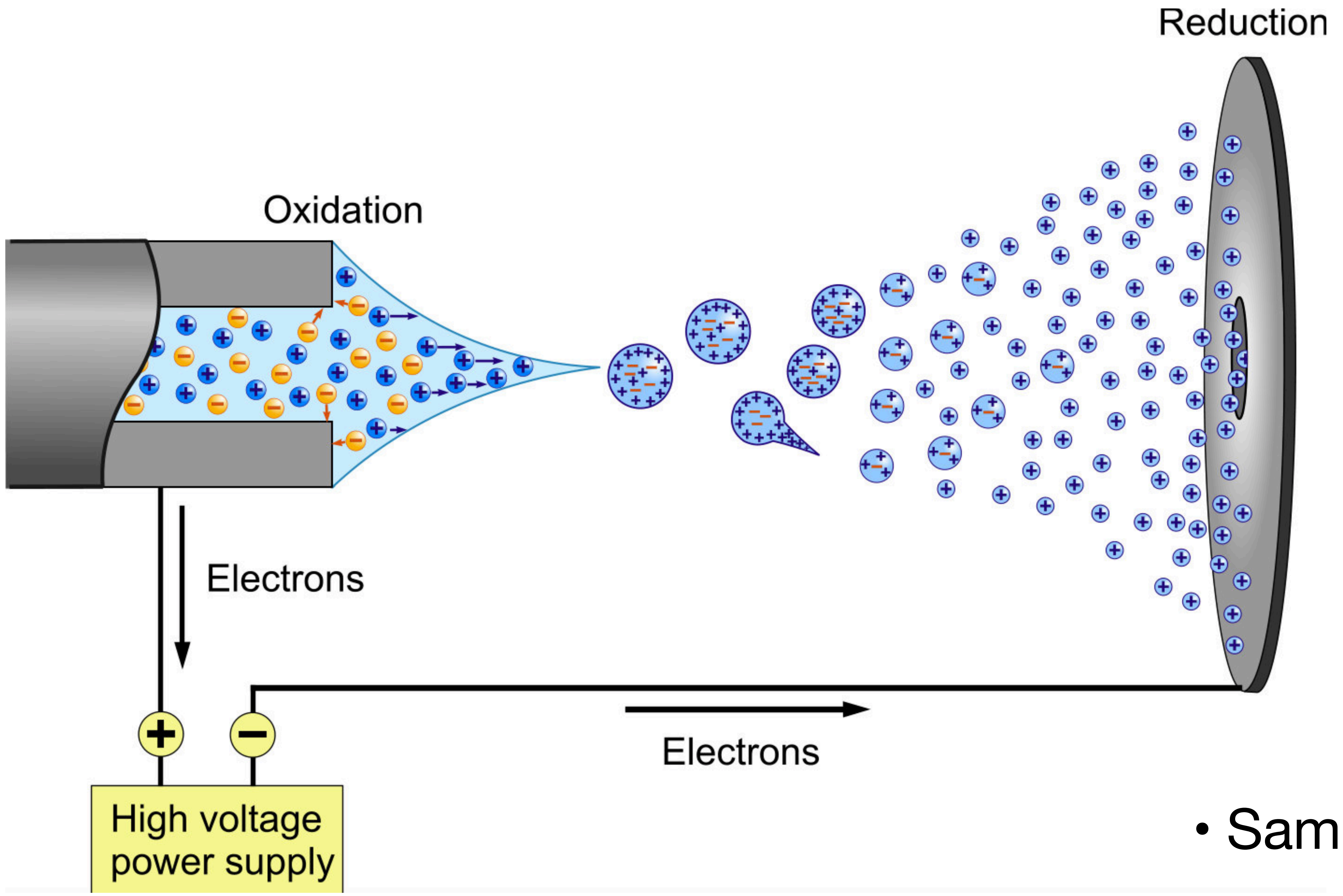
- Reproducible and well understood
- Extensive fragmentation occurs ↔
- High ionization efficiency
- Universal to all vaporized molecules
- Libraries of EI spectra allow for compound identification
- Very sensitive: 1 in 1000 molecules ionized

Disadvantages

- Only positive ions
- Extensive fragmentation occurs
- Radical cations formed
- Sample must be volatile and hence low MW
- Ionization is non-selective
- Deposits a lot of internal energy
- Not ideal for some classes of compounds
- Rearrangement process complicate the MS
- All vaporized molecules contribute

⇒ Harsh, universal, highly reproducible method for volatile molecules

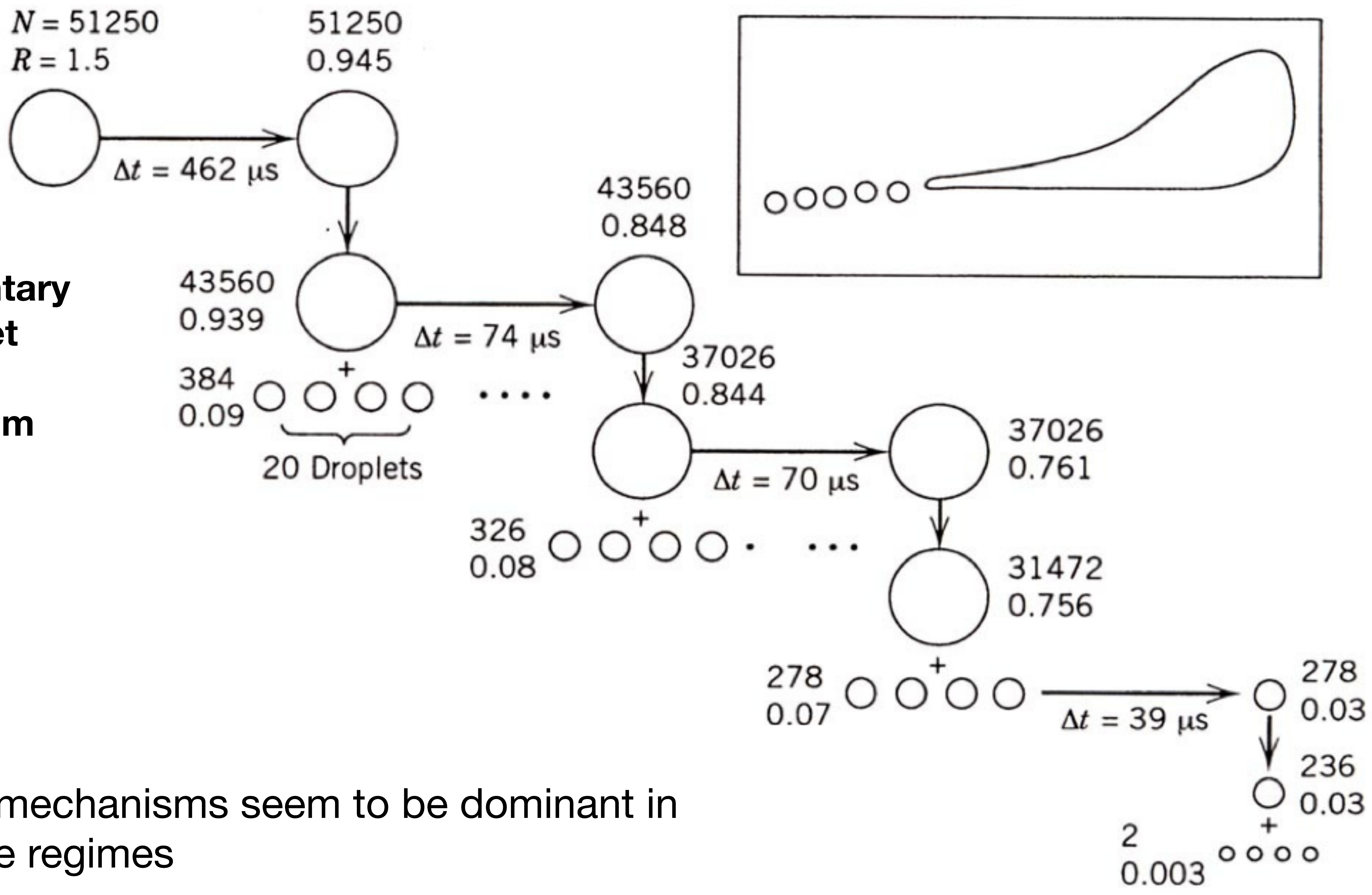
Electrospray ionization



John Fenn
Nobel Prize
2002

- Sample is introduced directly from the liquid
- A spray of charged droplets are formed
- Desolvation and breakup of droplets occurs
- Ions emerge from charged droplets
- Ions are sampled from the atmosphere

Desolvation/Ionization mechanism



N - number of elementary charges on the droplet

R - droplet radius in μm

Different ionization mechanisms seem to be dominant in different droplet size regimes

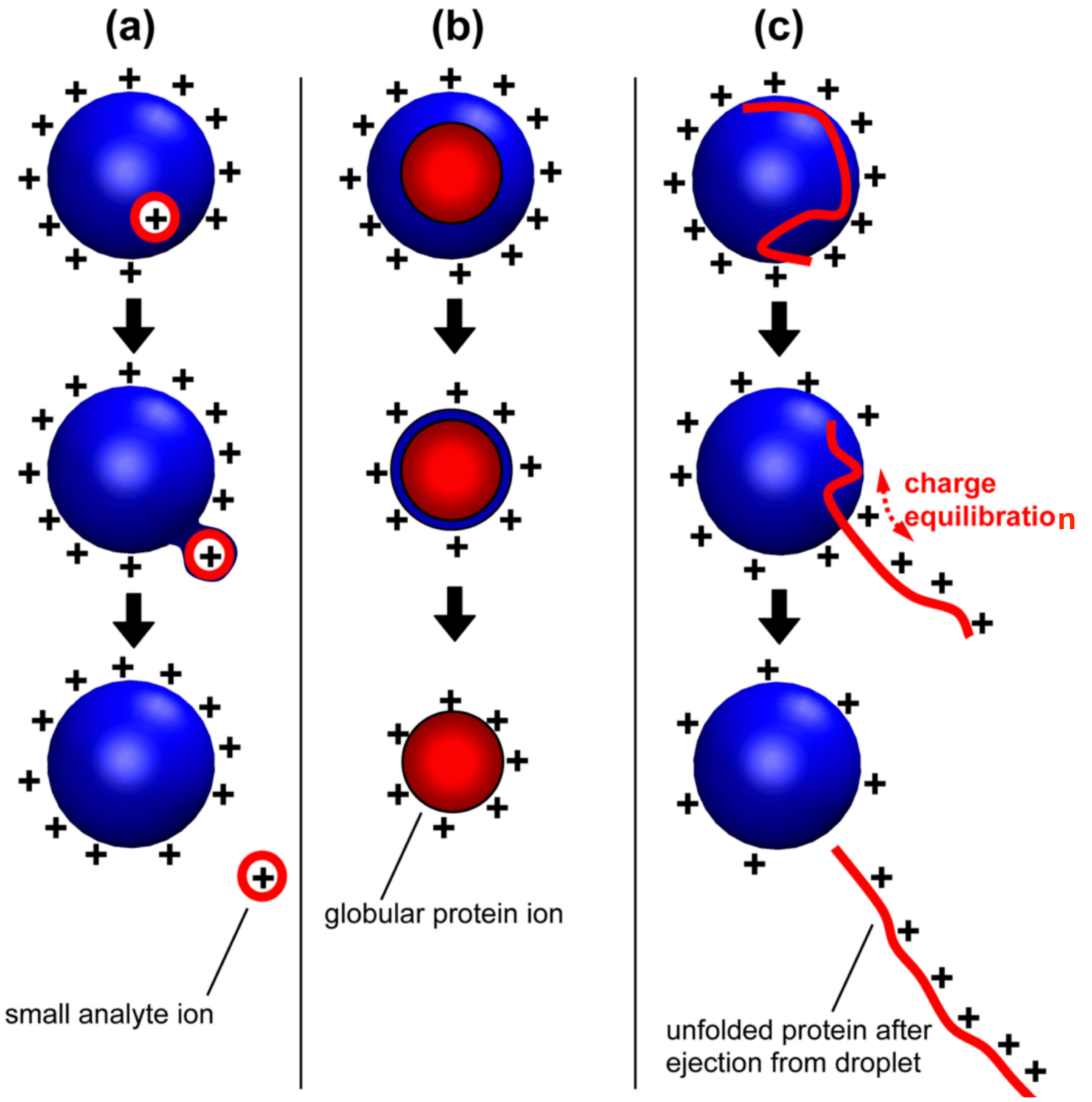
ESI mechanism

Different mechanisms seem to be dominant in different droplet size regimes

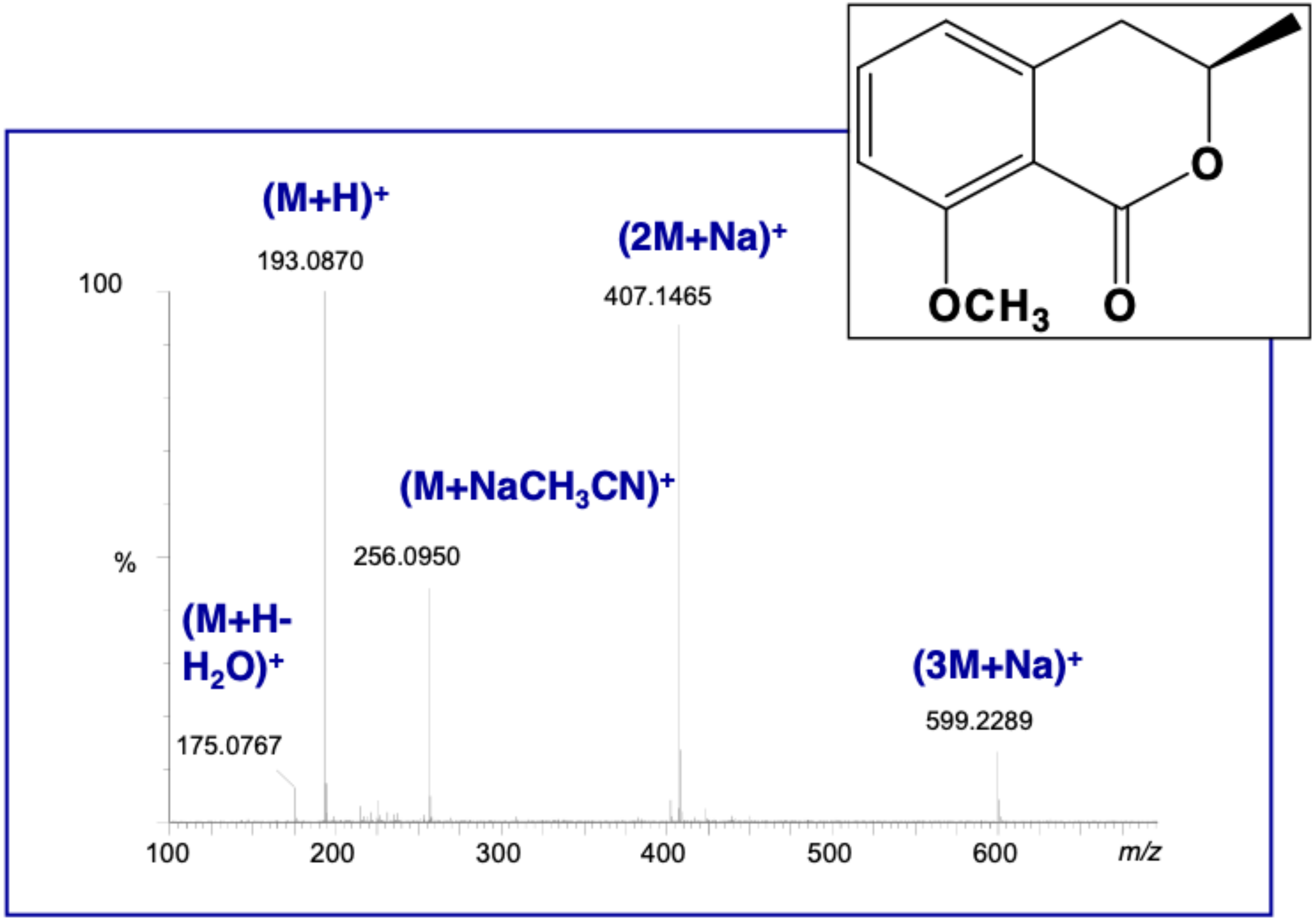
(a) IEM - Ion evaporation model

(b) CRM - Charge residue model

(c) CEM - Chain ejection model



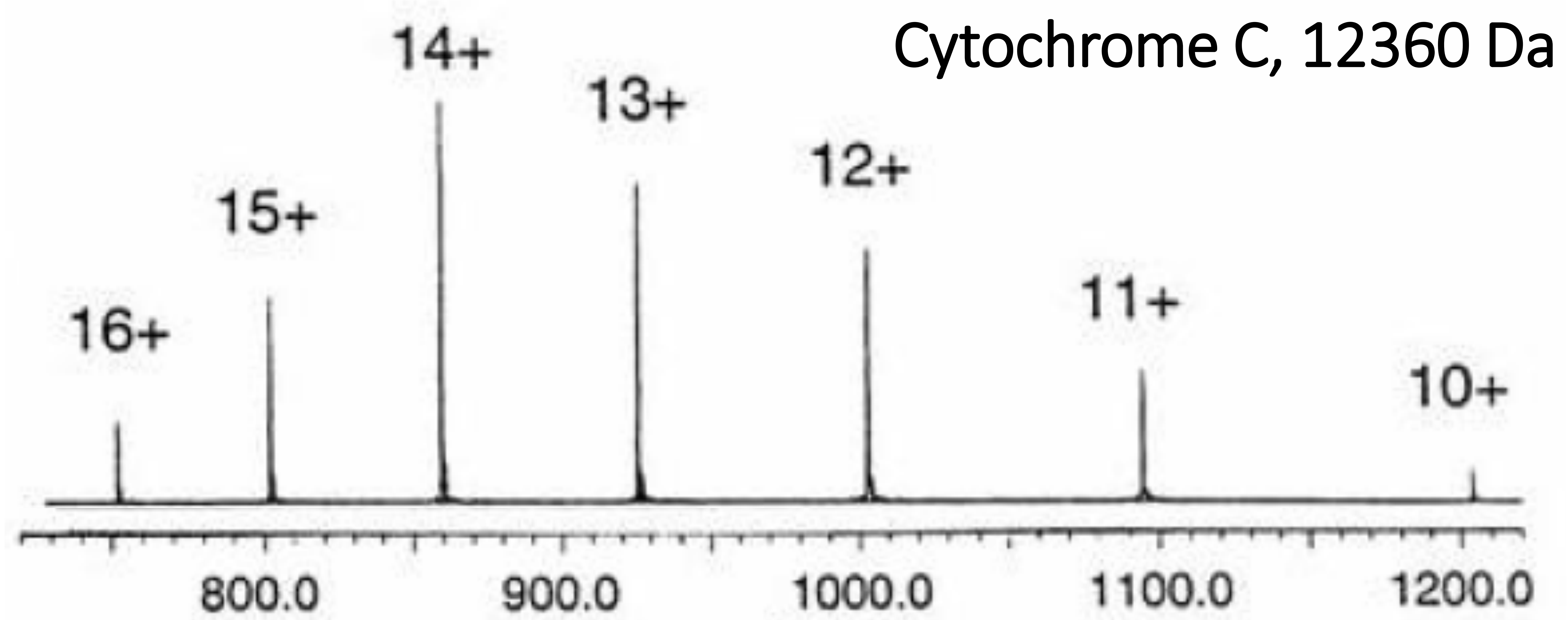
Adducts and MW identification

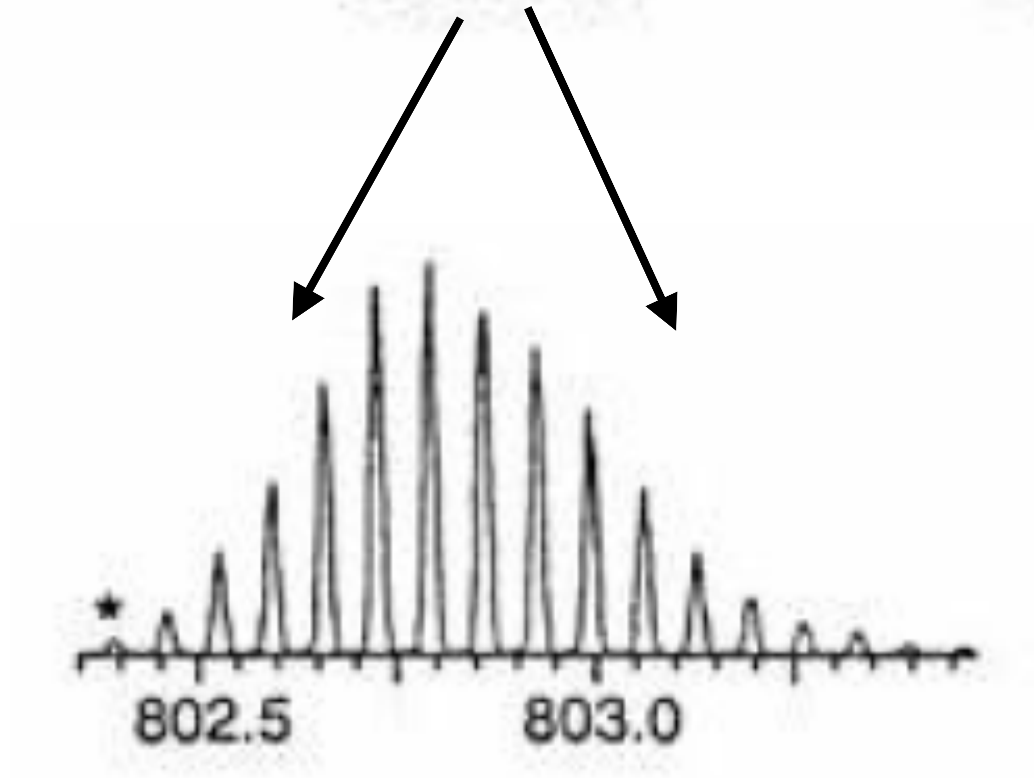


MW = 192

Multiple Charging in Electrospray Ionization

When spraying large, biological molecules, ESI tends to produced multiply-charged ions.



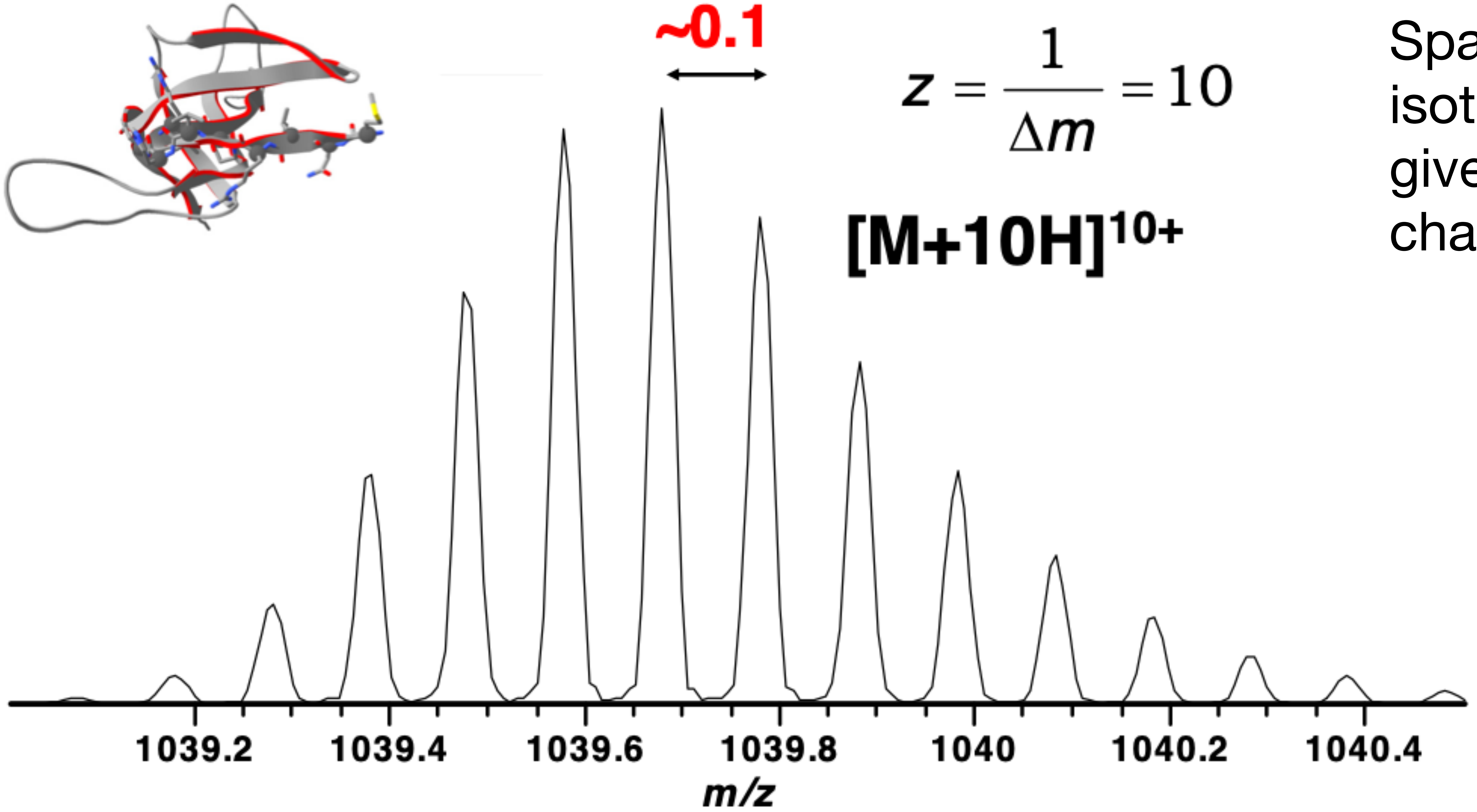


Multiple charge states in ESI allows for MS of heavy molecules in instruments with limited MAX m/z.

Analysis of multiply charged ions from ESI

Protein GroES

10.3 kDa



$$z = \frac{1}{\Delta m} = 10$$

$[M+10H]^{10+}$

Spacing of isotope peaks give you the charge state.

Interpretation of ESI-Mass Spectra

The m/z values can be expressed as follows:

$$\frac{m}{z} = \frac{MW + n\mathrm{H}^{+}}{n}$$

where m/z = mass-to-charge ratio
MW =molecular weight of the sample
n =integer number of charges on the ions
H^+ =mass of a proton = 1.00727 Da.

If n is known, use m/z to determine MW. Usually n is not known, but can be calculated.

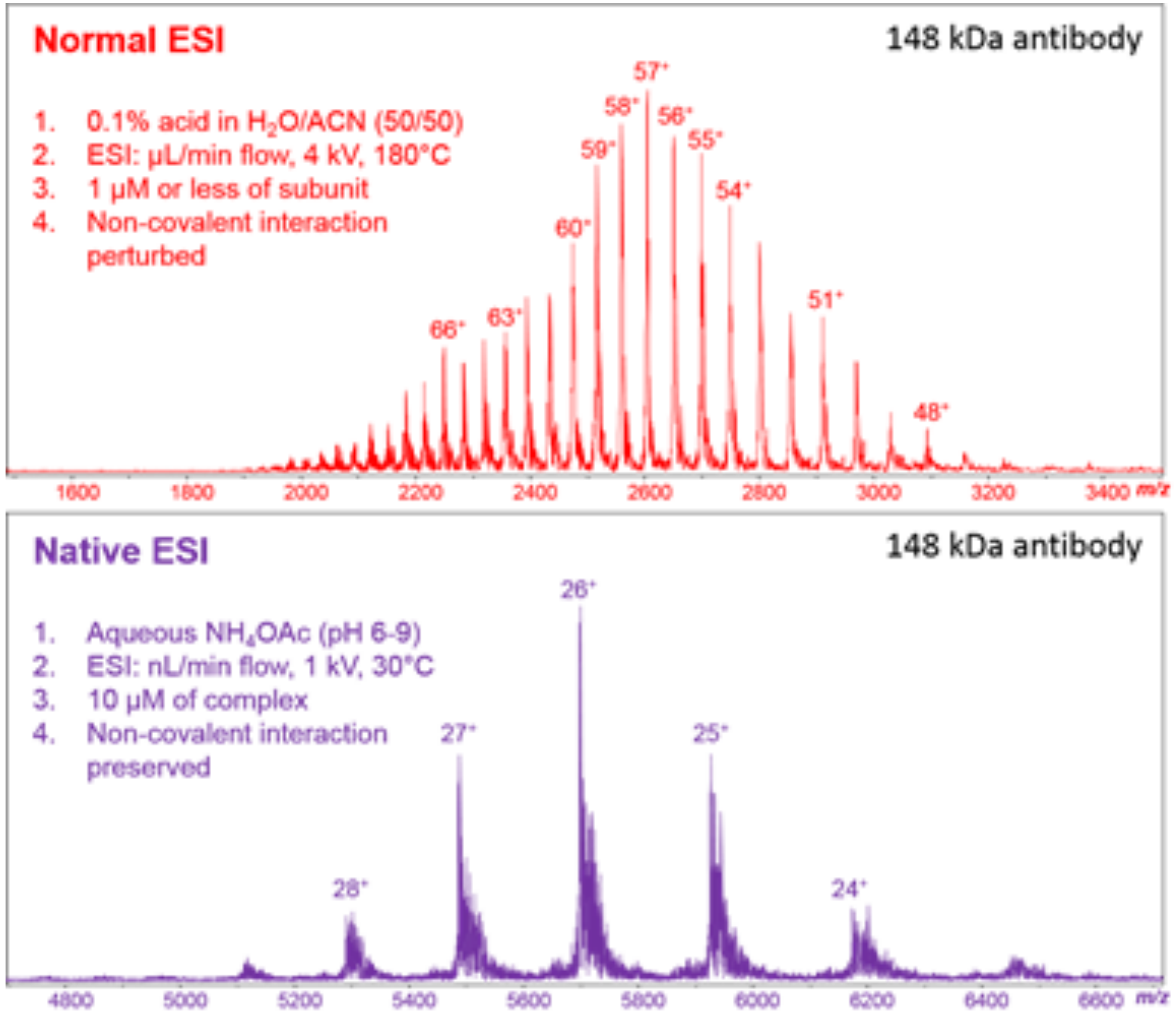
Assume any two adjacent peaks in series of multiply charged ions differ by one charge:

$$\left(\frac{m}{z}\right)_1 = \frac{MW + n\mathrm{H}^{+}}{n} \qquad \left(\frac{m}{z}\right)_2 = \frac{MW + (n+1)\mathrm{H}^{+}}{n+1}$$

Solve these two equations simultaneously

Native vs. Denaturing Conditions in ESI

148 kDa antibody



Normal ESI

1. 0.1% acid in H_2O/ACN (50/50)
2. ESI: µL/min flow, 4 kV, 180°C
3. 1 µM or less of subunit
4. Non-covalent interaction perturbed

Native ESI

1. Aqueous NH_4OAc (pH 6-9)
2. ESI: nL/min flow, 1 kV, 30°C
3. 10 µM of complex
4. Non-covalent interaction preserved

Denaturing conditions:

H2O/ACN/0.1% acid

180°C

4 kV

⟶ **Charge states 48 to 70**

Native conditions:

NH_4OAc pH 7

30°C

1 kV

⟶ **Charge states reduced to 23-29**

Electrospray ionization

Advantages

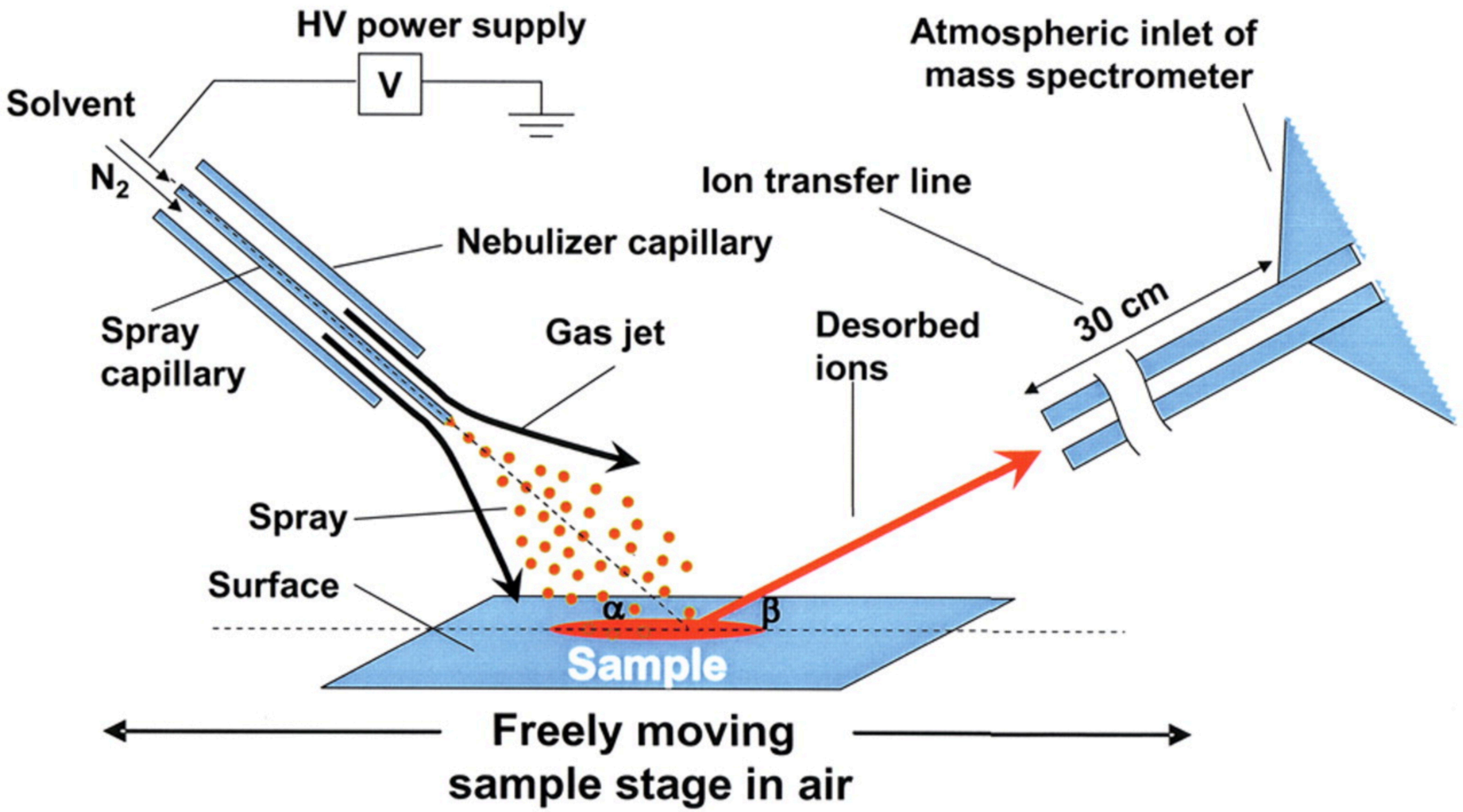
- Soft ionization
- Directly from solution
- Coupling with online separation (i.e., HPLC)
- High accuracy for large molecules
- Large mass range
- Fast
- Preserves non-covalent interactions

Disadvantages

- Complicated spectra
- Less tolerant to salts
- Relatively low ionization efficiency

Variants of Electrospray

Desorption Electrospray Ionization (DESI) was first reported in 2004 by Graham Cooks



DESI Mechanism

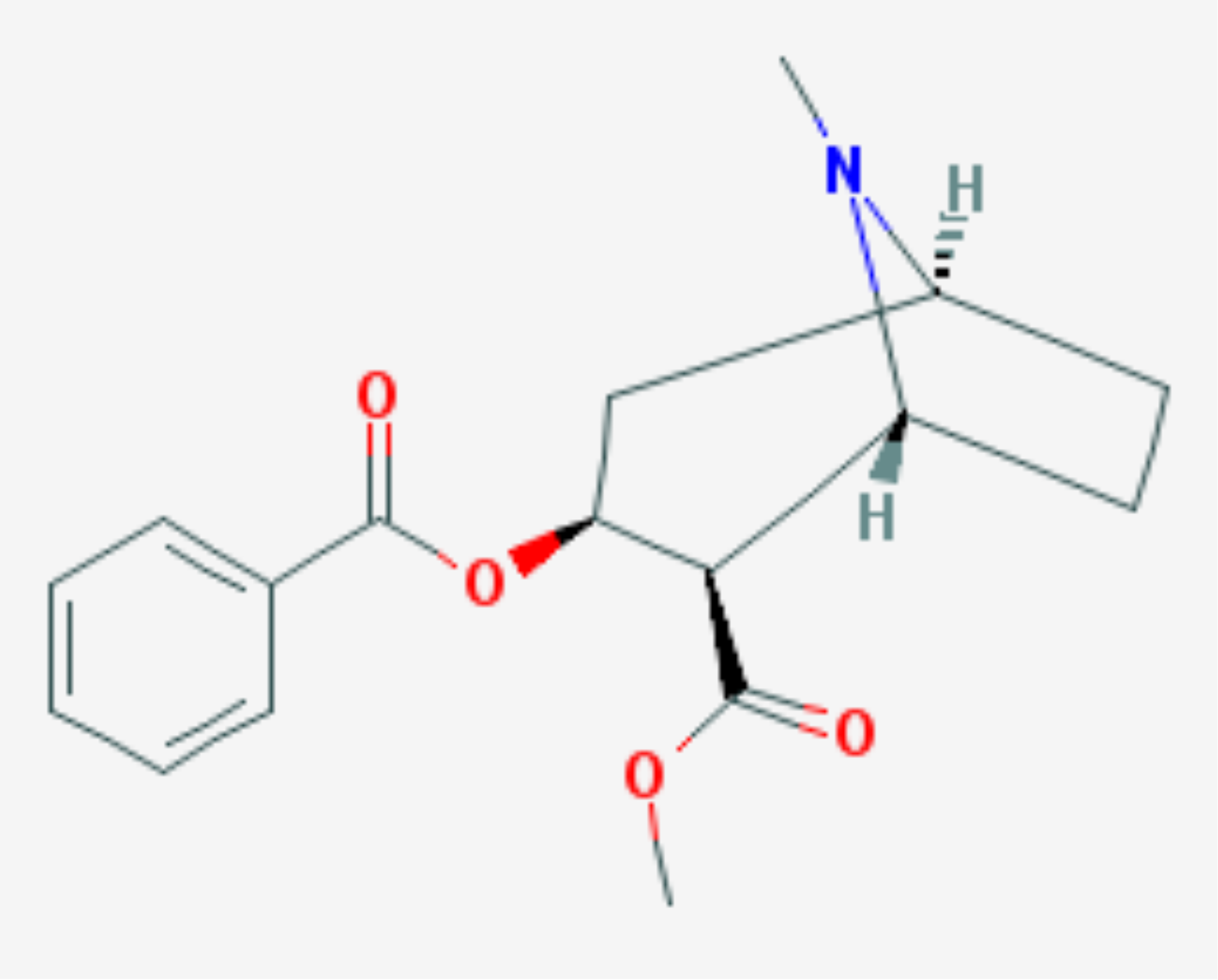
- DESI occurs when analyte particles are solvated by an ionized solvent flow.
  - The solvated analyte is ejected from the sample and swept toward the mass analyzer.
  - The mechanism and spectra are very similar to ESI.

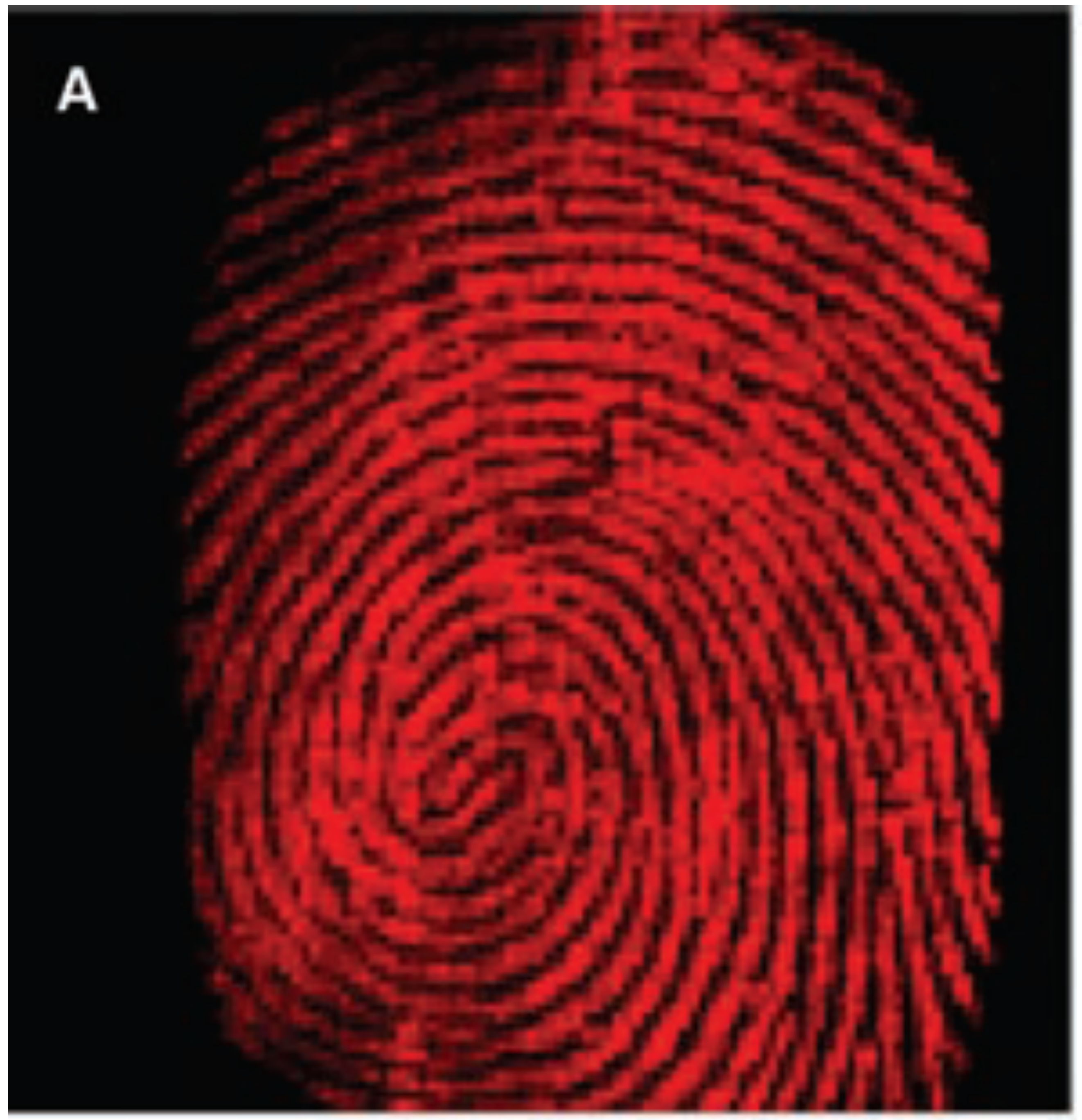
DESI Applications

DESI can be used in a wide variety of applications

1. Pharmaceutical testing
    - Quality control/assurance
    - Counterfeit identification
2. Chemical weapons
3. Explosive residues
4. Latent fingerprints

Cocaine Fingerprints





DESI of cocaine distribution
in a FP on glass.

FP generated from
ink blotted on paper

Imaging drug distribution in tissue

R. Zare, Stanford University

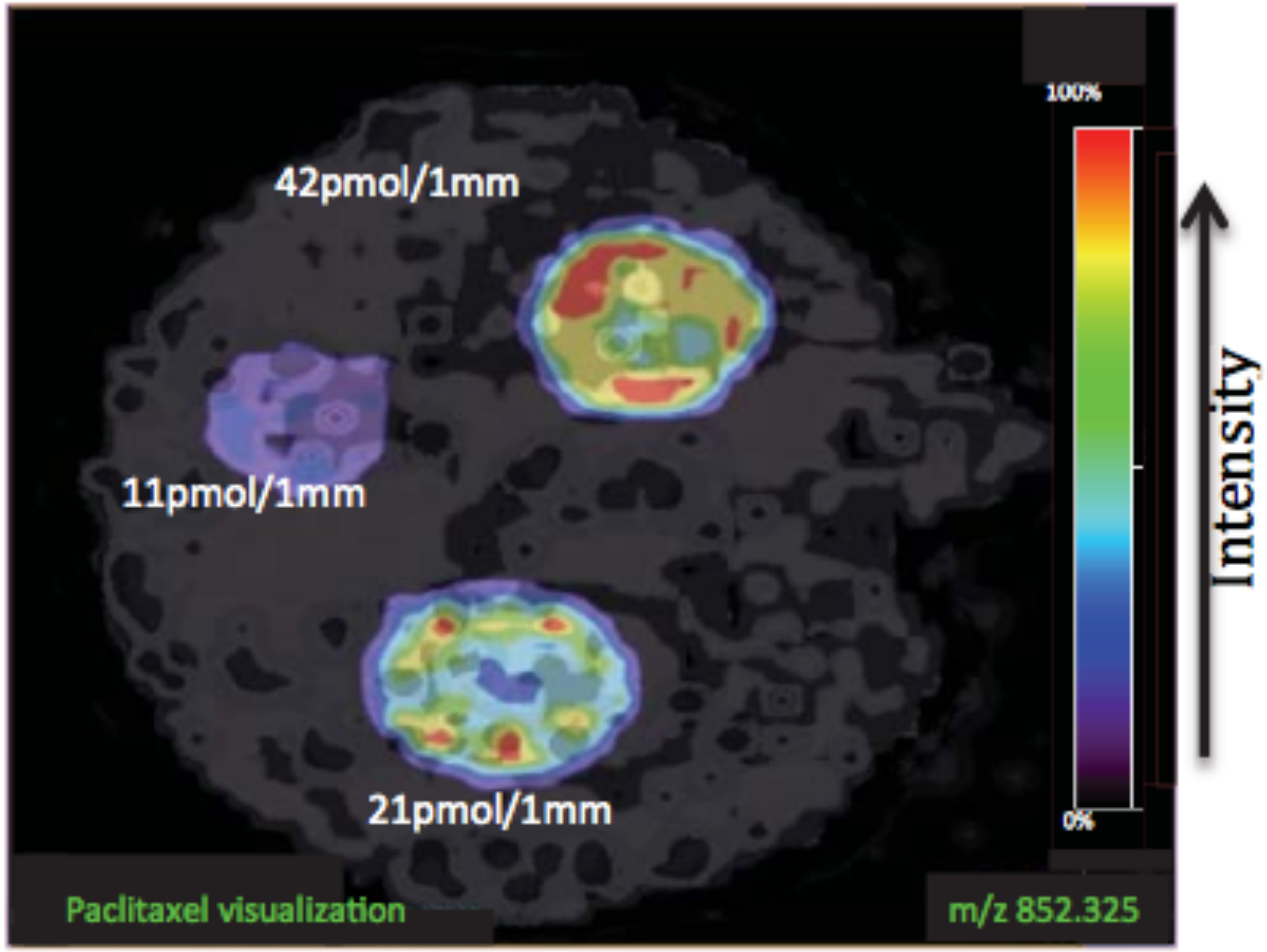
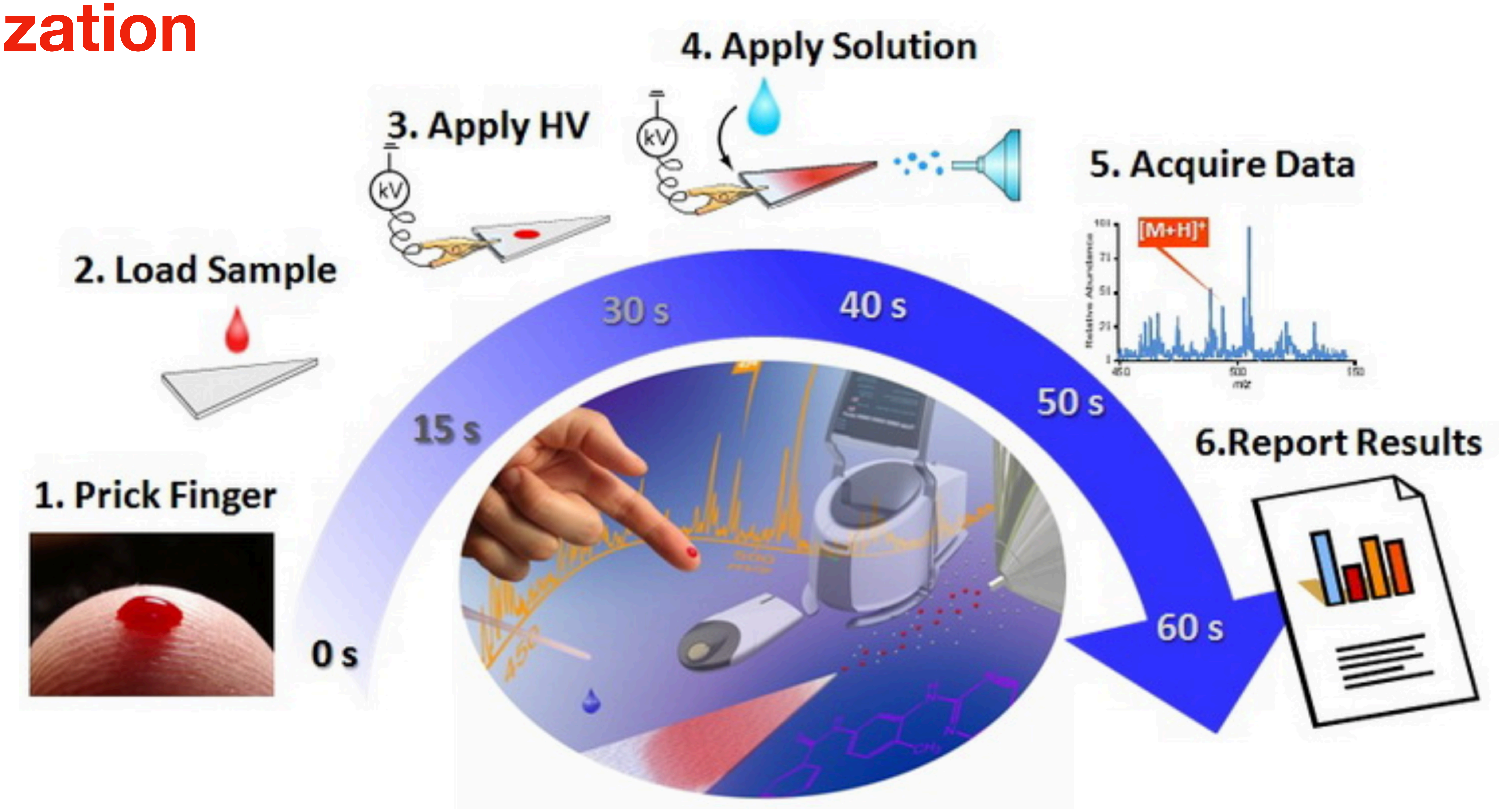


Fig.2 DESI-MSI generated image of anti-tumor drug, paclitaxel, applied in different concentrations on liver tissue (superimposed with the image of the tissue).

Variants of Electrospray

Paper spray ionization

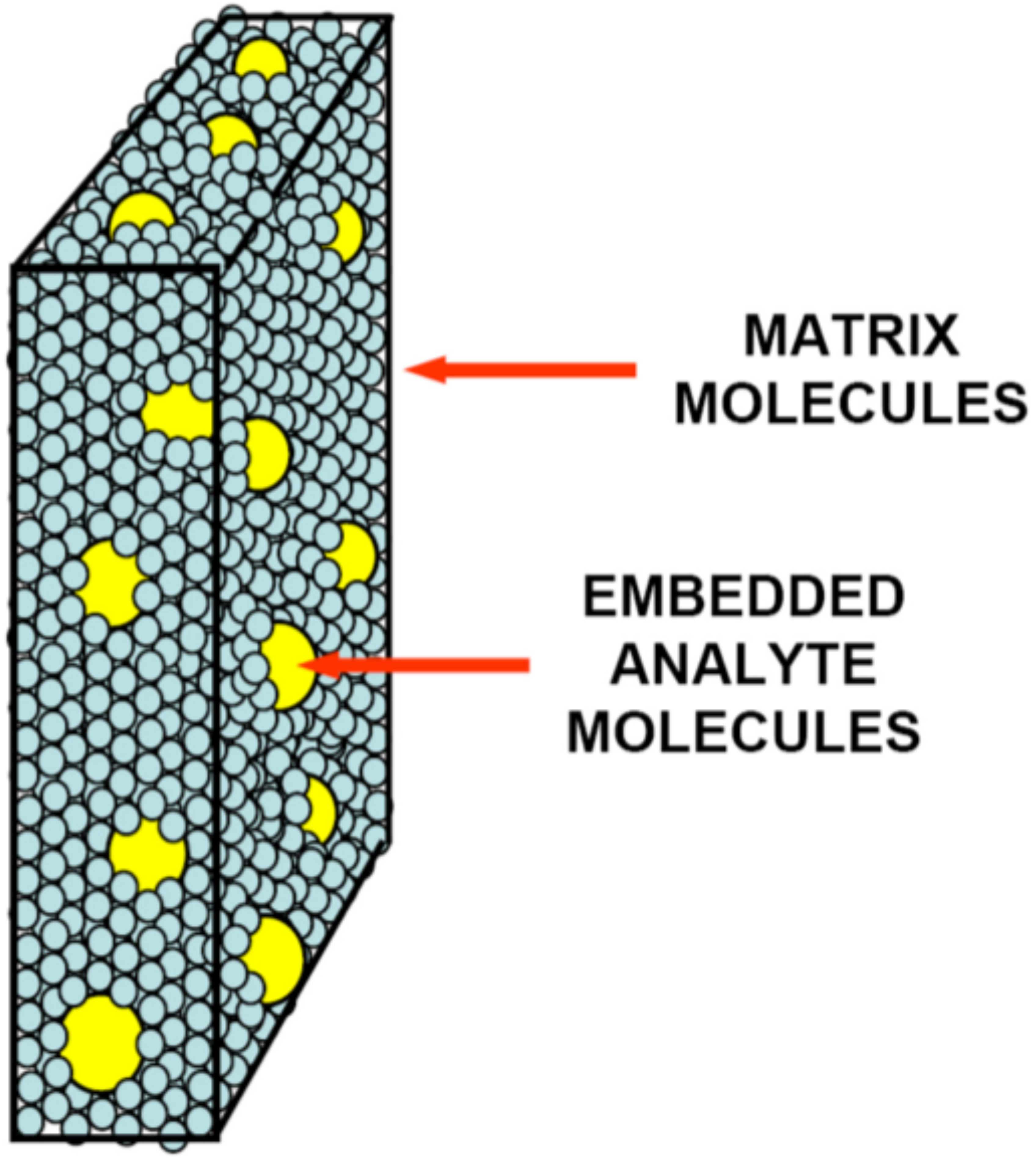
Can be used for fingerprints, blood samples, etc.



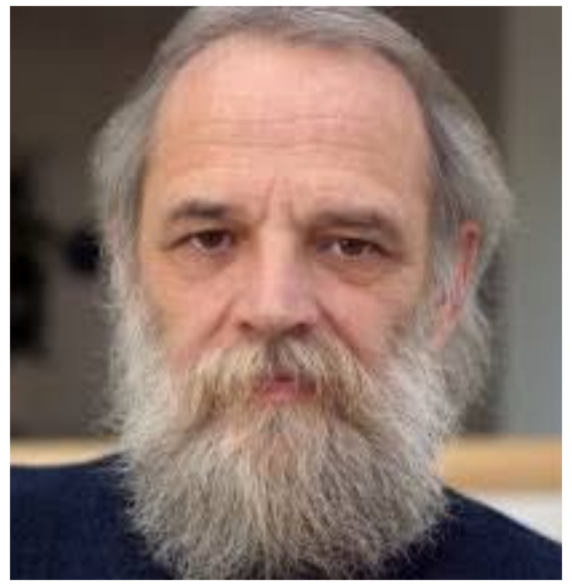
Wang, Liu, Cooks, and Ouyang *Angew. Chemie Int. Ed.*, **2010**, *49*, 877-880

Liu, Jiangjiang; Wang, He; Manicke, Nicholas E.; Lin, Jin-Ming; Cooks, R. Graham; Ouyang, Zheng. *Analytical Chemistry*. **82** (6): 2463–2471.

Matrix-assisted Laser Desorption Ionization (MALDI)

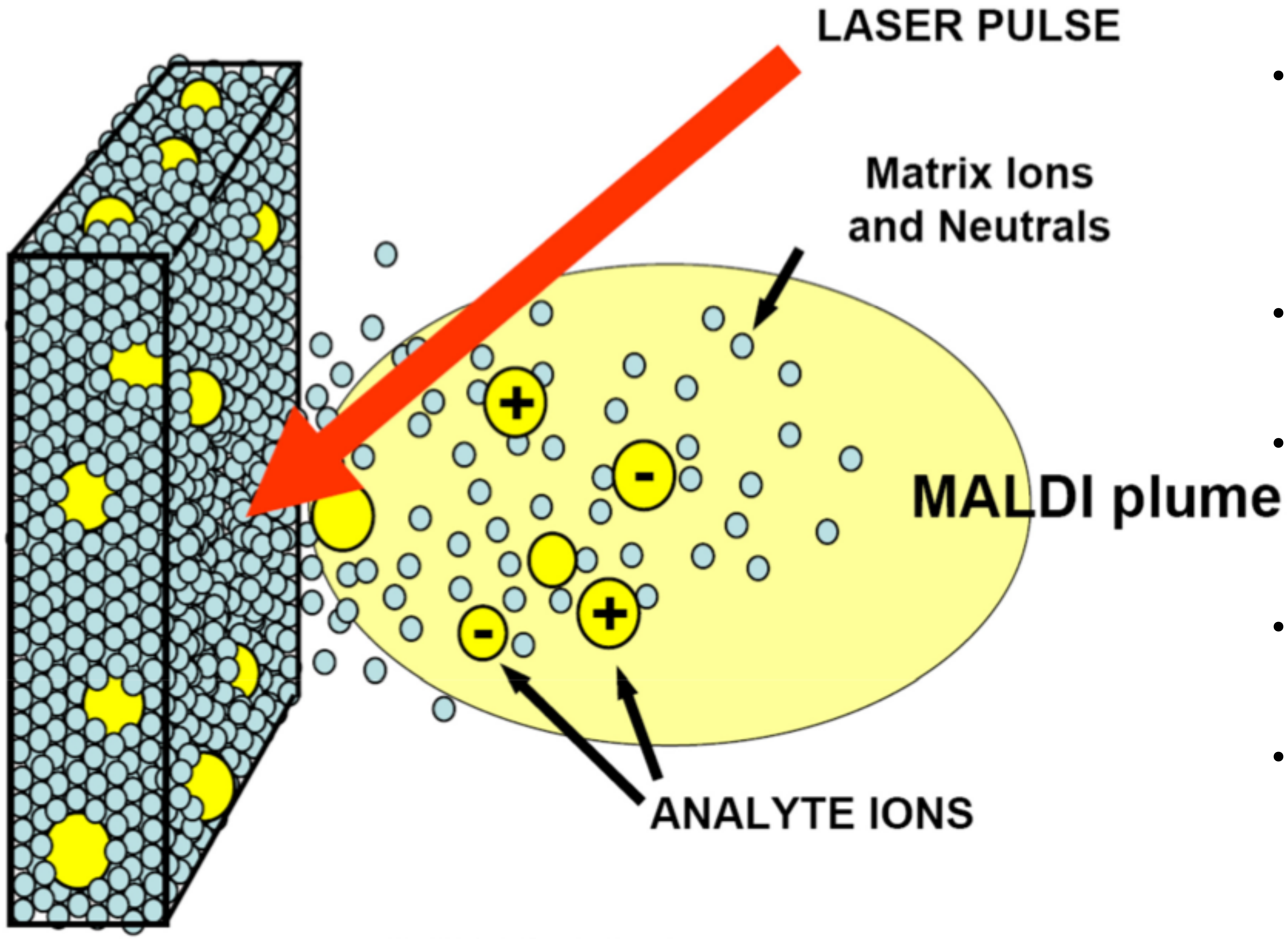


- Analyte molecules are embedded in a matrix after solvent evaporation.
- The dried mixture is struck with a short, intense laser pulse having a wavelength that is strongly absorbed by the matrix (often UV).


M. Karas


F. Hillenkamp

Matrix-assisted Laser Desorption Ionization (MALDI)



- Upon pulsed laser irradiation, rapid heating of the matrix causes sublimation and expansion into the gas phase in a fast cooling plasma called a MALDI plume.
- The most widely accepted ionization mechanism is gas-phase proton transfer.
- Efficient, “soft” (i.e., little fragmentation), and relatively universal (the wavelength is independent of the analyte).
- Allows analysis of large (100’s of kDa) intact biopolymers.
- Not quantitative due to heterogeneity.

K. Tanaka
Nobel Prize
2002

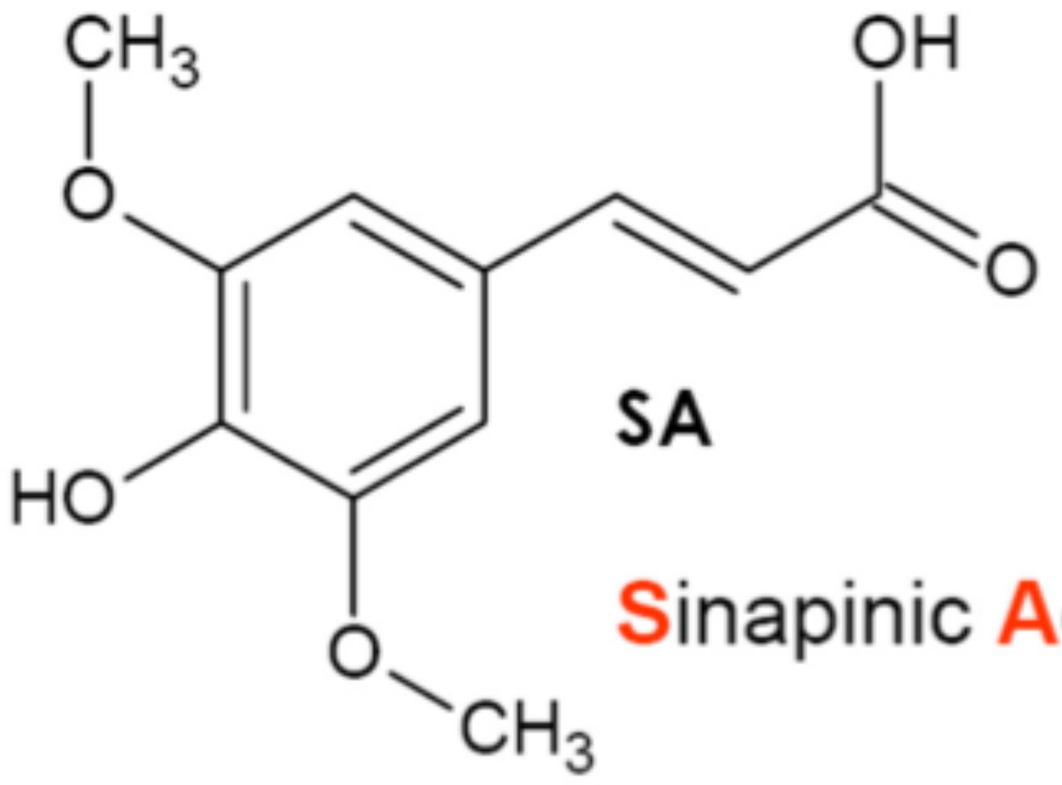
Properties of MALDI matrices

The ideal matrix should have the following properties:

- Strong absorption at the laser wavelength (chromophore)
- Solvent compatible with sample
- Homogeneous solid-state mixing with the analyte (co-crystallization)
- **Proton donor $M \longrightarrow [M+H]^+$**
  - Ability to undergo photochemical reaction leading to proton transfer to the analyte
- **Proton acceptor $M \longrightarrow [M-H]^-$**
  - Ability to undergo photochemical reaction leading to proton transfer from the analyte

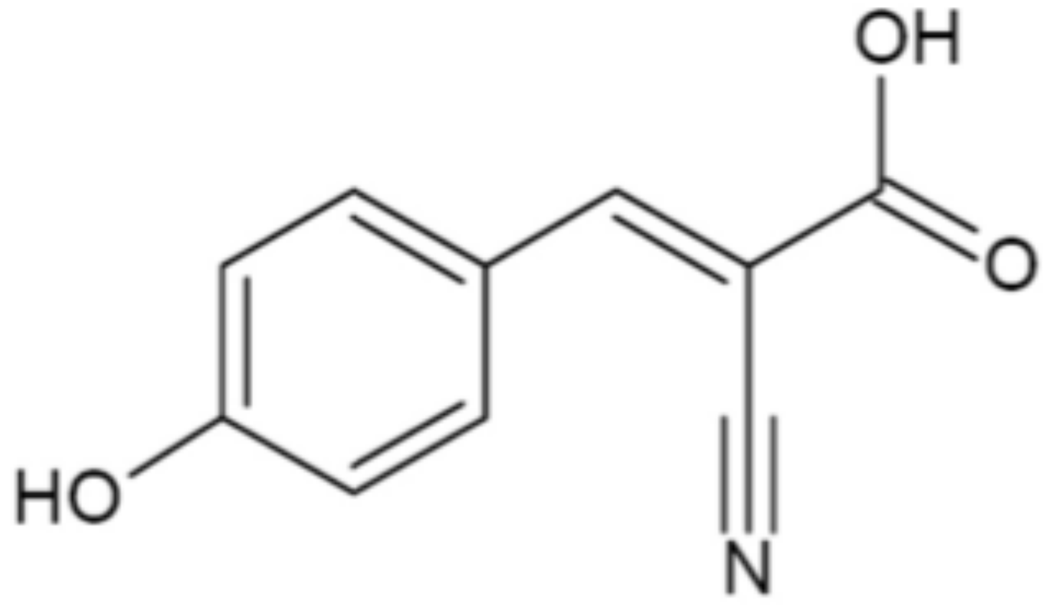
MALDI matrices

Structure of the most versatile matrices



SA

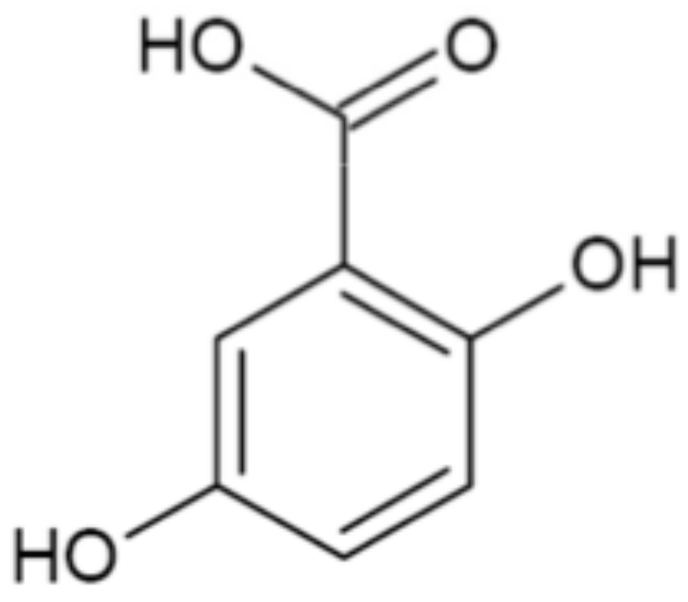
Sinapinic Acid



HCCA (α-CN)

α-Cyano-4-HydroxyCinnamic Acid

DHB



2,5-DiHydroxyBenzoic Acid

- Absorbance @ 337 and 355 nm
- Easy crystallization
- Soluble in aqueous organic solvents

Lasers used in MALDI

Pulsed Lasers

Lasers are pulsed (duration 1 to 10 ns) in UV or in IR regions

UV

N_2 laser:

3 ns pulse, λ = 337 nm

Nd-YAG laser (3rd harmonic):

7-10 ns pulse, λ = 355 nm

Short pulses

Most common for MALDI sources

IR

Er-YAG:

200 ns pulse, λ = 2.94 µm

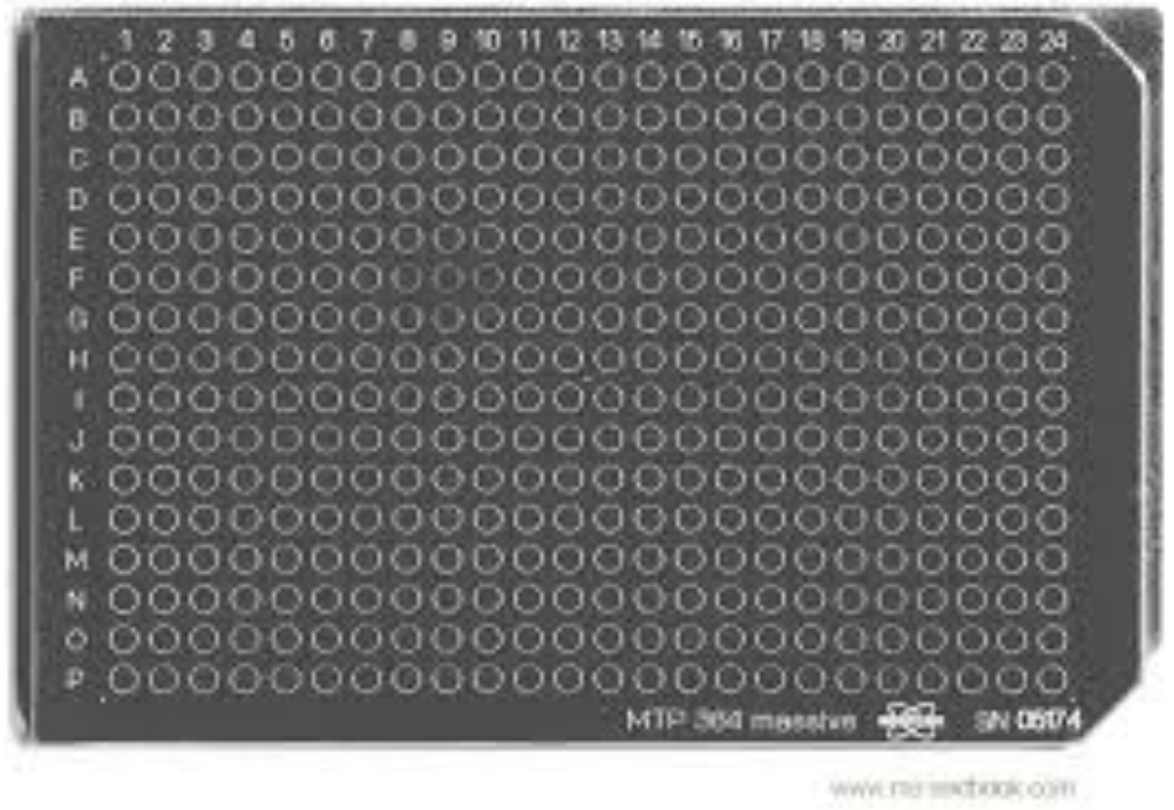
CO_2 laser:

70 ns pulse, λ = 10.6 nm

Softer desorption

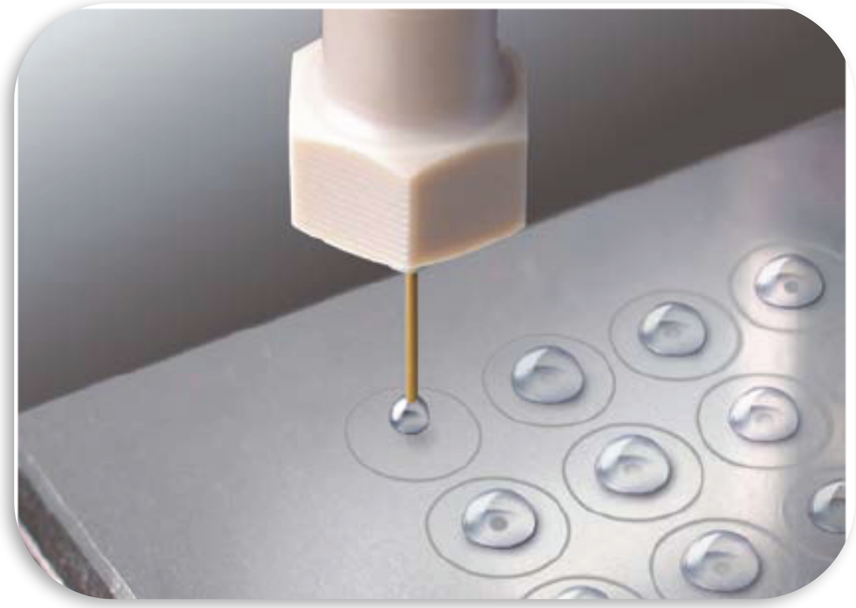
For large and labile compounds (high MW proteins and DNA)

MALDI targets

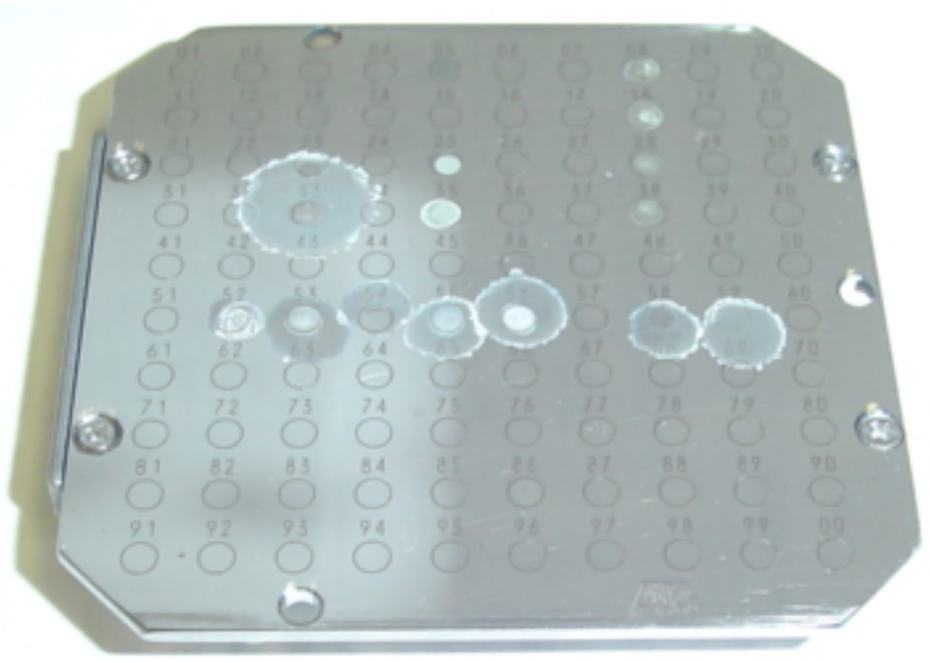


Manual deposition

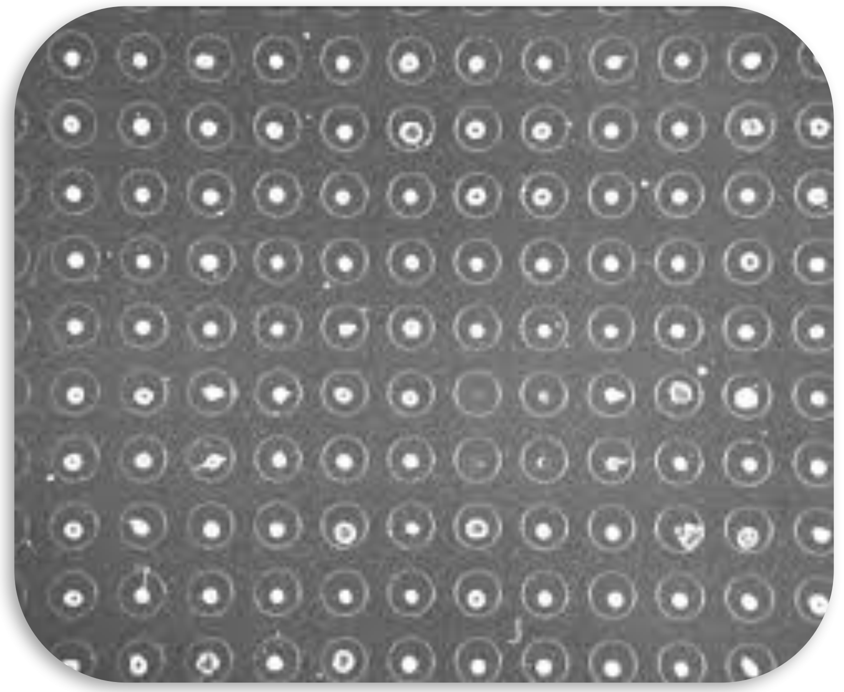
MALDI spotter



Crystallization

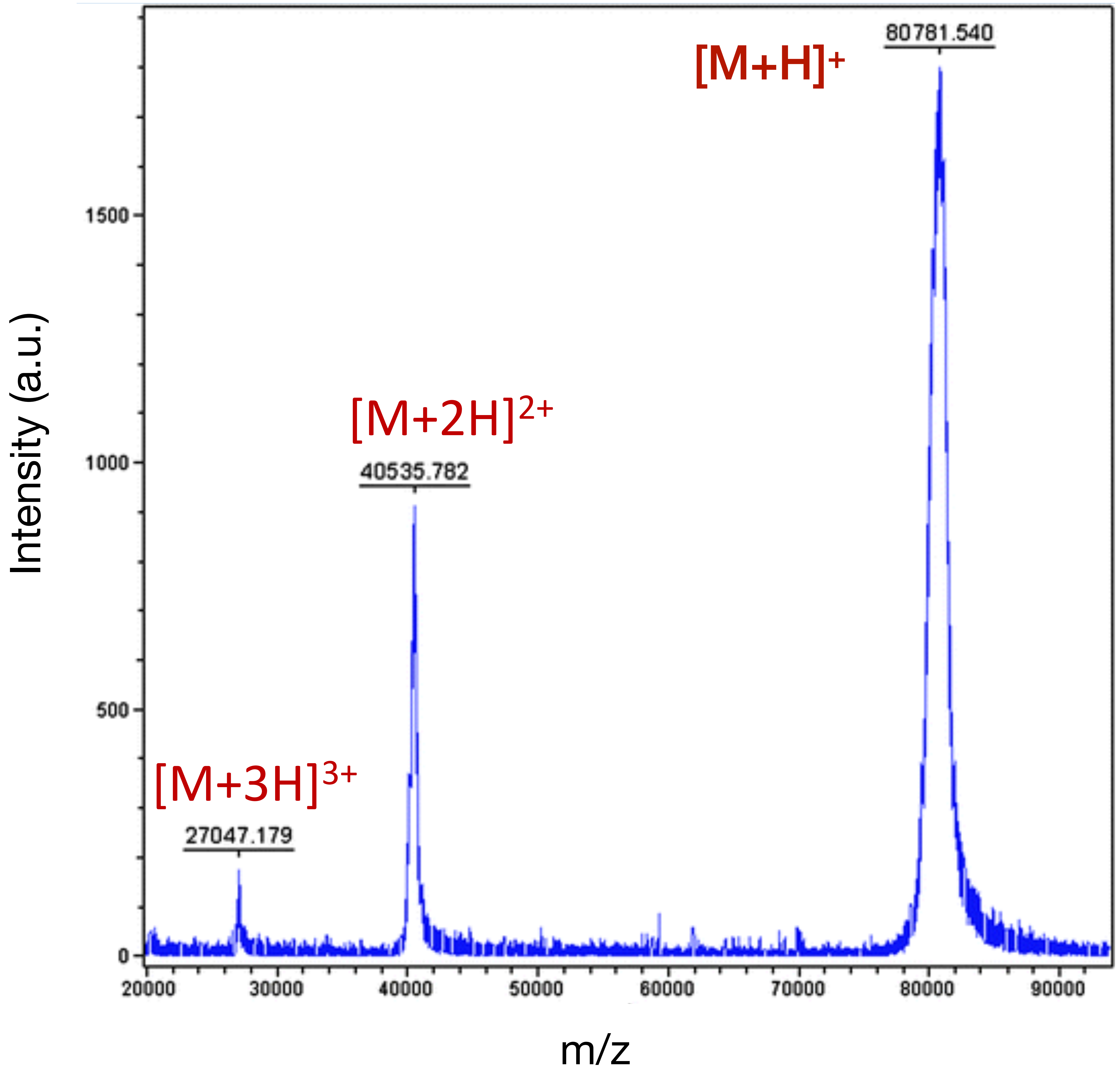


Anchorchip (Bruker)

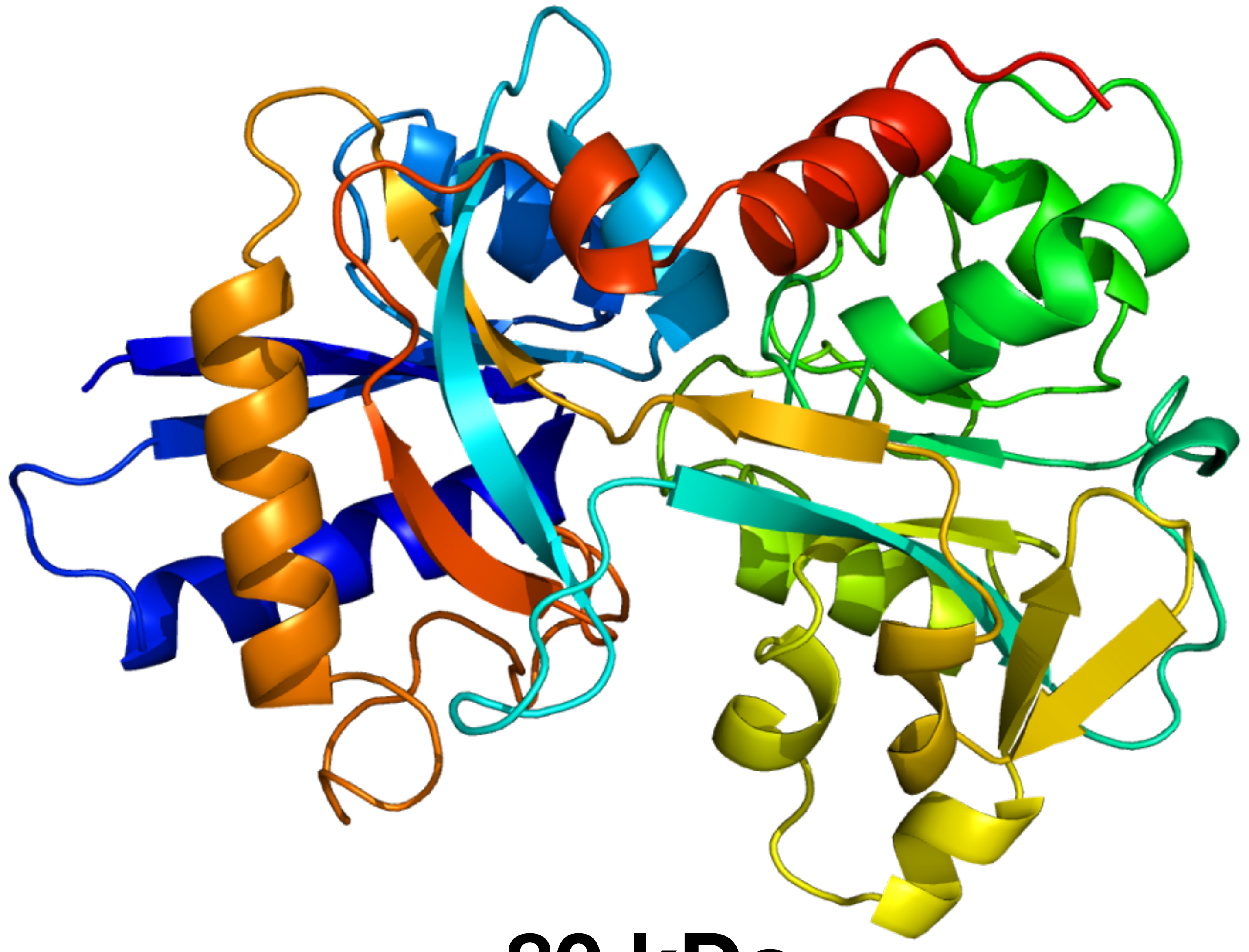


- Sample is mixed with matrix and 1 µL is deposited on the target
- Many different protocoles: Dried-droplets (DD), Sandwich…

MALDI of Biomolecules



Transferrin



~80 kDa

Protein is co-crystalized with SA matrix

Proteins up to 200 kDa can be measured

Matrix-assisted Laser Desorption Ionization (MALDI)

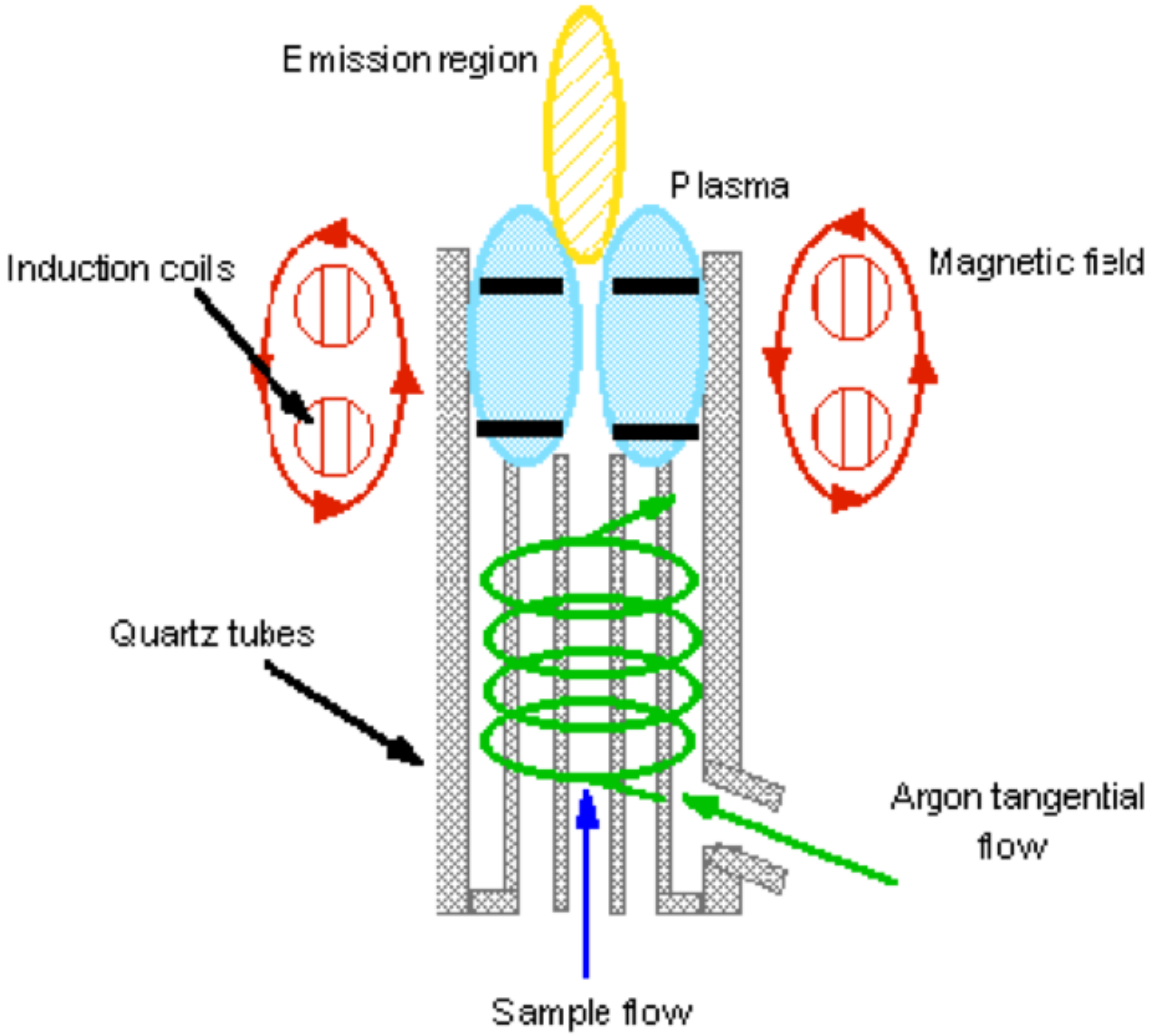
Advantages

- Preferable for large molecules
- Very fast
- Sensitive to small amounts of sample
- Simple spectra
- Accurate
- Not affected by salts
- Soft ionization

Disadvantages

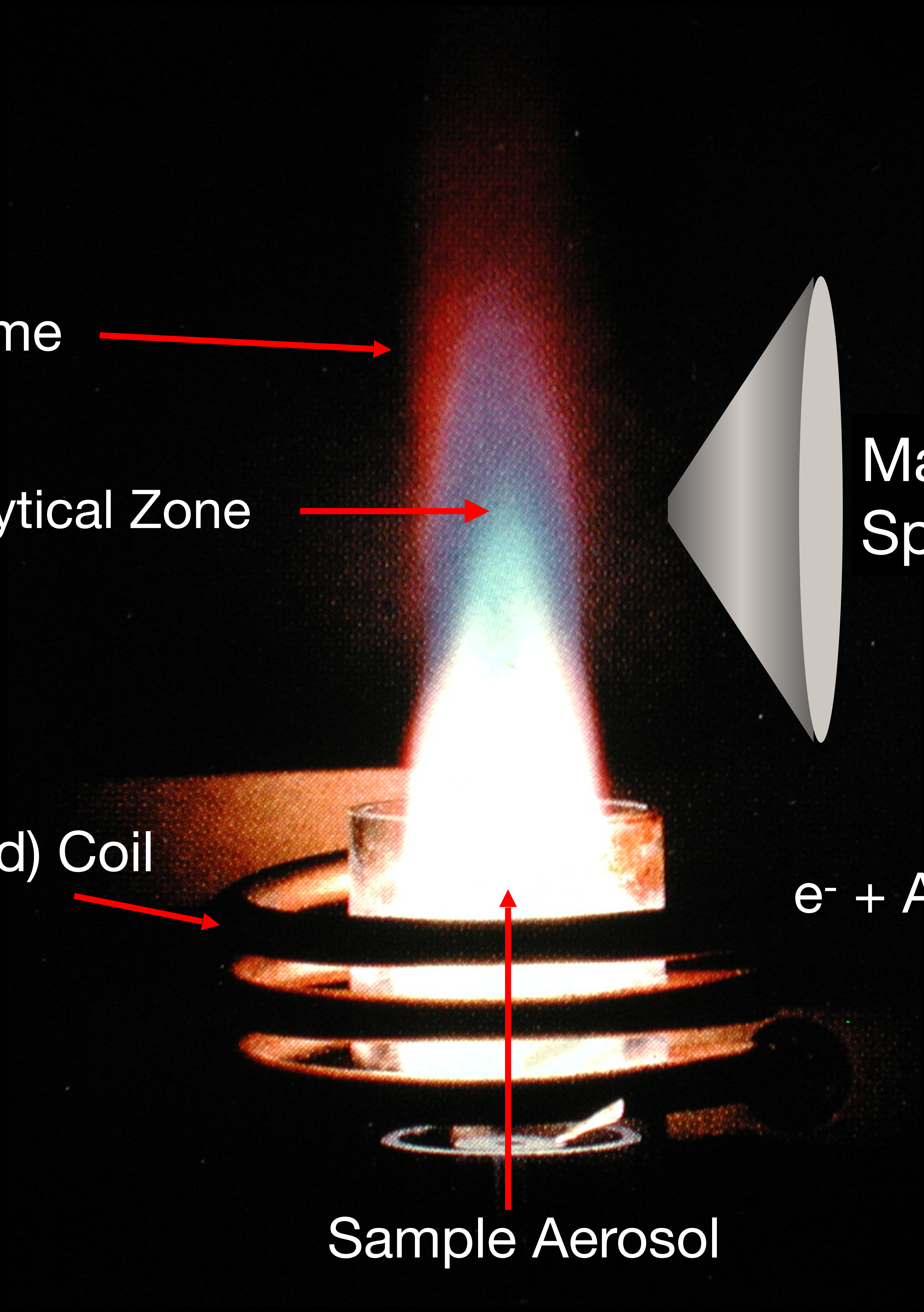
- Needs preparation of crystals, adjusting intensity of laser, finding crystals on plate with sample
- Low shot to shot reproducibility
- Short sample life
- Singly charged ions

Inductively Coupled Plasma (ICP)



The temperature in the central analyte channel ranges from about 6000 to 8000° K

1. Ionization of Ar in a radio frequency plasma.
2. Atomization of sample due to high temperature and ionization by the plasma.



Tail Flame

Normal Analytical Zone

Induction (Load) Coil

Sample Aerosol

Mass Spectrometer

$e^- + Ar \longrightarrow Ar^+ + 2e^-$

Inductively Coupled Plasma MS

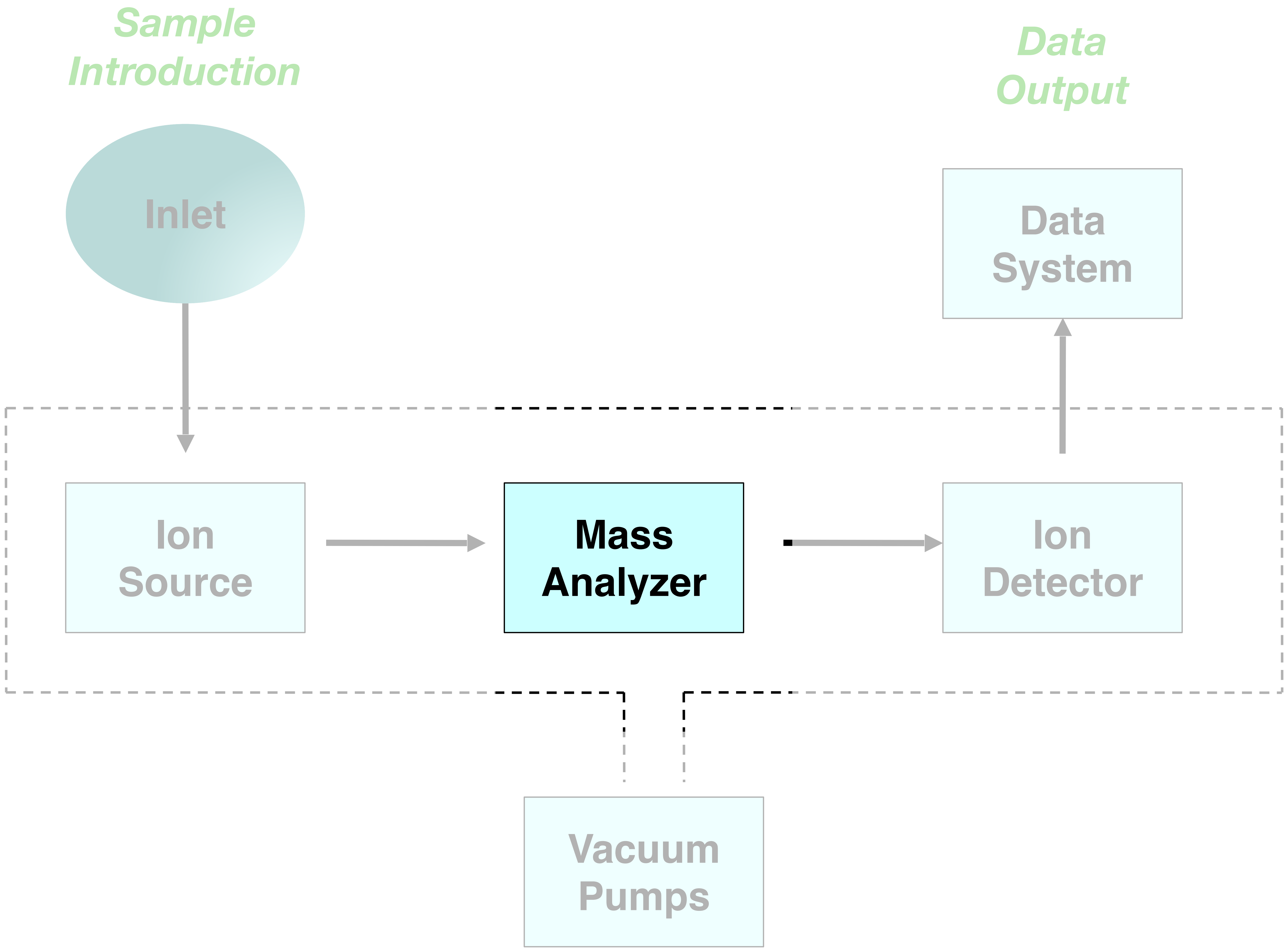
Advantages

- Multi-element analysis
- High sensitivity
- Nearly complete isotope coverage
- Liquid, solid or gas samples
- Short analysis times
- Less “art”

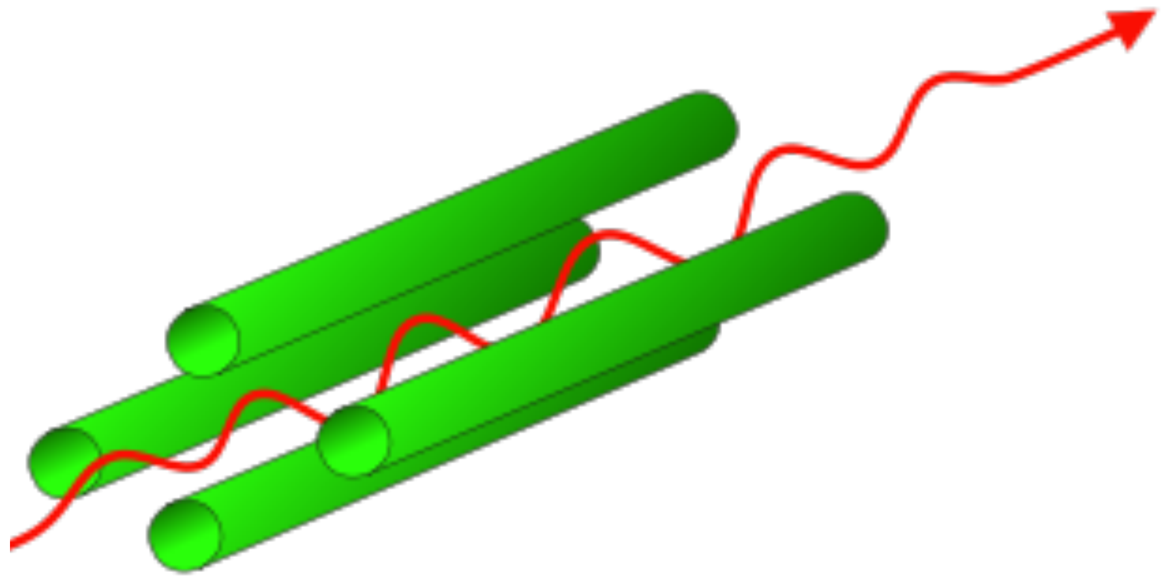
Disadvantages

- Isobaric interferences
- Relatively noisy
- Wide ion energy spread
- Inefficient
- Spectral complexity

Mass Analyzers

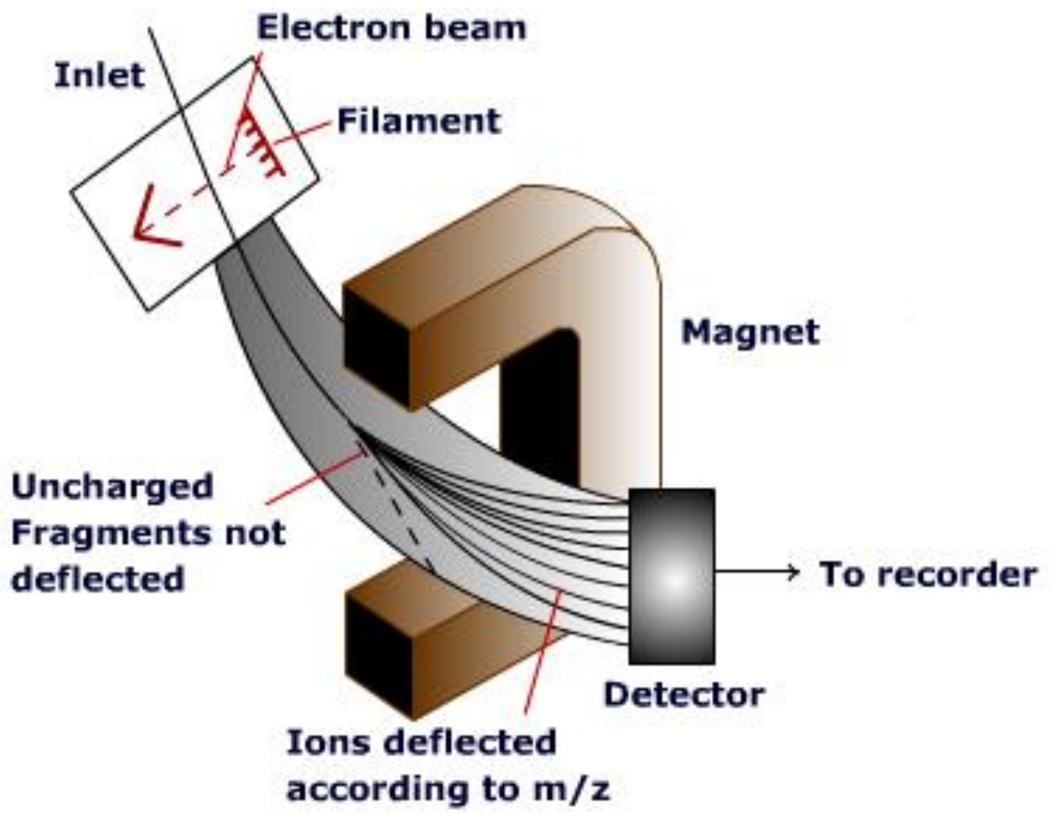


Mass Analyzers

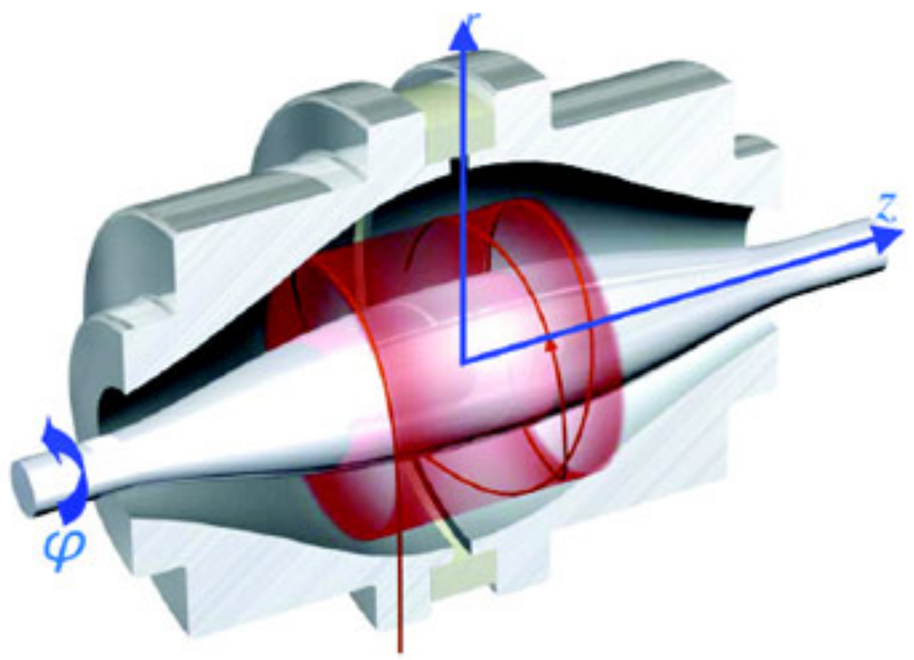


Quadrupole (Q)

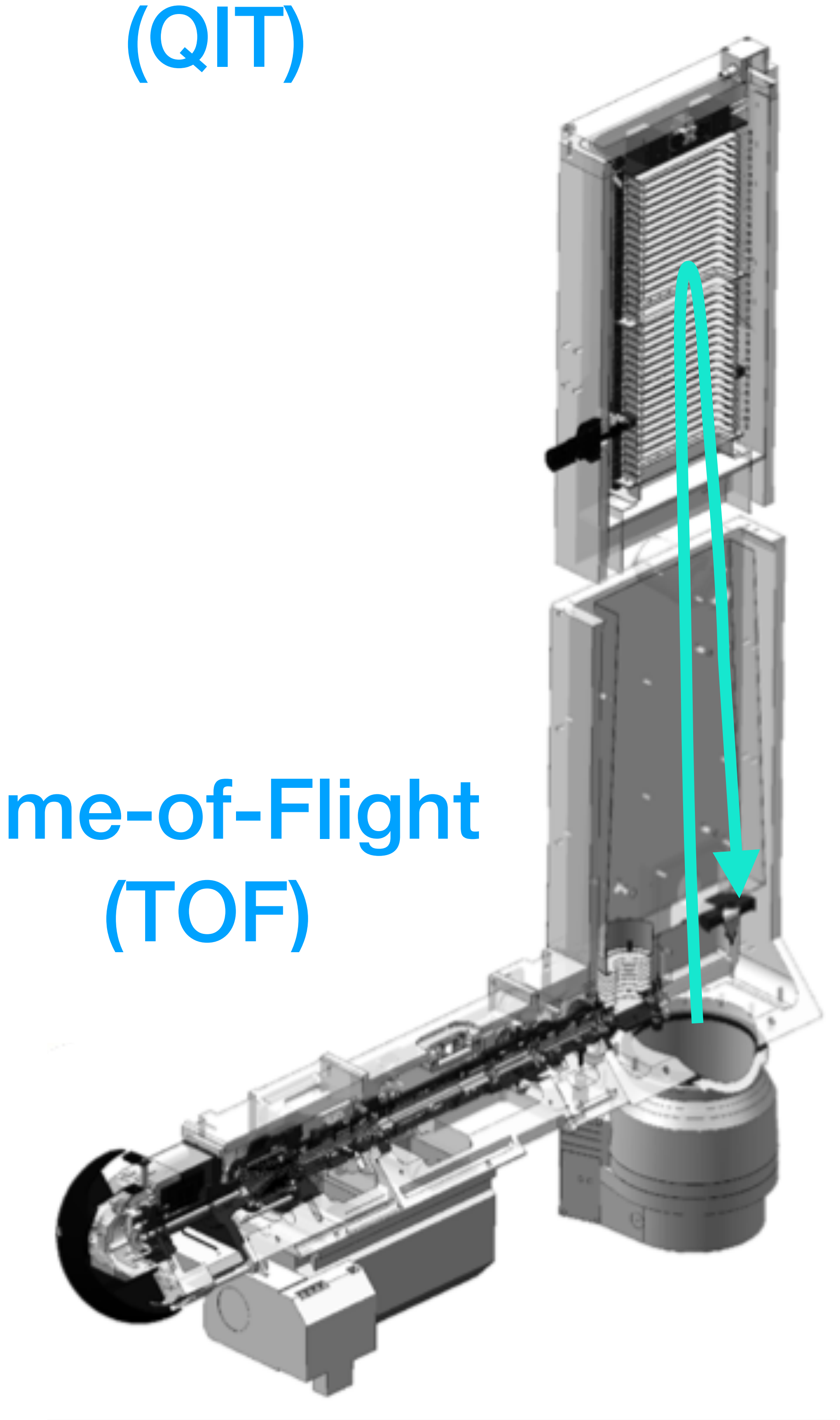
Quadrupole ion trap (QIT)



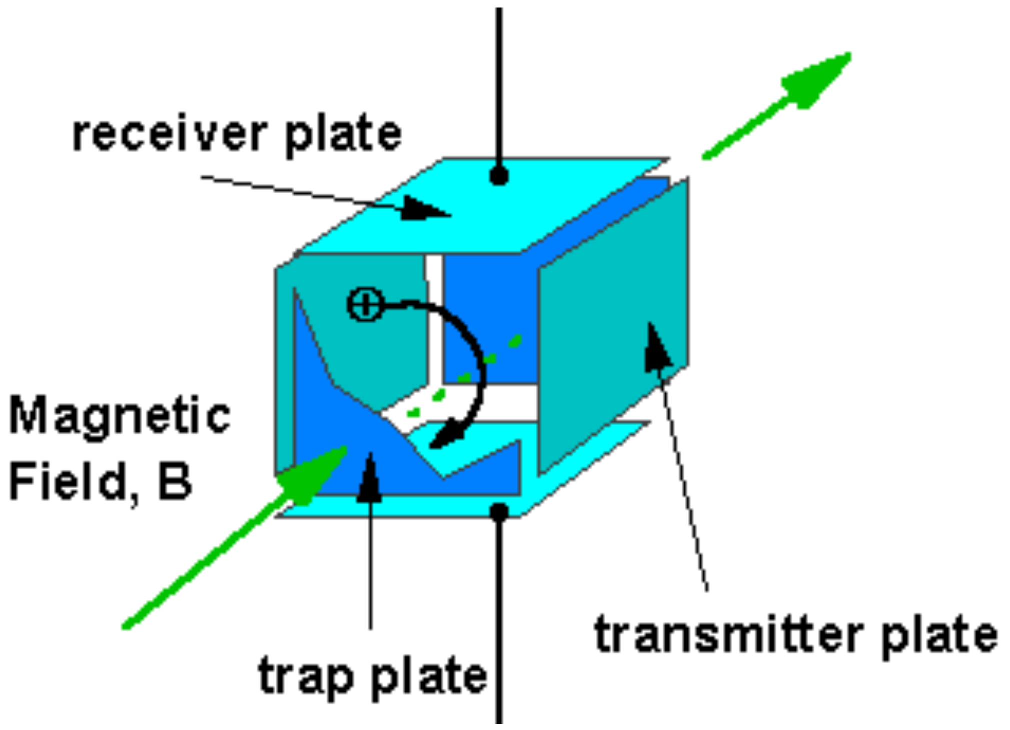
Magnetic sector



Orbitrap



Time-of-Flight (TOF)



Ion cyclotron resonance (ICR)

Principle of mass separation

$$\vec{F} = m \cdot \vec{a} = m \frac{d\vec{v}\left(\vec{r},t\right)}{dt}$$

Newton’s second law

The **force on a charged particle** moving through and electric field E and magnetic field B is given by

$$\vec{F} = \underbrace{q\vec{E}\left(\vec{r},t\right)}_{\text{interaction with the electric field}} + \underbrace{q\left[\vec{v}\left(\vec{r},t\right) \times \vec{B}\left(\vec{r}\right)\right]}_{\text{interaction with the magnetic field}}$$

This is called the **Lorentz force**

We can classify the types of mass analyzers by the type of force applied to the ion to separate different masses.

Classification of mass analyzers

1. Field-free based analyzers

$$\vec{F} = m\frac{d\vec{v}\left(\vec{r},t\right)}{dt} = 0 \qquad \vec{E}\left(\vec{r},t\right) = 0 \qquad \vec{B}\left(\vec{r}\right) = 0$$

➡ **Time-of-Flight (TOF) MS**

Give the ions an initial amount of energy, but then let them drift through a field-free region.

Classification of mass analyzers

1. Field-free based analyzers

$$\vec{F} = m\frac{d\vec{v}\left(\vec{r},t\right)}{dt} = 0 \qquad \vec{E}\left(\vec{r},t\right) = 0 \quad \vec{B}\left(\vec{r}\right) = 0$$

→ **Time-of-Flight (TOF) MS**

Give the ions an initial amount of energy, but then let them drift through a field-free region.

2. Electric field based analyzers

$$\vec{F} = m\frac{d\vec{v}\left(\vec{r},t\right)}{dt} = q\,\vec{E}\left(\vec{r},t\right) \qquad \vec{B}\left(\vec{r}\right) = 0$$

→ **Quadrupole**
Ion trap
Orbitrap

Classification of mass analyzers

1. Field-free based analyzers

$$\vec{F} = m\frac{d\vec{v}(\vec{r},t)}{dt} = 0 \qquad \vec{E}(\vec{r},t) = 0 \quad \vec{B}(\vec{r}) = 0$$

➡ **Time-of-Flight (TOF) MS**

Give the ions an initial amount of energy, but then let them drift through a field-free region.

2. Electric field based analyzers

$$\vec{F} = m\frac{d\vec{v}(\vec{r},t)}{dt} = q\,\vec{E}(\vec{r},t) \qquad \vec{B}(\vec{r}) = 0$$

➡

Quadrupole

Ion trap

Orbitrap

3. Magnetic field based analyzers

$$\vec{F} = m\frac{d\vec{v}(\vec{r},t)}{dt} = q\left[\vec{V}(\vec{r},t)\times\vec{B}(\vec{r})\right] \qquad \vec{E}(\vec{r},t) = 0$$

➡

Magnetic sector

Ion cyclotron resonance (ICR)

Desirable characteristics of mass analyzers

They should:

- be able to sort ions by m/z
- have good transmission (improves sensitivity)
- have appropriate resolution (helps selectivity)
- have appropriate upper m/z limit
- be compatible with source output (pulsed or continuous)

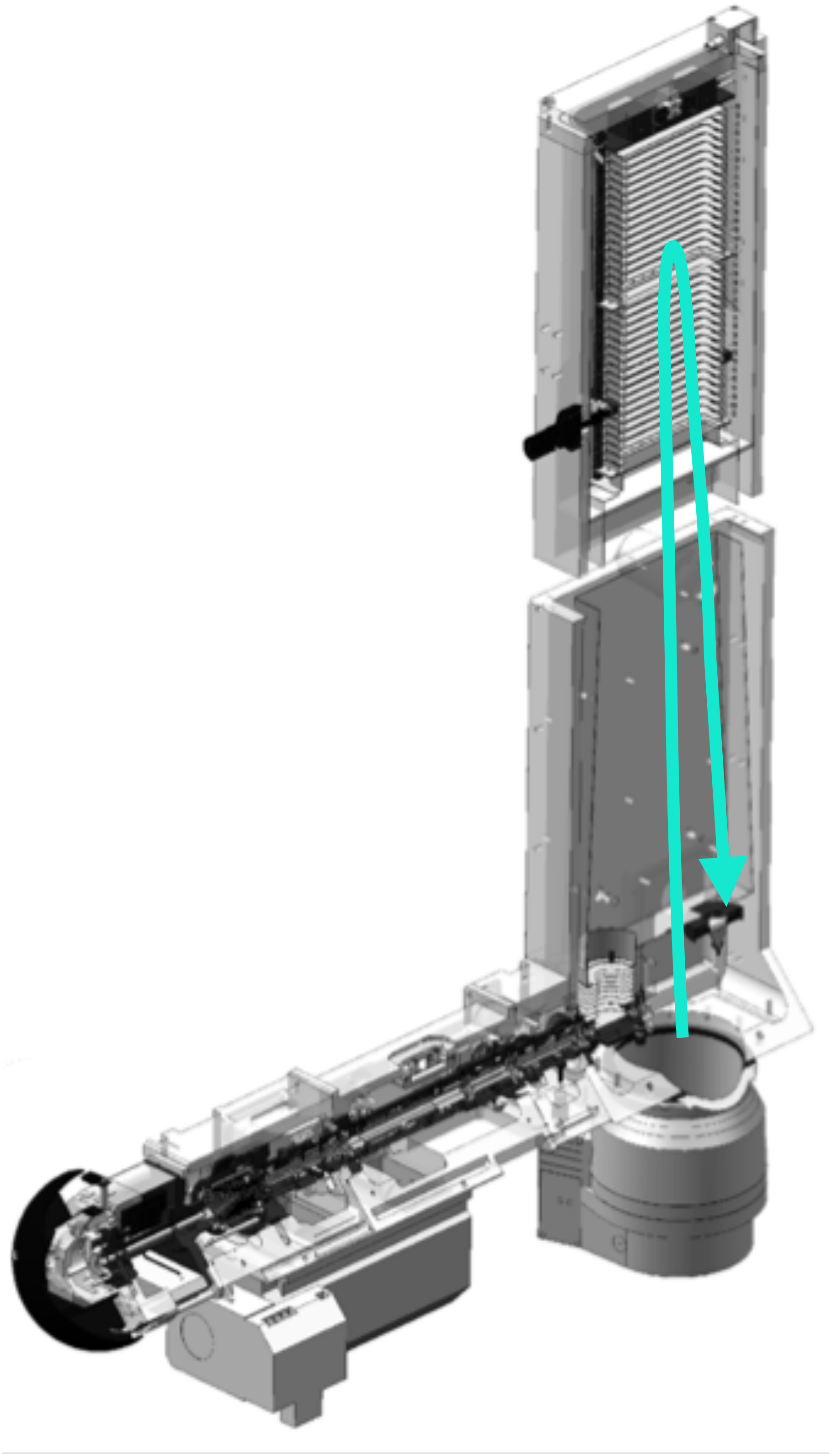
Characteristics of mass analyzers

- **m/z limitation**
  - Depends on the mass analyzer: 100-4000 Th common range for Q and IT (32'000 for special Q), unlimited for TOF, 50000 for Orbitrap
- **Resolution: how it varies across m/z**
  - Q: RP decreases for increasing m/z
  - TOF: RP constant across m/z
  - Orbitrap: RP decreases with increasing m/z
- **Time for achieving high resolution**
  - Should be compatible with LC peaks
- **Duty cycle:** number of different m/z monitored at the same time
- **Costs:** to buy, to own (maintenance, spare parts, etc.)

Comparison of mass analyzers

Type	Resolving Power (RP)	Mass Accuracy (ppm)	Ion sampling	Scan Rate	Cost
Quadrupole	2-5000	100	Continuous	< 1 sec	$
Ion Trap	4000	100	Pulsed		$
TOF	20-50,000	5	Pulsed	< 0.1 sec	$$
Orbitrap	240,000	< 2	Pulsed	Depends on RP	$$$
ICR	500,000	< 2	Pulsed	Depends on RP	$$$$
Magnetic Sector (Double-focusing)	100,000	< 5	Continuous	~ 1 sec	$$$$

Time-of-flight mass spectrometer (TOF MS)



Time-of-flight MS (TOF MS): the basics

- Mass analysis is achieved because at the same energy, ions of different *m/z* have different velocities and therefore reach the detector at different times

- If 2 ions of different *m/z* starting at the same location, with same kinetic energy and traveling in the same direction:

the ion with the lower m/z will travel faster
and reach the detector first

- Requires that ions emerge from **a pulsed ion source** or by **pulsing ion packages** out of a continuous beam

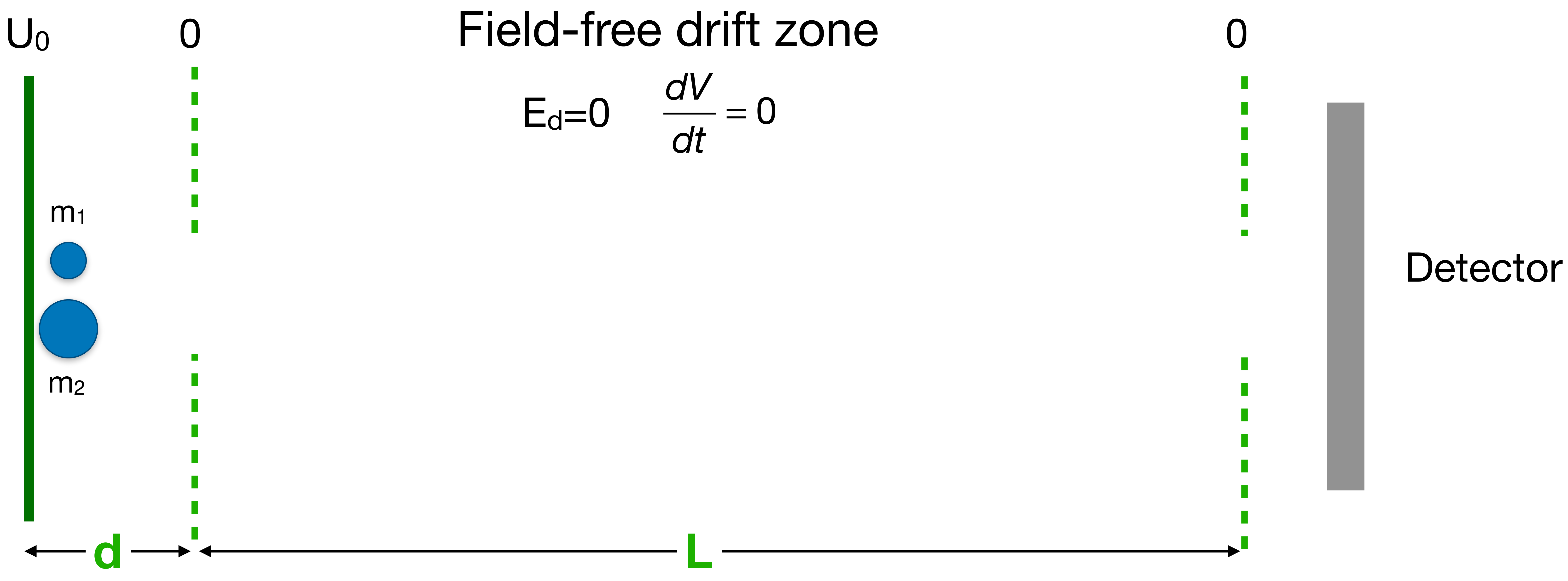
TOF: starting with a pulse

- TOF analyzers need a t_0 starting gate to give a start to the packet of ions

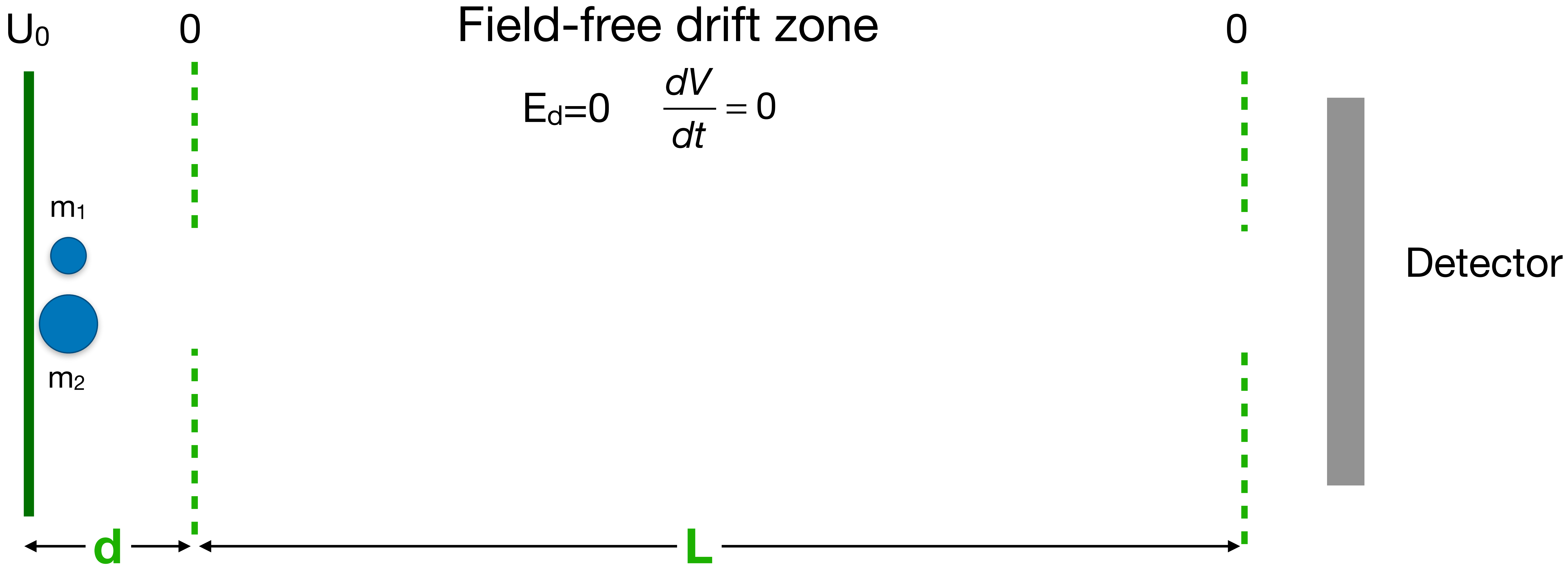
- Pulsed sources (such as MALDI) therefore have an inherent compatibility advantage: laser pulse initiates ion formation in very short time

- For continuous sources (such as ESI), a pusher is used to send packet of ions in the TOF

Time-of-Flight Mass Spectrometer



Time-of-Flight Mass Spectrometer



Field-free drift zone

$E_d=0 \quad \frac{dV}{dt}=0$

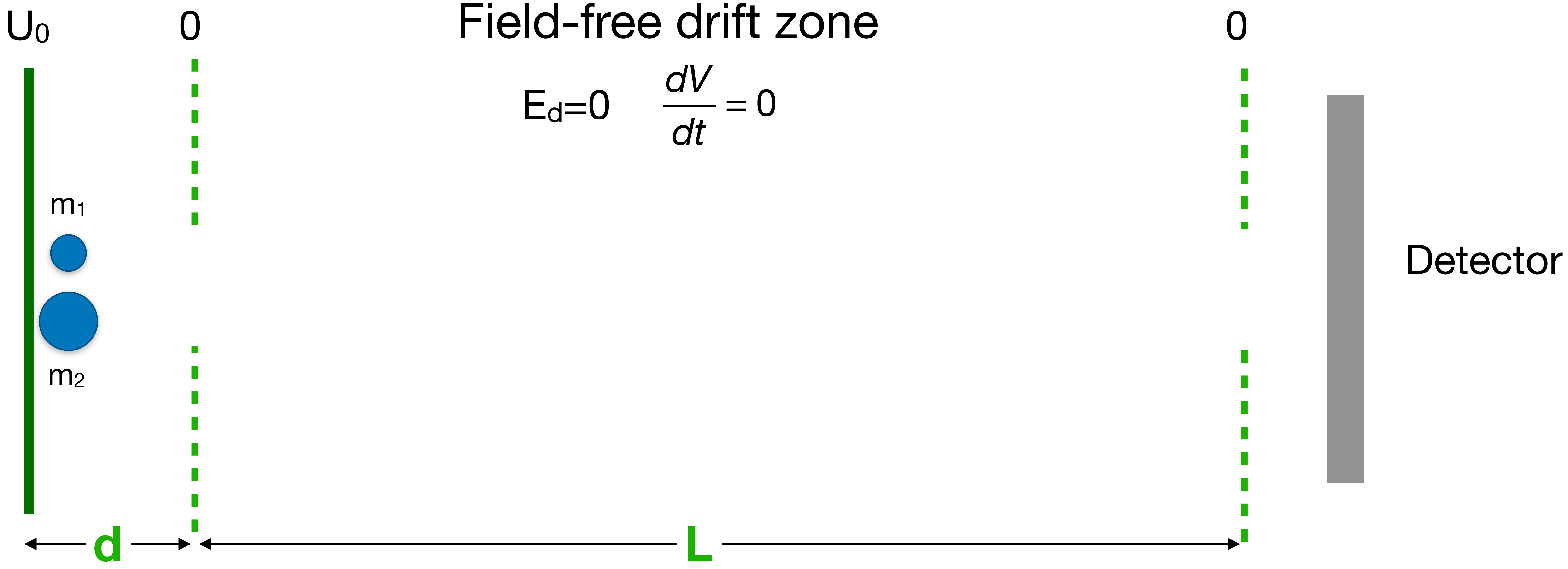
converted to kinetic energy $\frac{1}{2}m_j v_j^2$

Electrical potential energy

volts

q_i (coulombs) × U_0(Joules/coulomb) = Potential energy (Joules)

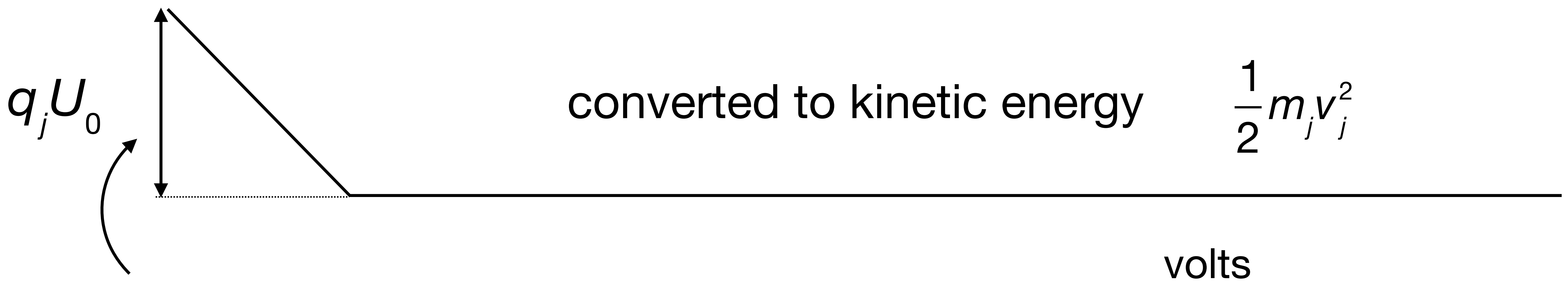
Time-of-Flight Mass Spectrometer



Field-free drift zone

$E_d=0 \quad \frac{dV}{dt}=0$

$$KE = q_j U_0 = \frac{1}{2} m_j v_j^2$$



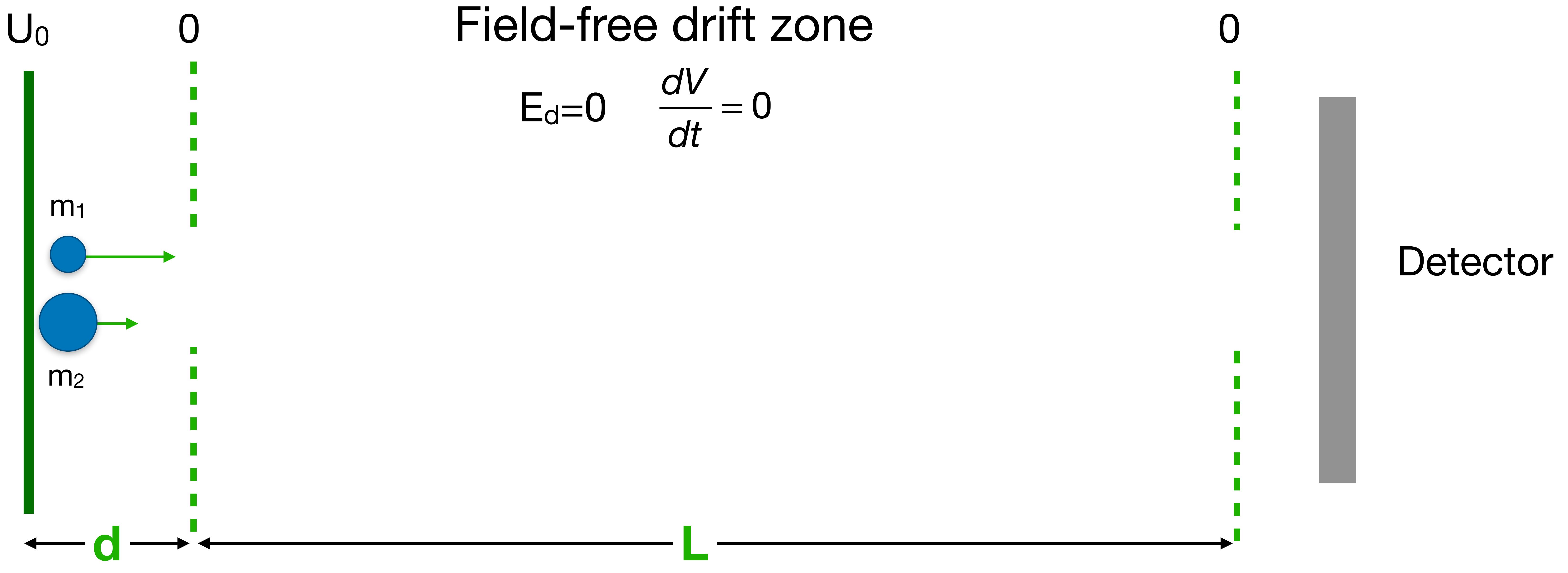
converted to kinetic energy $\frac{1}{2} m_j v_j^2$

Electrical potential energy

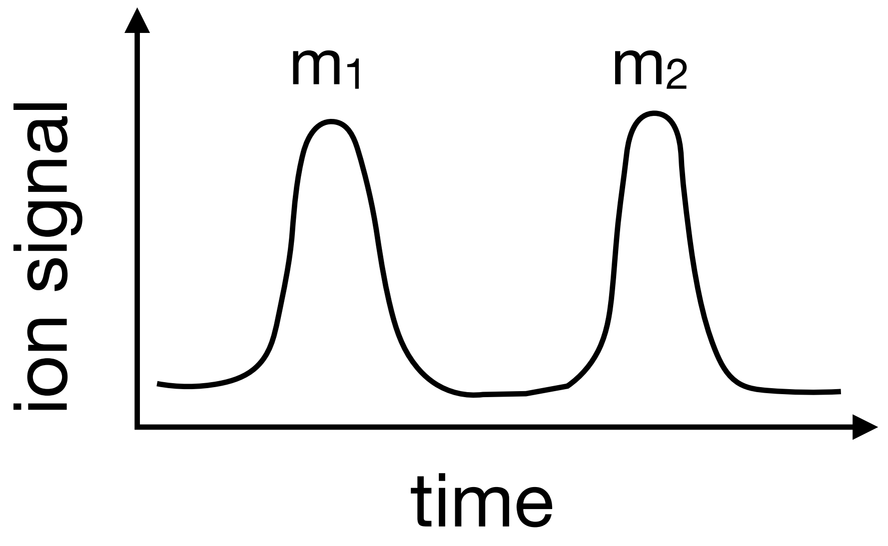
volts

q_i (coulombs) × U_0(Joules/coulomb) = Potential energy (Joules)

Time-of-Flight Mass Spectrometer



$$KE = q_j U_0 = \frac{1}{2} m_j v_j^2 \Rightarrow v_j = \sqrt{\frac{2 q_j U_0}{m_j}}$$



converted to kinetic energy $\frac{1}{2} m_j v_j^2$

Electrical potential energy

volts

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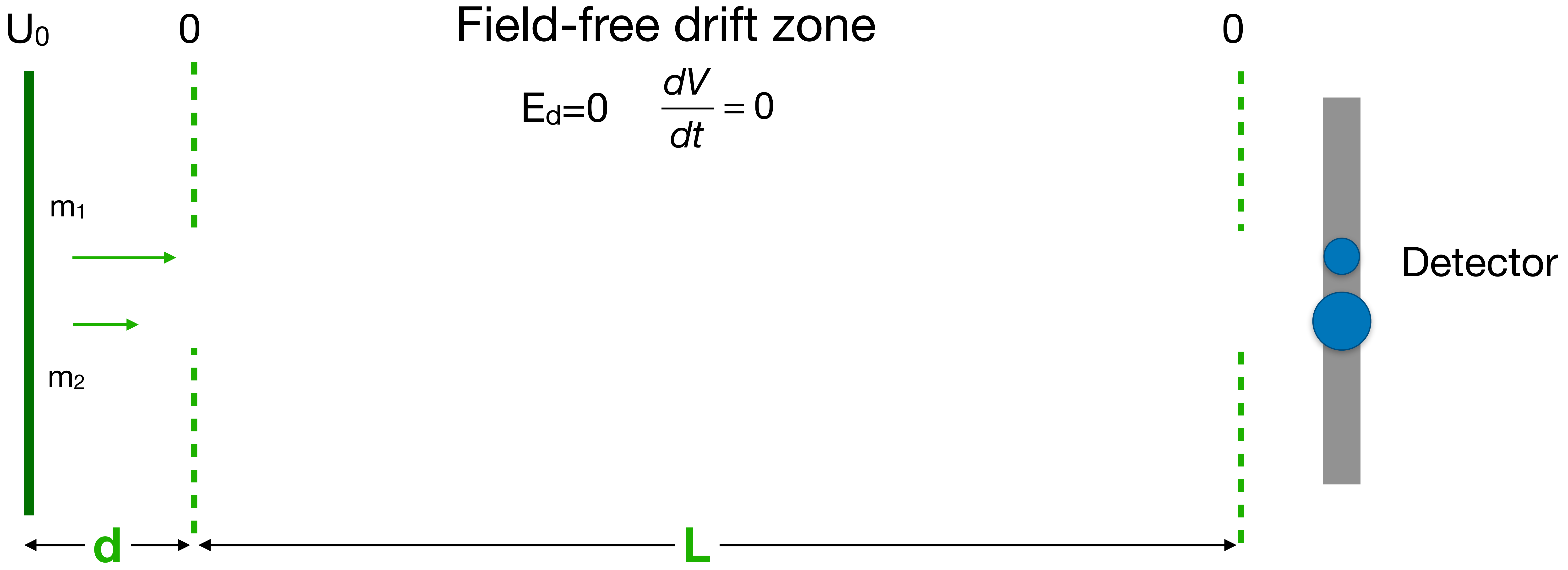
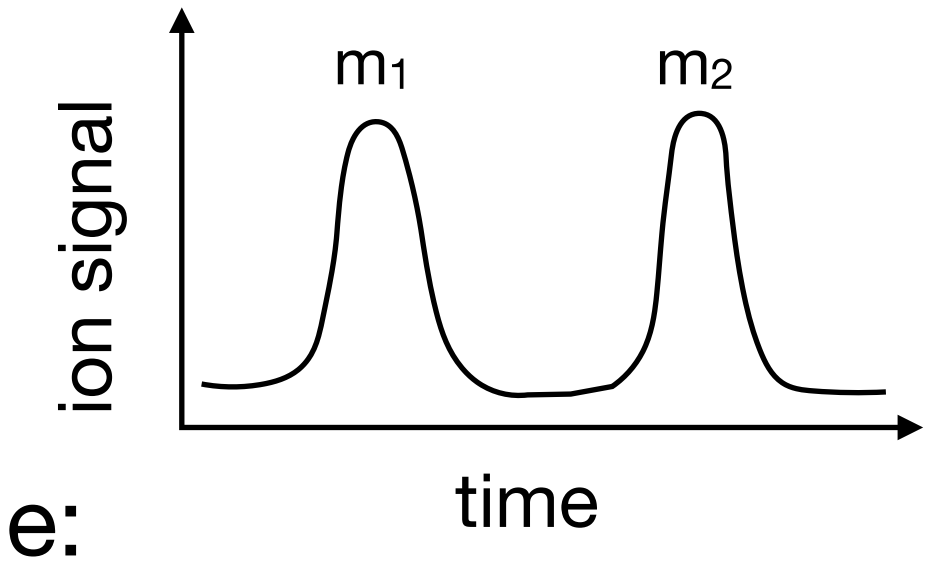
Time-of-Flight Mass Spectrometer



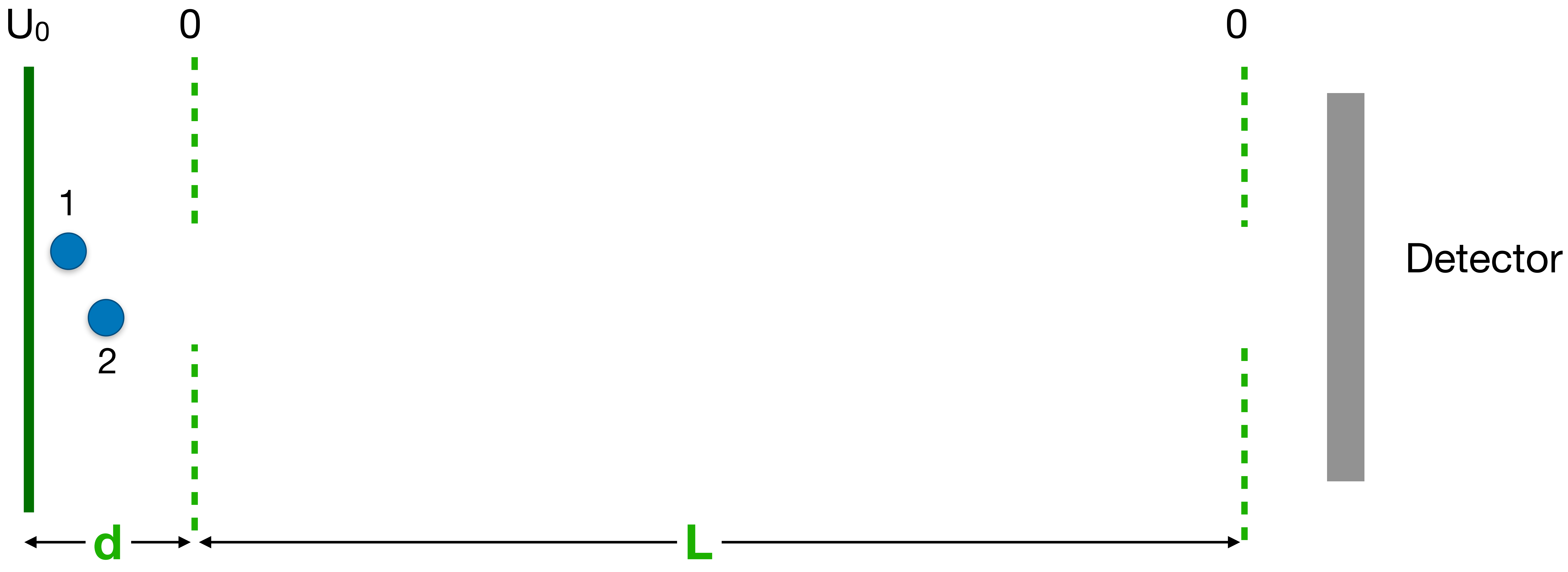
$$KE = q_j U_0 = \frac{1}{2} m_j v_j^2 \quad \Rightarrow \quad v_j = \sqrt{\frac{2 q_j U_0}{m_j}}$$



If we ignore the flight time through the acceleration zone:

$$\tau_j = \frac{L}{v_j} = L\sqrt{\frac{m_j}{2 q_j U_0}} \qquad \left(\frac{m}{q}\right)_j = \frac{2U_0}{L^2}\tau_j^2$$

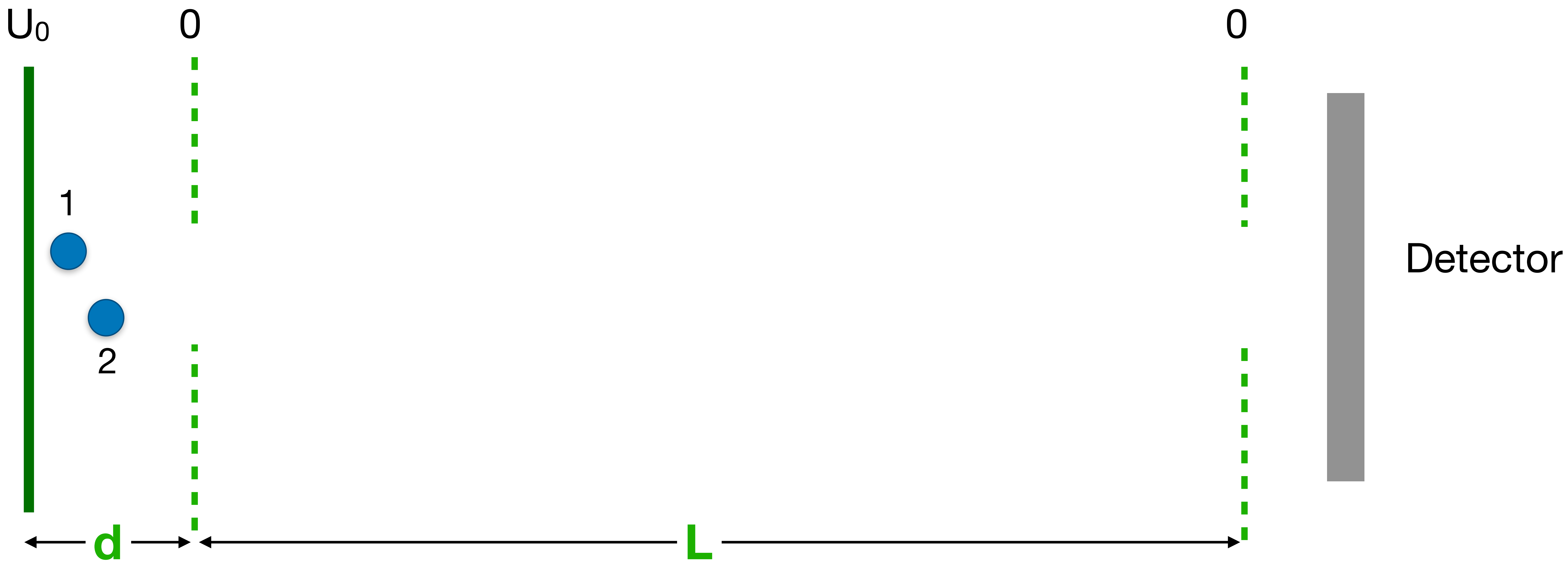
Clicker question



Consider two ions of the same mass that are ionized at slightly different positions. What will be the relative energies of the two ions?

1. Particle 1 will be faster than 2.
2. Particle 2 will be faster than 1.
3. They will both have the same speed but arrive at different times.
4. None of the above.

Answer to clicker question



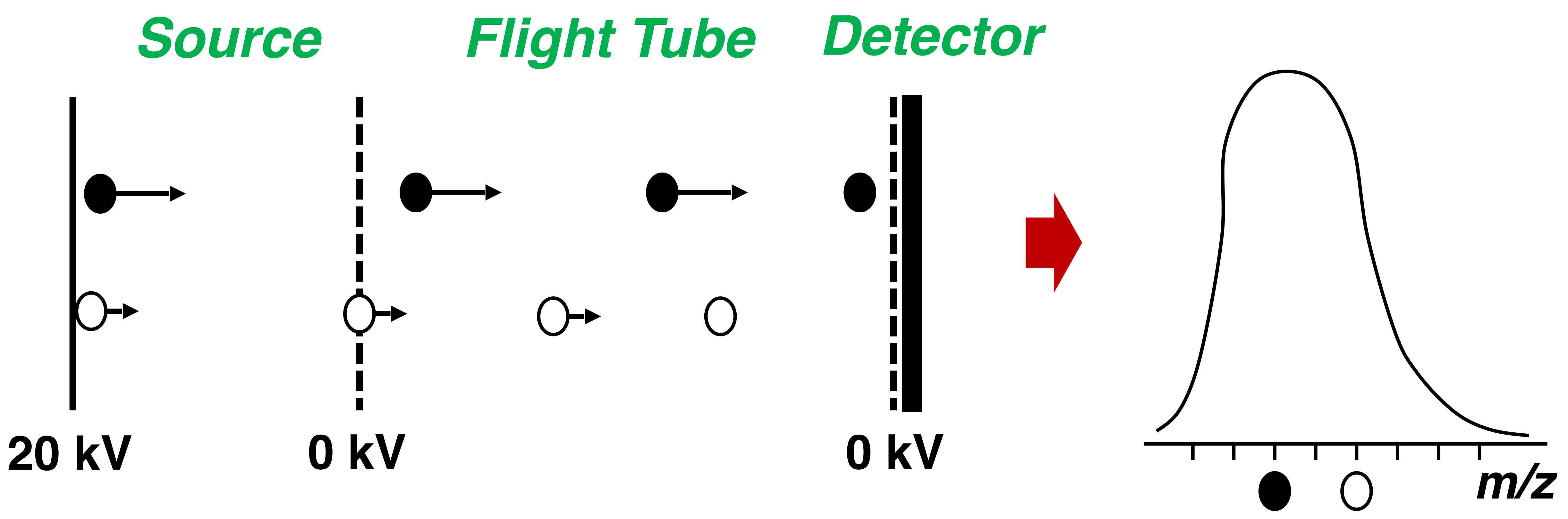
Consider two ions of the same mass that are ionized at slightly different positions. What will be the relative energies of the two ions?

TOF limitations & factors affecting R

- Time distribution: laser pulse length (nsec) and desorption/ionization process forms ions quickly (5-100 ns) but not instantaneously.

- Spatial distribution: The finite size of the ionization region means that ions do not start at the same point in space and will thus have different distances to travel.

- Energy distribution: ions of the same m/z do not all start with the same energy/velocity.



○ Ion of a given mass with lower kinetic energy

● Ion of the same mass with higher kinetic energy

Limiting the spread in kinetic energies

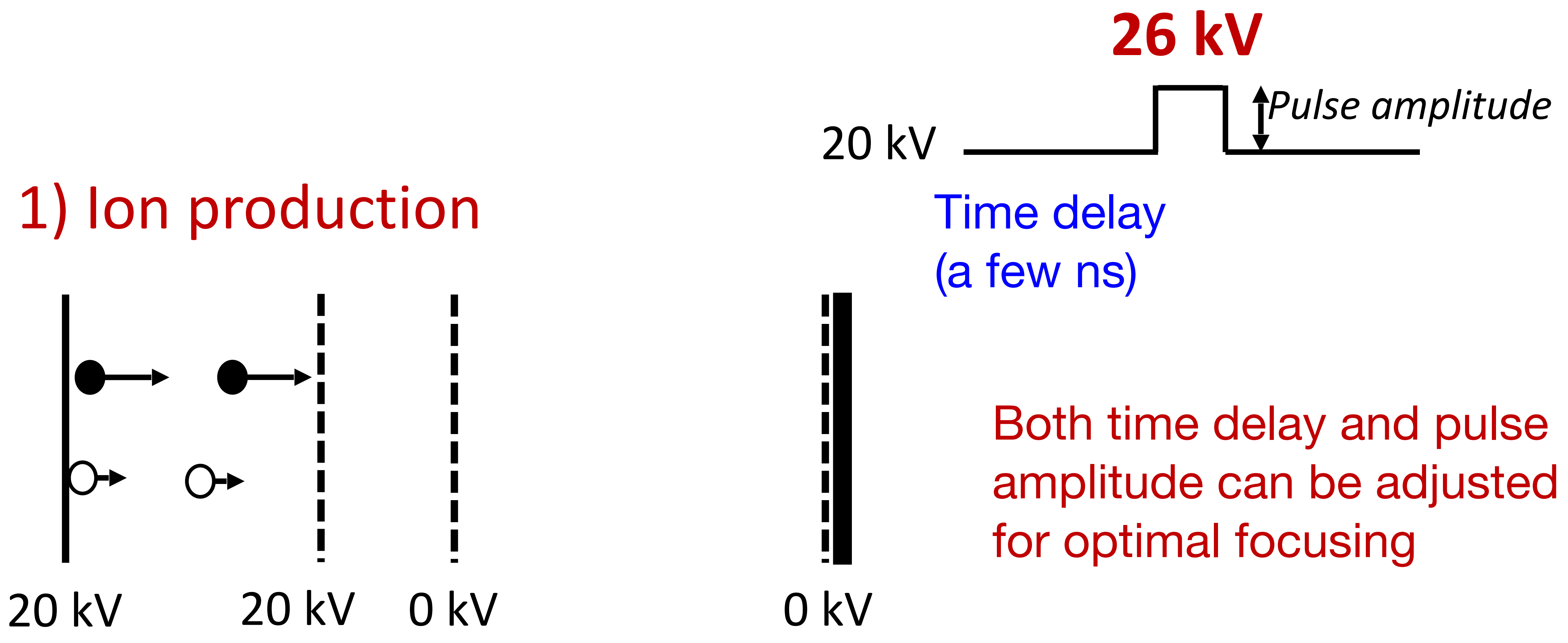
There are numerous approaches to narrow the energy distributions of ions or compensate their effects:

- Time lag (100 ns – 1 µs) between ion formation and ion extraction for ion focusing in time : the **Pulsed Ion Extraction (PIE)** delay
- Reflectron / ion mirror
- Increase acceleration voltage to decrease the relative contribution of energy distribution during ionization process

Pulsed ion extraction (PIE)

- Time lag of 100 ns-1 μs between ion formation and ion extraction

1) Ion production



Both time delay and pulse amplitude can be adjusted for optimal focusing

1- Ion desorption by laser Pulse

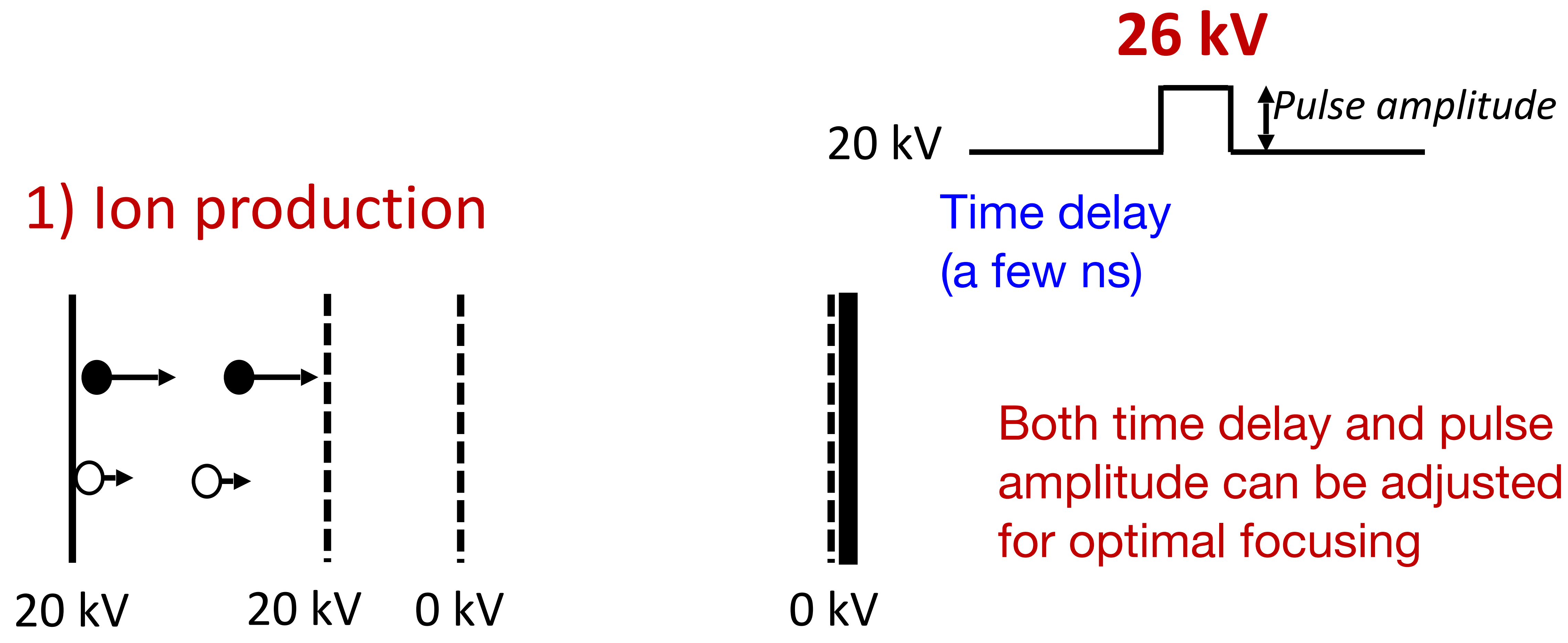
Wait…..
(ions moving, colliding)

2- Fast Pulse source voltage

Pulsed ion extraction (PIE)

- Time lag of 100 ns-1 μs between ion formation and ion extraction

1) Ion production



Time delay
(a few ns)

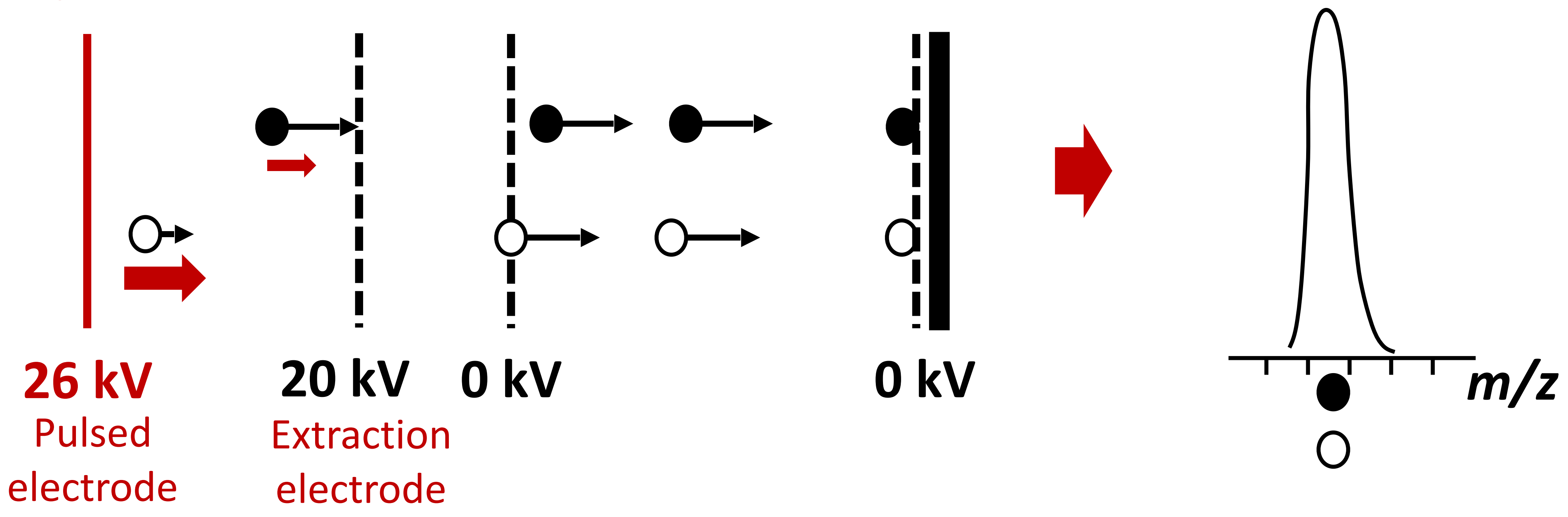
Both time delay and pulse amplitude can be adjusted for optimal focusing

1- Ion desorption by
laser Pulse

Wait…..
(ions moving, colliding)

2- Fast Pulse source voltage

2) Ion extraction

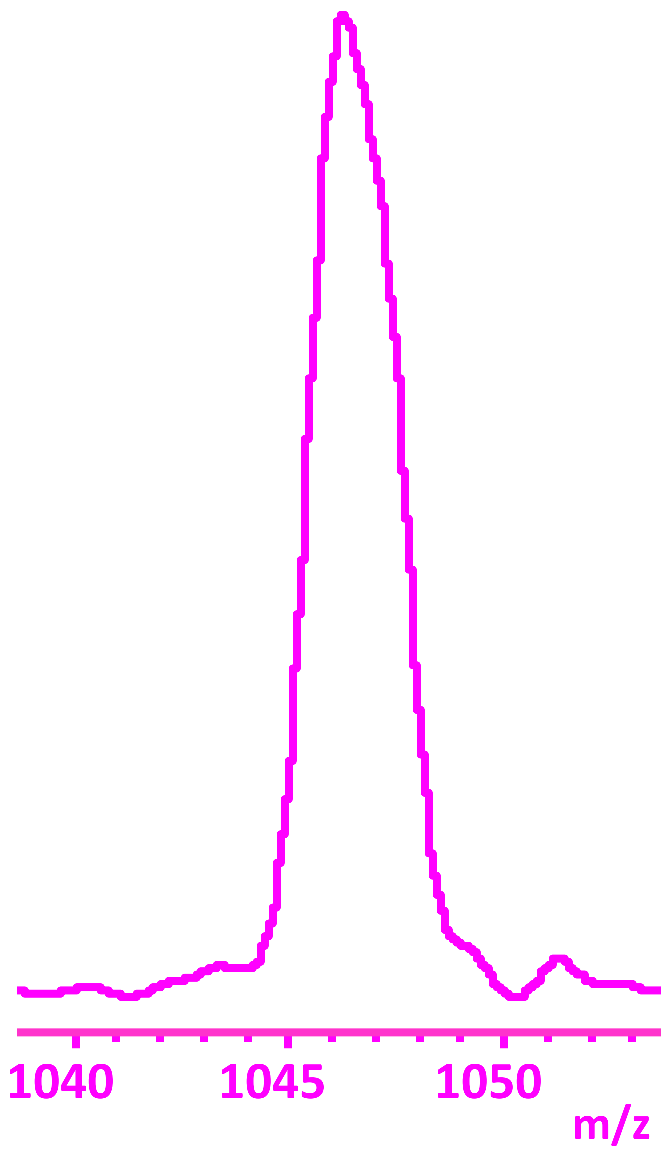


Slower ions stay closer to the surface of the pulsed electrode, therefore start being accelerated at a greater potential compared to the ions farther from the pulsed electrode

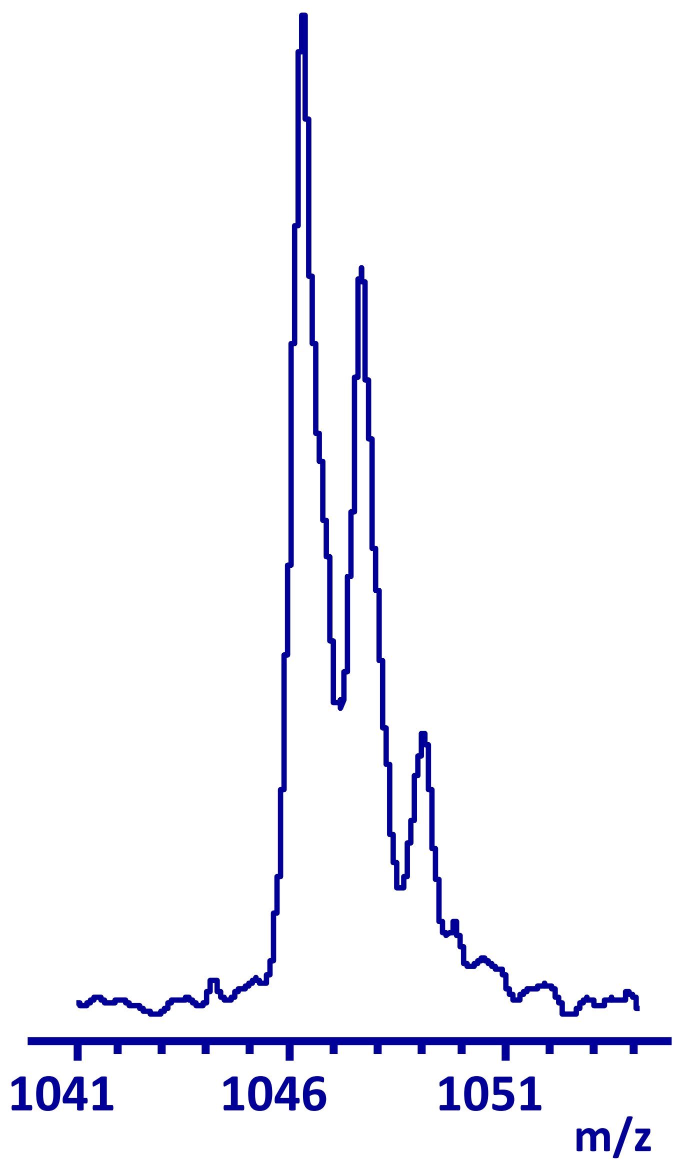
Pulsed ion extraction (PIE)

Effect on the Angio II MS spectrum

MALDI-TOF



MALDI-TOF,
+ PIE

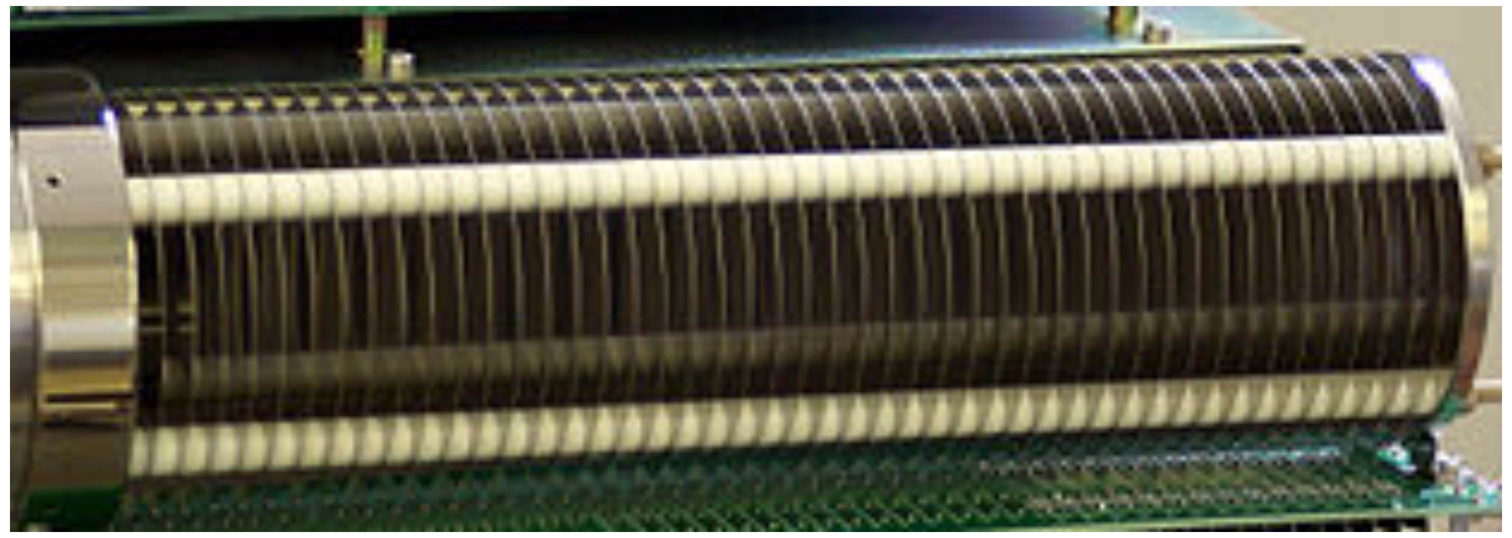


PIE compensates:
- **initial energy spread**
- **initial spatial spread**

Energy focusing

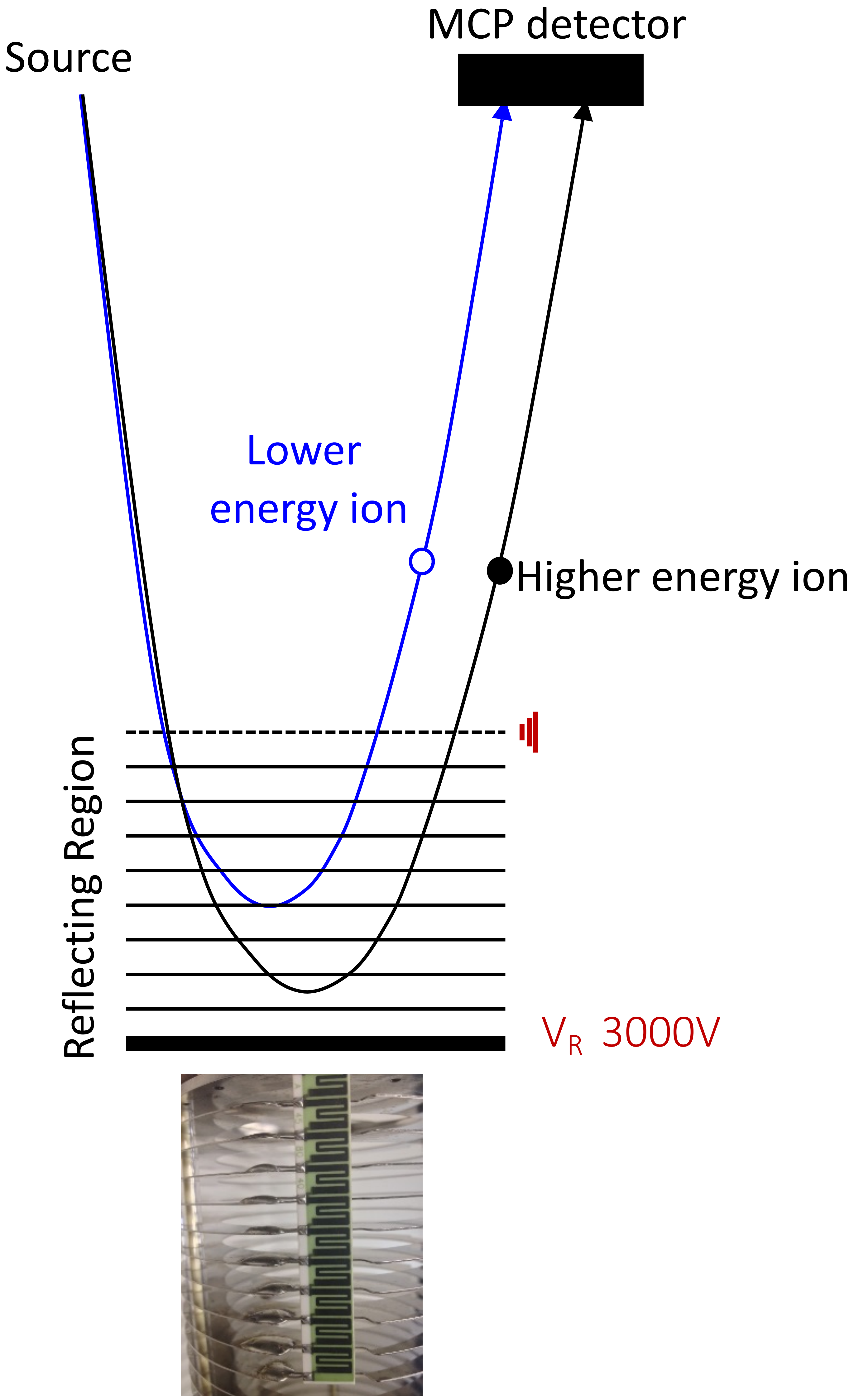
- The spread of initial kinetic energy is considered as the most significant parameter affecting resolution in MALDI
- Use of high acceleration voltage and PIE helps by minimizing significance of initial kinetic energy.
- How to improve kinetic energy distribution issue beyond the source ?

➡ **Ion Mirror or Reflectron**



Introduced by Mamyrin et al. in 1973

TOF: Reflectron



- Series of spaced metallic electrodes onto which a positive gradient of potential is applied
- The resulting electric field slows down the ions entering in the mirror: ions stop, reverse course and are reaccelerated
- Higher energy ion penetrates further into the field before reversing, yielding longer flight path
- The detector is positioned off-axis

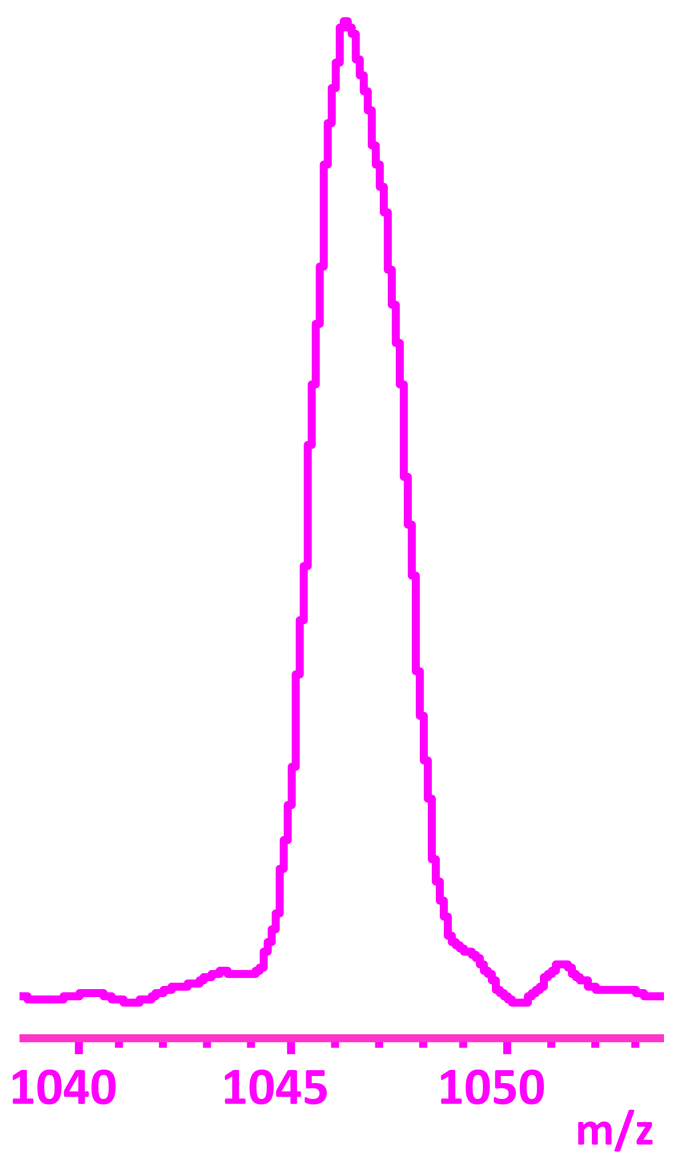
⬇

Ions of same *m/z* arrive at detector at the same time

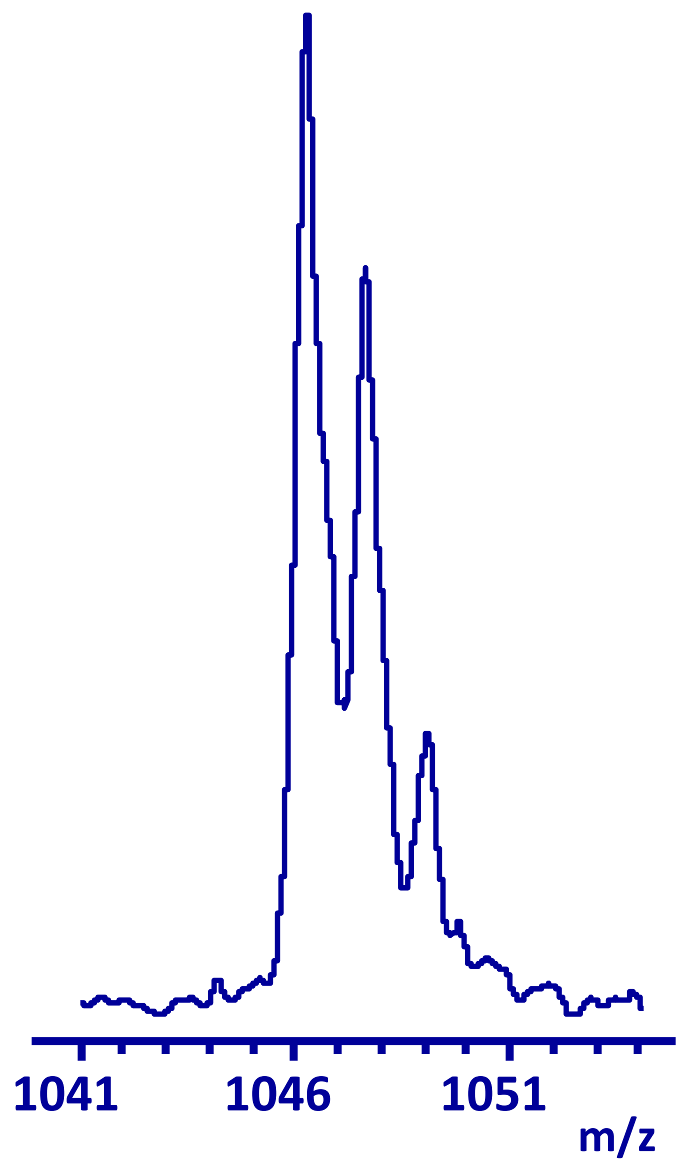
TOF: PIE and reflectron

Effect on the Angio II MS spectrum

MALDI-TOF,
linear

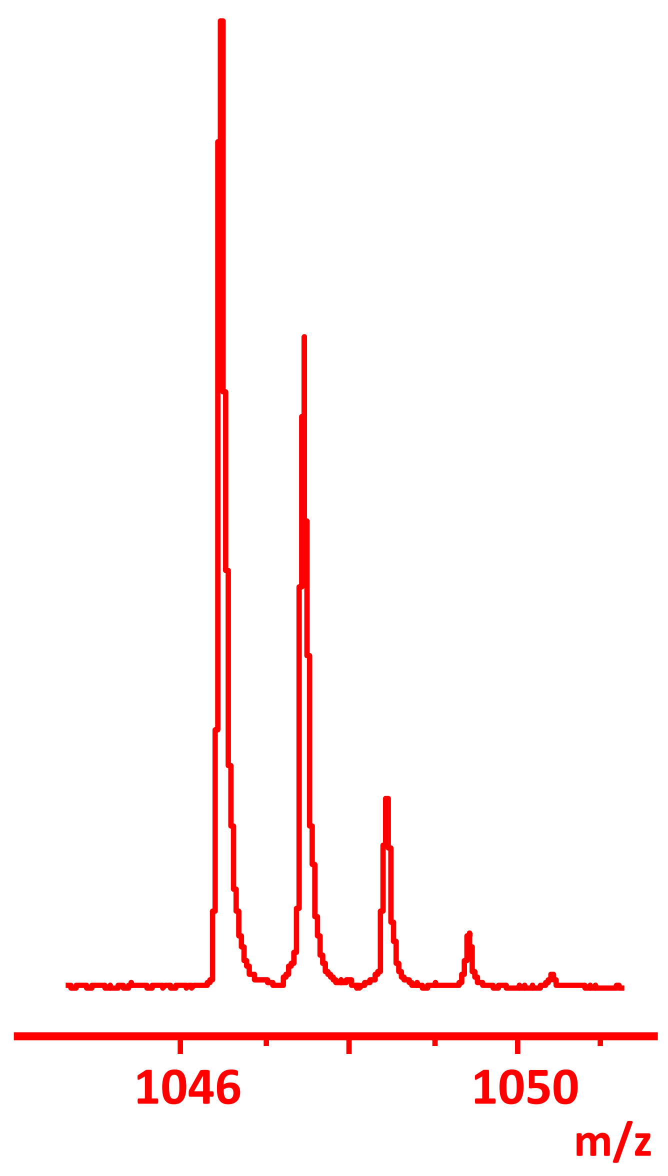


MALDI-TOF,
linear + PIE



PIE compensates
- initial energy spread
- initial spatial spread

MALDI-TOF,
reflectron + PIE



Reflector compensates
- remaining energy spread

TOF: PIE and reflectron

- Reflectron increases mass resolution (factor 2-5) at the expense of sensitivity

- Delayed Extraction (2-4X) + Reflectron (2-5x) yield a 4-20X increase in resolution

ESI-TOF: challenges

- Maintaining a high vacuum in the TOF with a continuous electrospray flow inlet is challenging

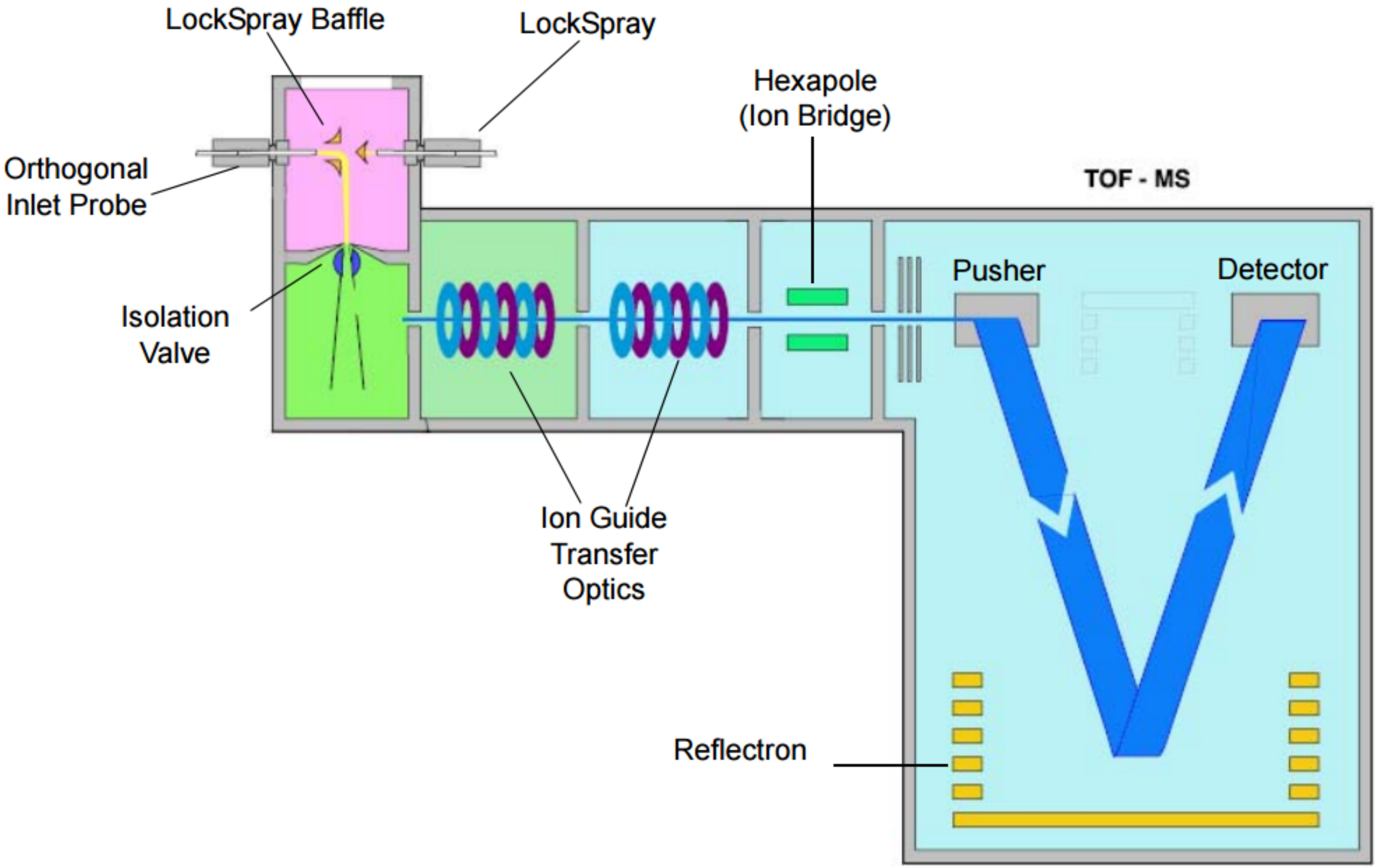
  - Spray off-axis (orthogonal, Z-spray sources)

- ESI is a <u>continuous</u> flow inlet. TOF is pulsed and needs a gated start for detection

Orthogonal Acceleration (OA)
ESI-oa-TOF

- The **pusher** generates high voltage orthogonal pulses to push out and accelerate ions

TOF Example (Waters)



V mode

Orthogonal extraction

- Initially, ESI continuously creates ions with broad range of Ec focused into X axis

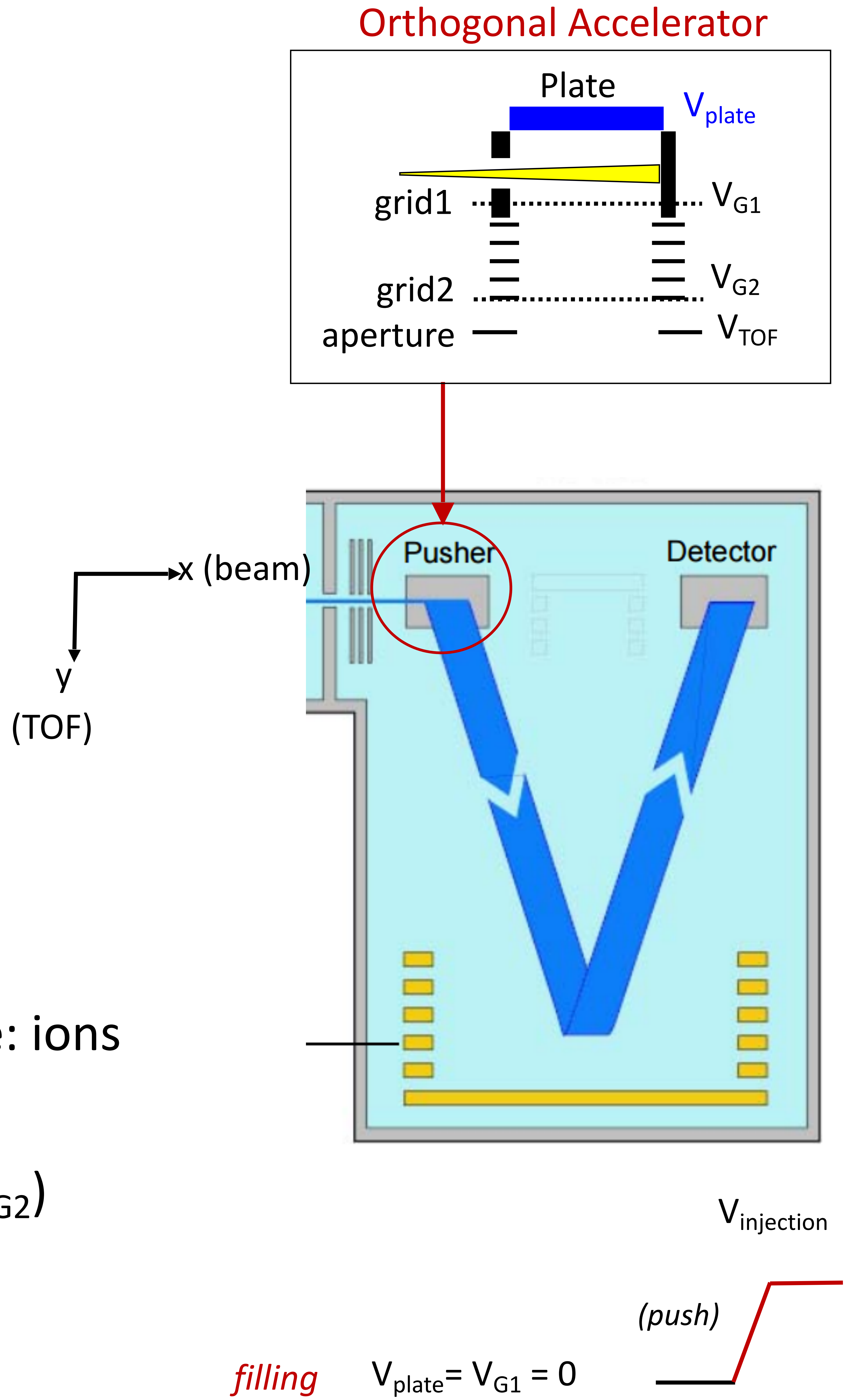
- TOF oriented at right-angle (Y-axis) to ESI

- TOF start gated by OA pulse (pusher):

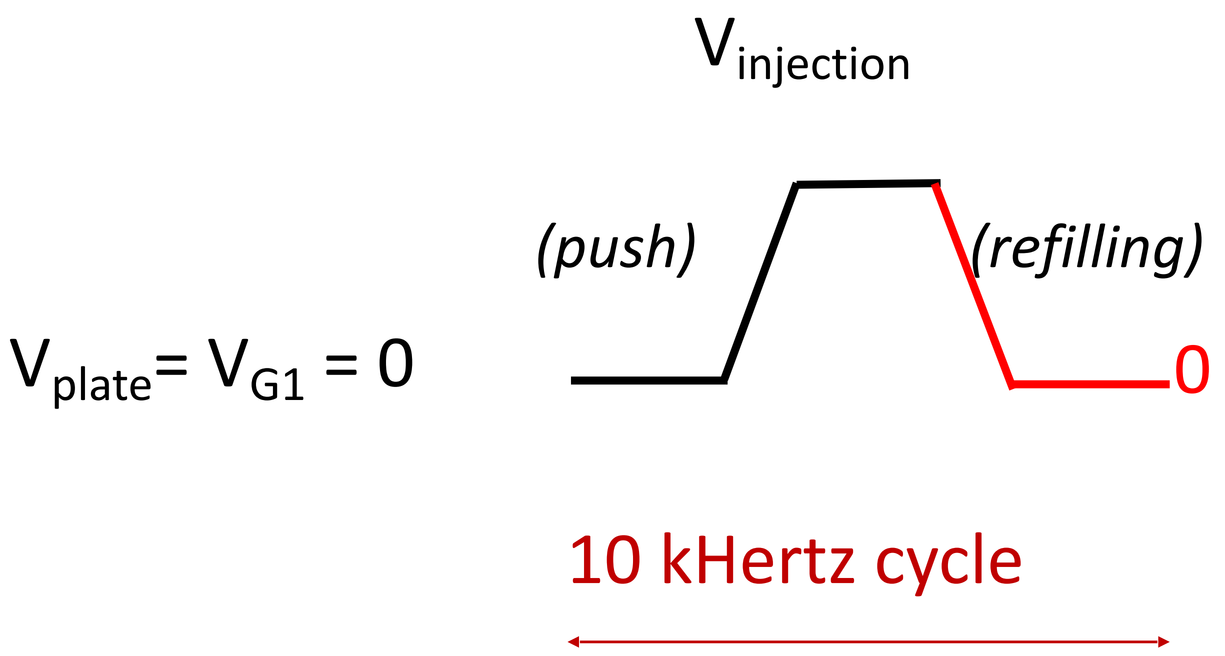
  - Initially (filling) $V_{plate} = V_{G1} = 0$ (ground)

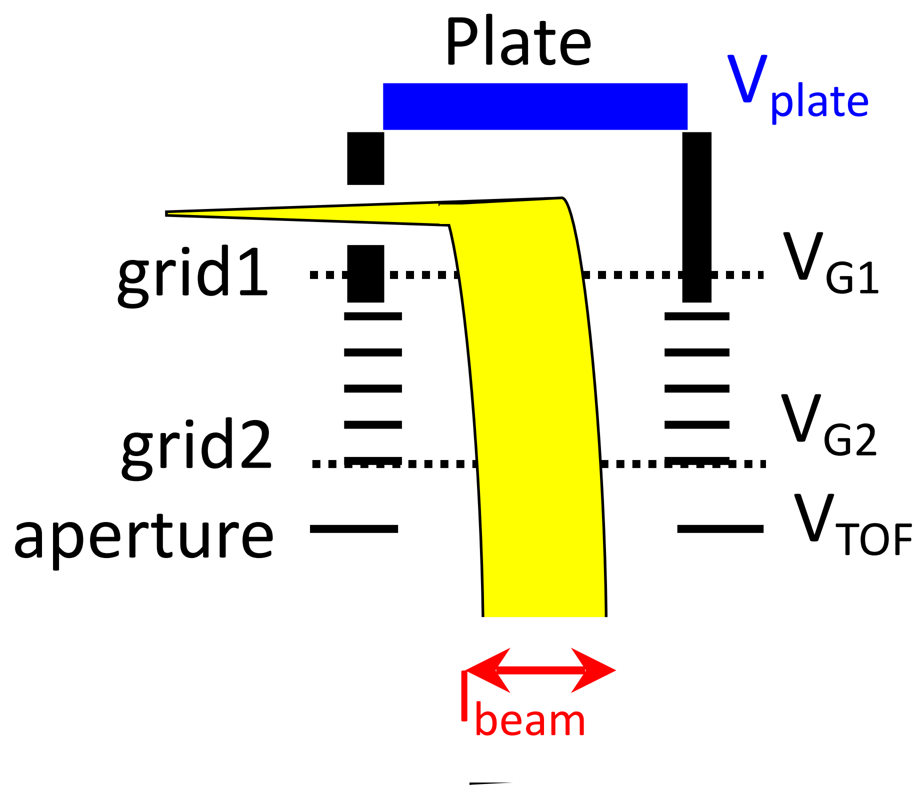
  - Then injection pulse V_{inj} is applied to the plate: ions are pushed by the resulting electric field

  - Ions are further accelerated towards grid 2 (V_{G2})



OA Firing Rate





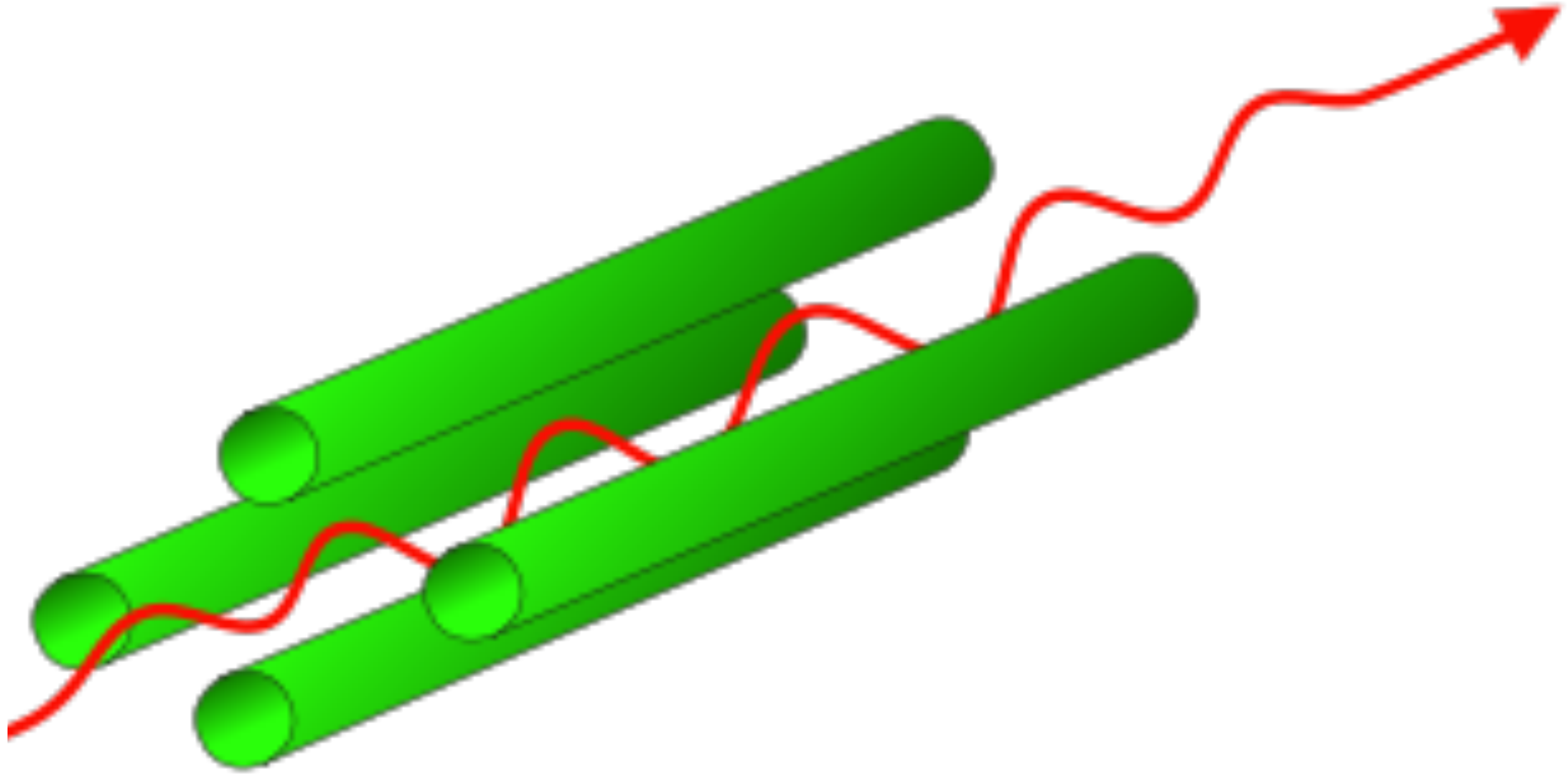
- When all ions have moved into the field-free region, V_{plate} is restored to 0 (refilling)
- OA is refilled during analysis, ready for next pulse
- Cycle time (duty cycle) of OA should not be faster than the longest flight time of higher *m/z* ions (typically 10 kHz = 10000 cycle/s ⇒ 100 µs/cycle)
- The detector diameter should be wide enough (several cm) to enable ion detection anywhere from the whole path (l_{beam}) to hit its surface

Time-of-Flight Mass Spectrometer (TOF MS)

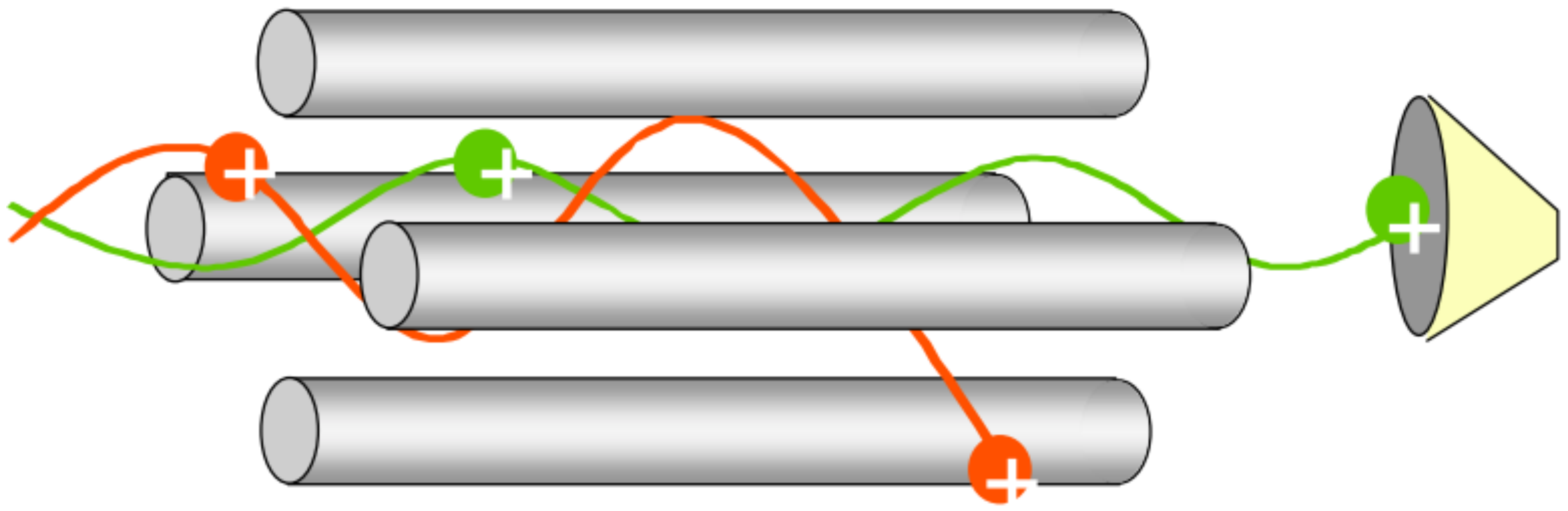
Advantages

- Good mass accuracy: 5-10 ppm
- High mass resolution: Up to 40’000
- High mass range: $> 10^5$ Da
- Acceptable linearity
- Very good reproducibility
- Very fast acquisition time

Quadrupole mass spectrometer



Linear quadrupole mass analyzer



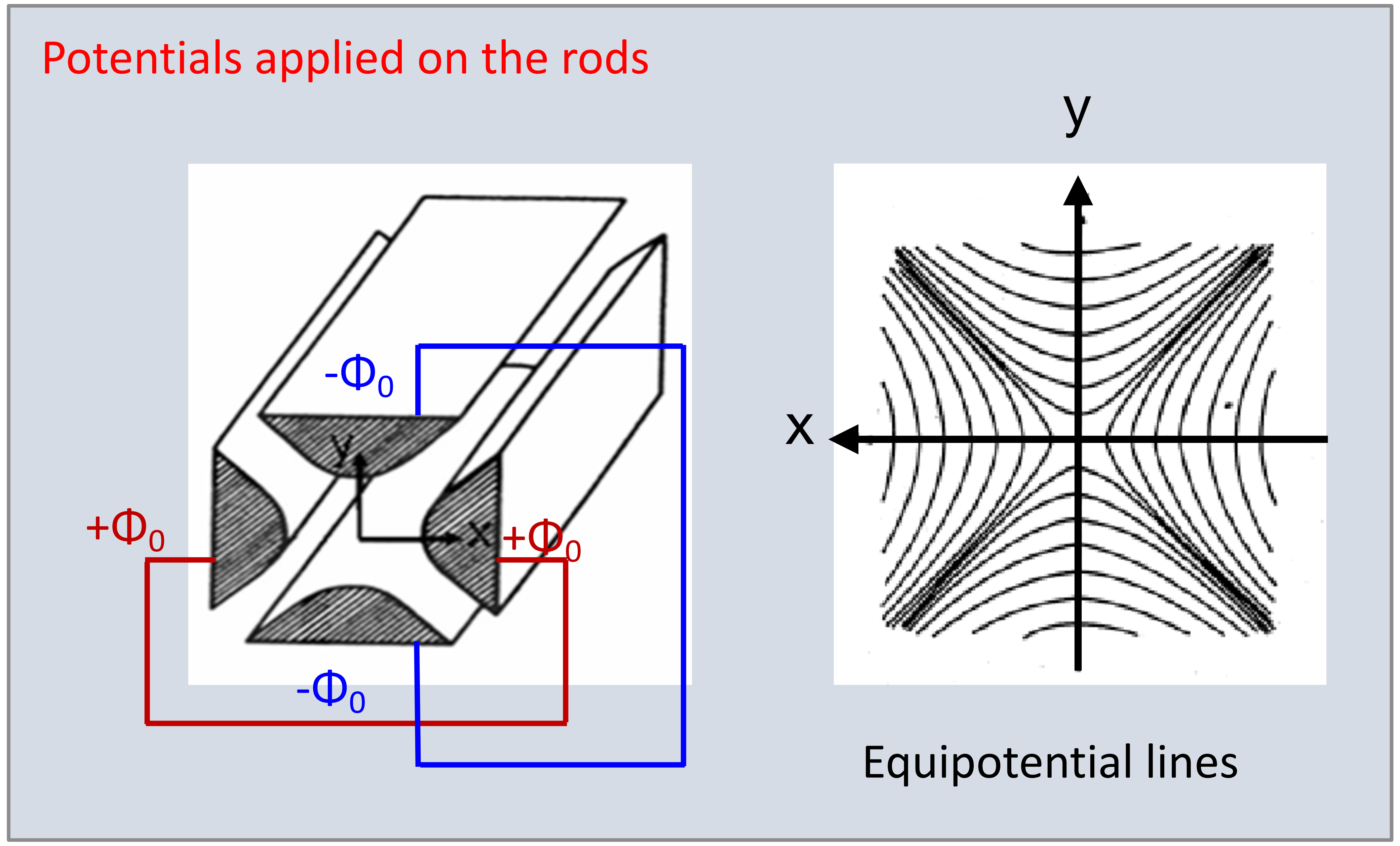
🟩 Ions transmitted: stable trajectory

🟥 Ions ejected: unstable trajectory

Rods can be cylindric or hyperbolic

- Each pair of rods has a DC (U) + AC($V_0 \cos\omega t$) RF voltage applied
- For a given DC and AC amplitude, only ions with a give m/z (or m/z range) have stable oscillations and are transmitted
- By continuously varying the applied voltage, the operator selects an ion with a particular *m/z* or scans for a range of *m/z*
- *Ions with unstable trajectories collide with the rods*
- Ion trajectories are modeled by Mathieu differential equations

Linear quadrupole mass analyzer



Potentials applied on the rods

Equipotential lines

U: Direct potential (DC)
V: RF amplitude (AC)

Typically
U: 500-2000V
V: 0-3000 V

$\omega = 2\pi f$ where f is the frequency of the RF field (typically 1 MHz)

X-rods $$\Phi_0 = +(U - V\cos\omega t)$$

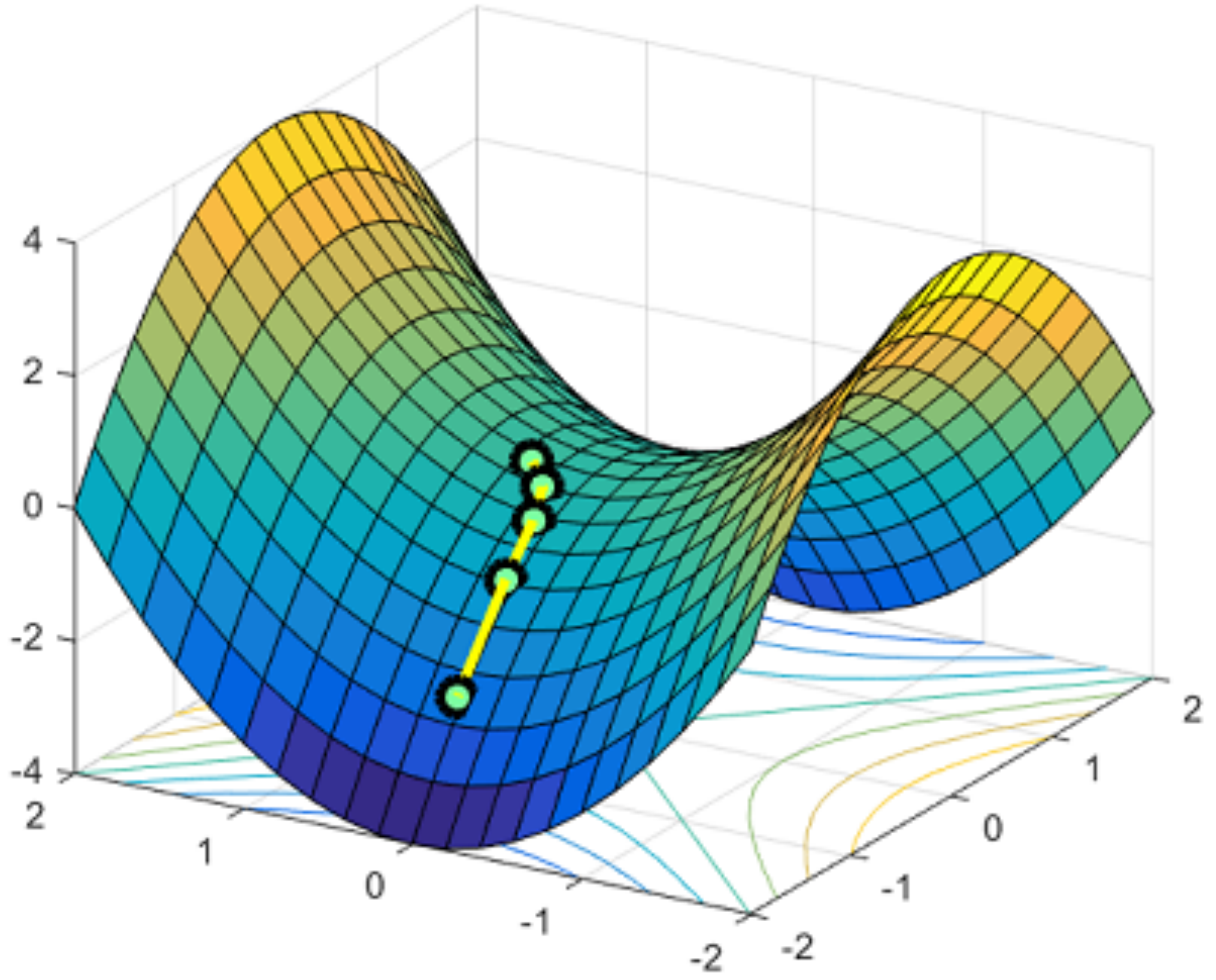
Y-rods $$-\Phi_0 = -(U - V\cos\omega t)$$

(180° out of phase)

Quadrupoles are operated at fixed frequency but variable U & V

Qualitative picture of ion confinement

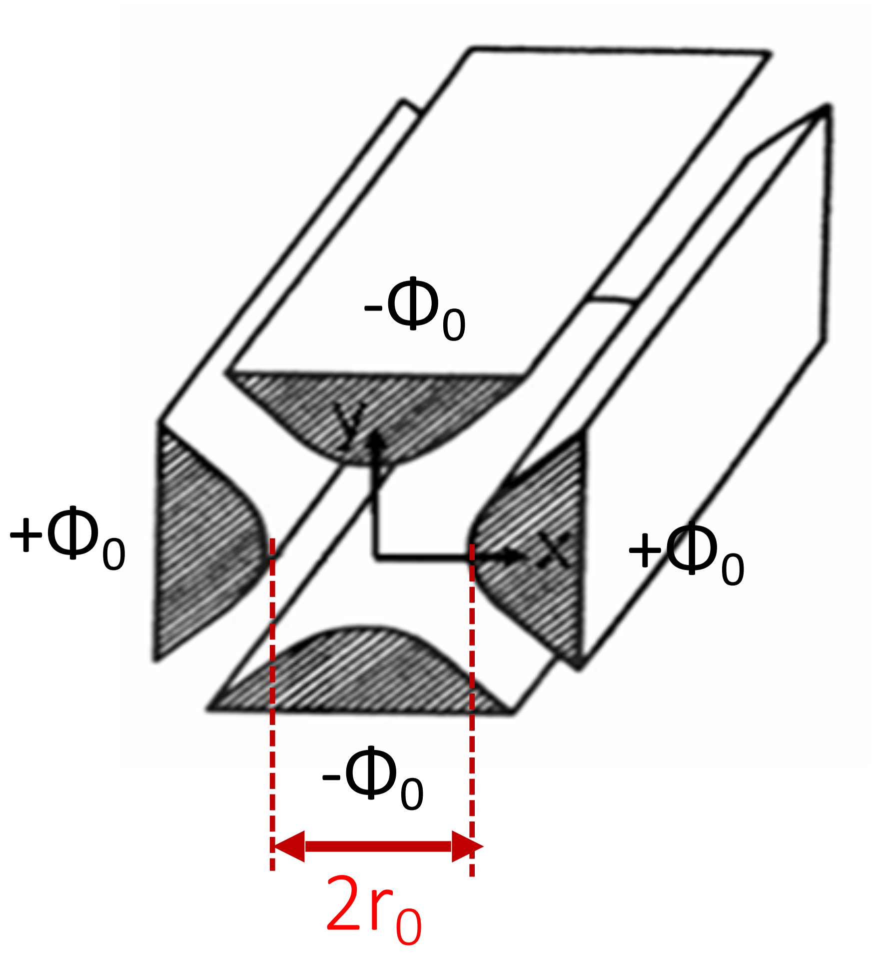
The potential energy diagram of a quadrupole showing the saddle point in the electric field.



Video demonstration

Equation of ion motion

The electric potential inside the quadrupole is given by: $$\Phi(x,y)=\frac{\Phi_0(x^2-y^2)}{r_0^2}$$



Equation of ion motion

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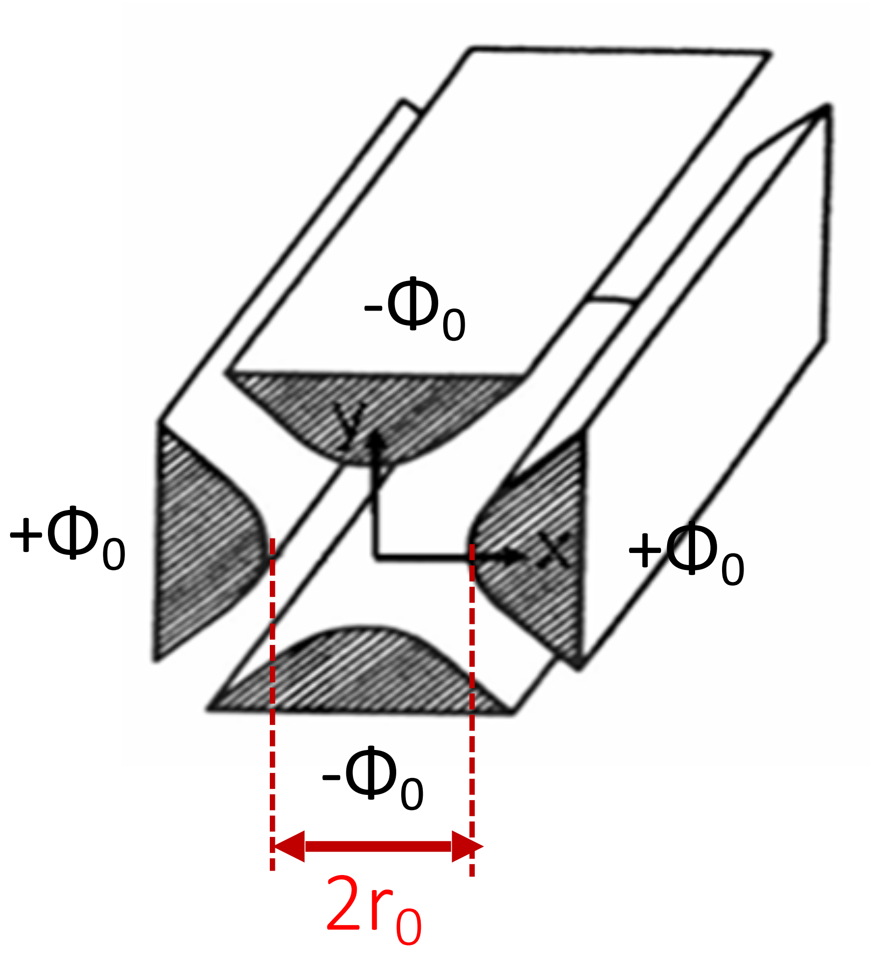


The force on the ion is given by the gradient of the potential:

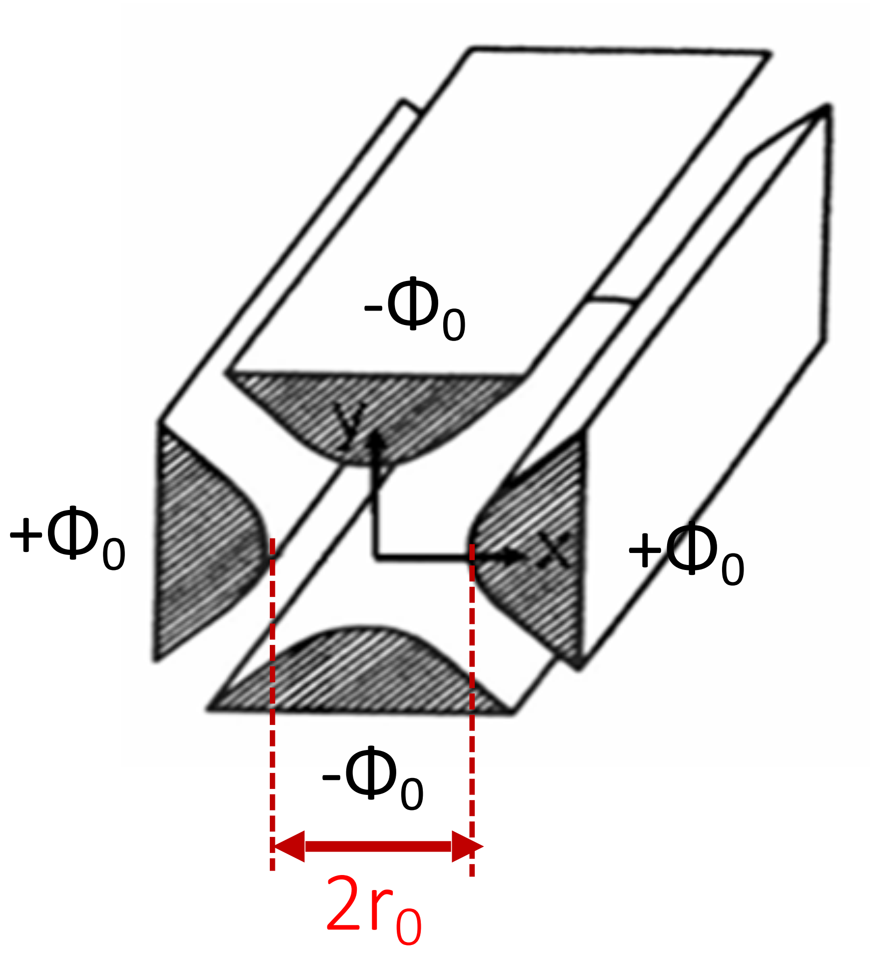
$$F_x = m\frac{d^2x}{dt^2} = -ze\frac{\partial\Phi}{\partial x}$$

$$F_y = m\frac{d^2y}{dt^2} = -ze\frac{\partial\Phi}{\partial y}$$

$$F_z = 0$$

Equation of ion motion

The electric potential inside the quadrupole is given by: $\Phi(x,y) = \frac{\Phi_0 (x^2 - y^2)}{r_0^2}$



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$$F_y = m\frac{d^2y}{dt^2} = -ze\frac{\partial\Phi}{\partial y}$$

$$F_z = 0$$

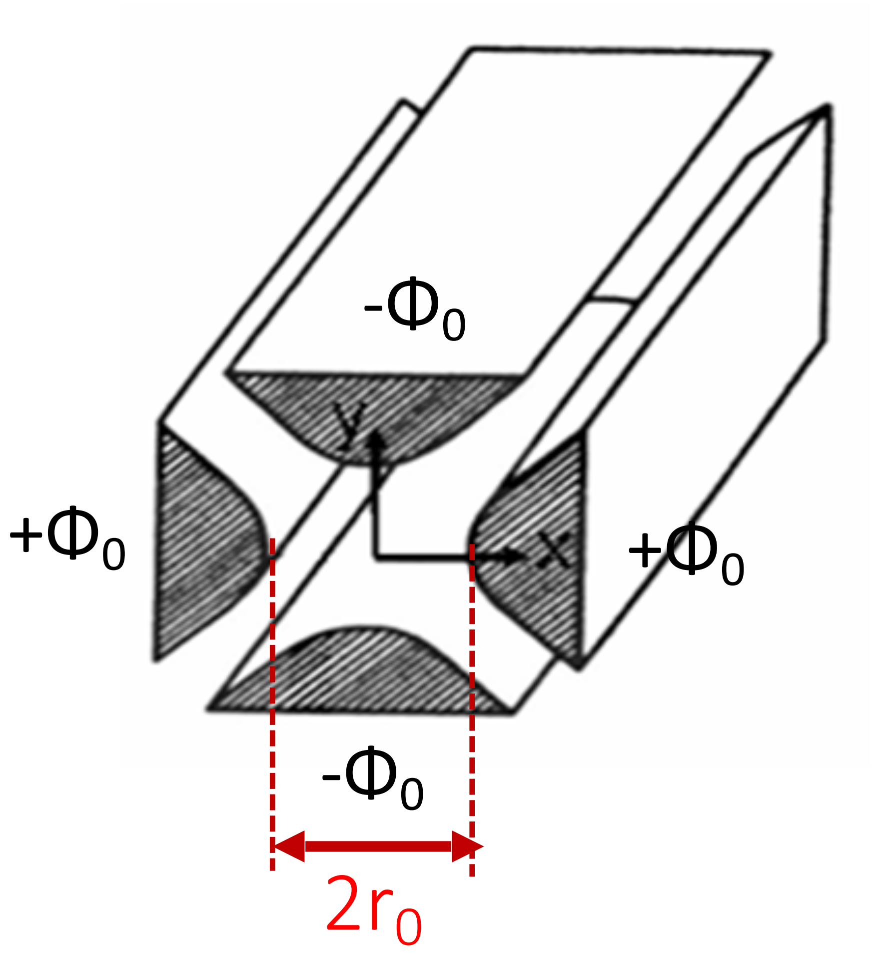
which gives rise to:

$$\frac{d^2x}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 x$$

$$\frac{d^2y}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 y$$

$$\frac{d^2z}{dt^2} = 0$$

Equation of ion motion



$$\frac{d^2x}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 x$$

$$\frac{d^2y}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 y$$

$$\frac{d^2z}{dt^2} = 0$$

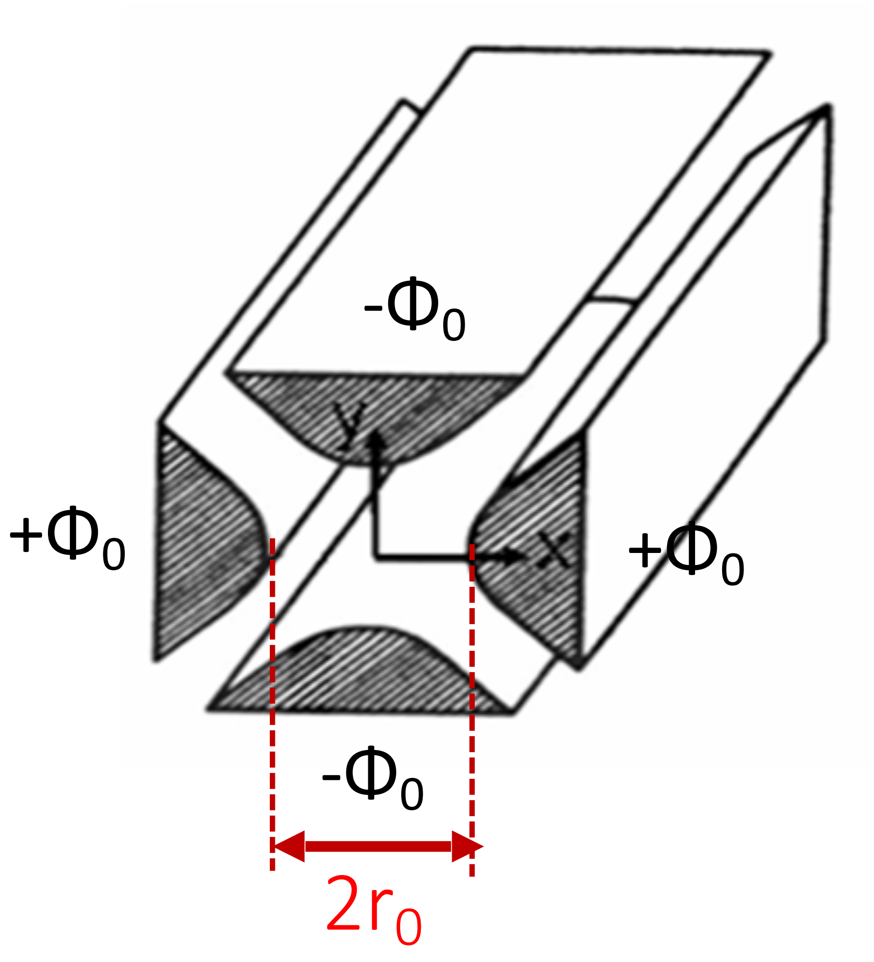
Equation of ion motion

If we now put in the time varying potential:

$$\Phi_0 = +\left(U - V\cos\omega t\right)$$ X-rods

$$-\Phi_0 = -\left(U - V\cos\omega t\right)$$ Y-rods

(180° out of phase)



$$\frac{d^2x}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 x$$

$$\frac{d^2y}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 y$$

$$\frac{d^2z}{dt^2} = 0$$

Equation of ion motion

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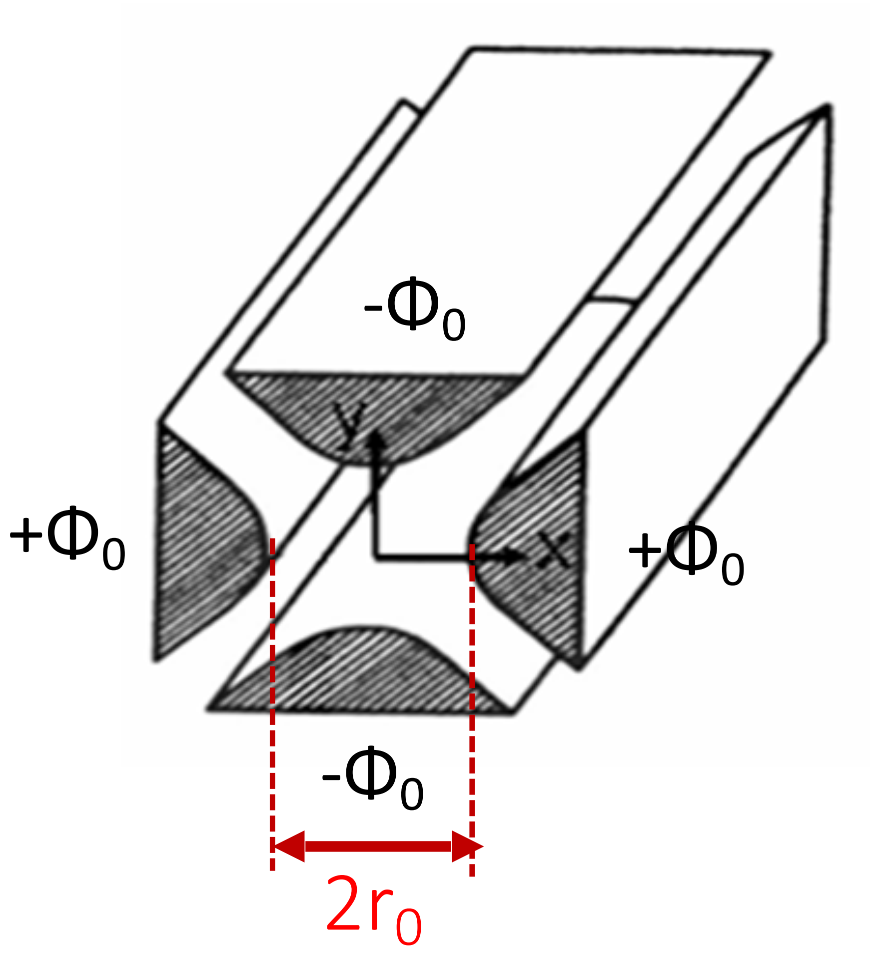


$$\frac{d^2x}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 x$$

$$\frac{d^2y}{dt^2} = -\frac{2ze}{mr_0^2}\Phi_0 y$$

$$\frac{d^2z}{dt^2} = 0$$

$$\boxed{\begin{aligned}\frac{d^2x}{dt^2} + \frac{2ze}{mr_0^2}(U - V\cos\omega t)x = 0\\ \frac{d^2y}{dt^2} - \frac{2ze}{mr_0^2}(U - V\cos\omega t)y = 0\end{aligned}}$$

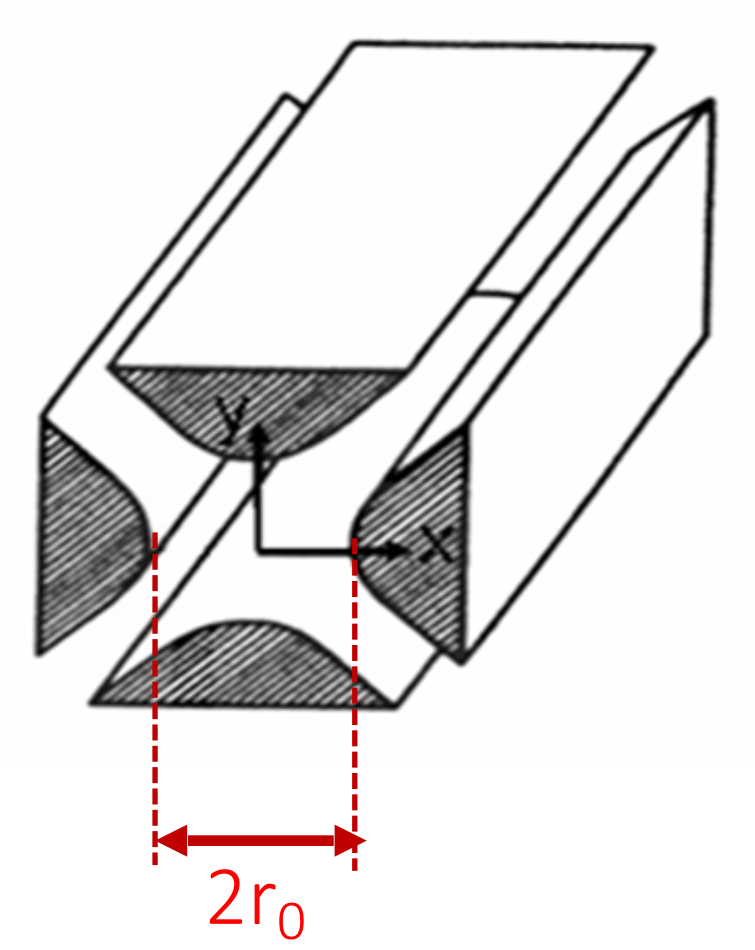
Mathieu Equations

Trajectories will be stable if x, y < r_0

Mathieu Equations

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

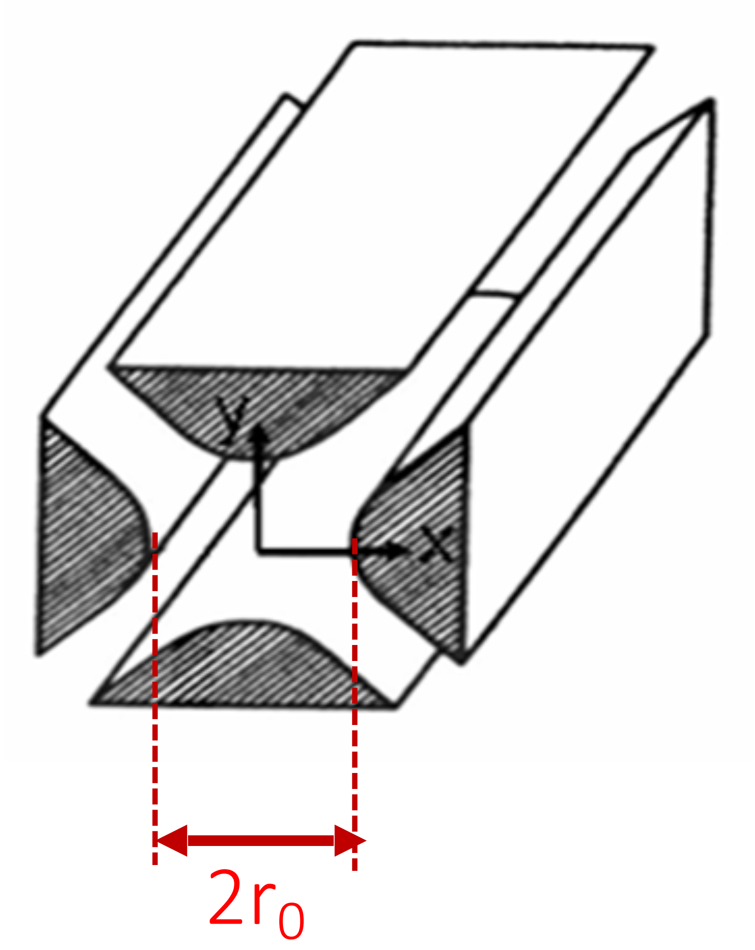
$$\frac{d^2y}{dt^2} - \frac{2ze}{mr_0^2}(U - V\cos\omega t)y = 0$$



Mathieu Equations

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

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



Let u = x, y

$$a_u=a_x=-a_y=\frac{8zeU}{m\omega^2r_0^2}$$

proportional to the DC voltage U

$$q_u=q_x=-q_y=\frac{4zeV}{m\omega^2r_0^2}$$

proportional to the AC voltage V

Mathieu Equations

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

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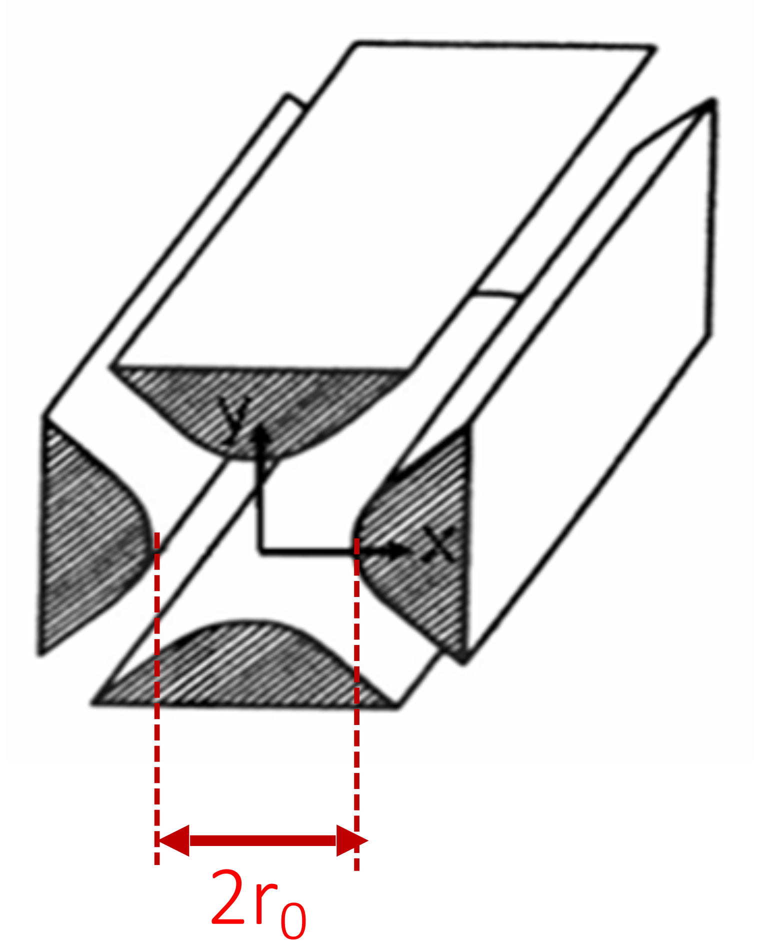
proportional to the AC voltage V



The ion trajectory will be stable if the values of x and y never reach r_0 (thus never hits the rods)

$$x < r_0$$
$$y < r_0$$

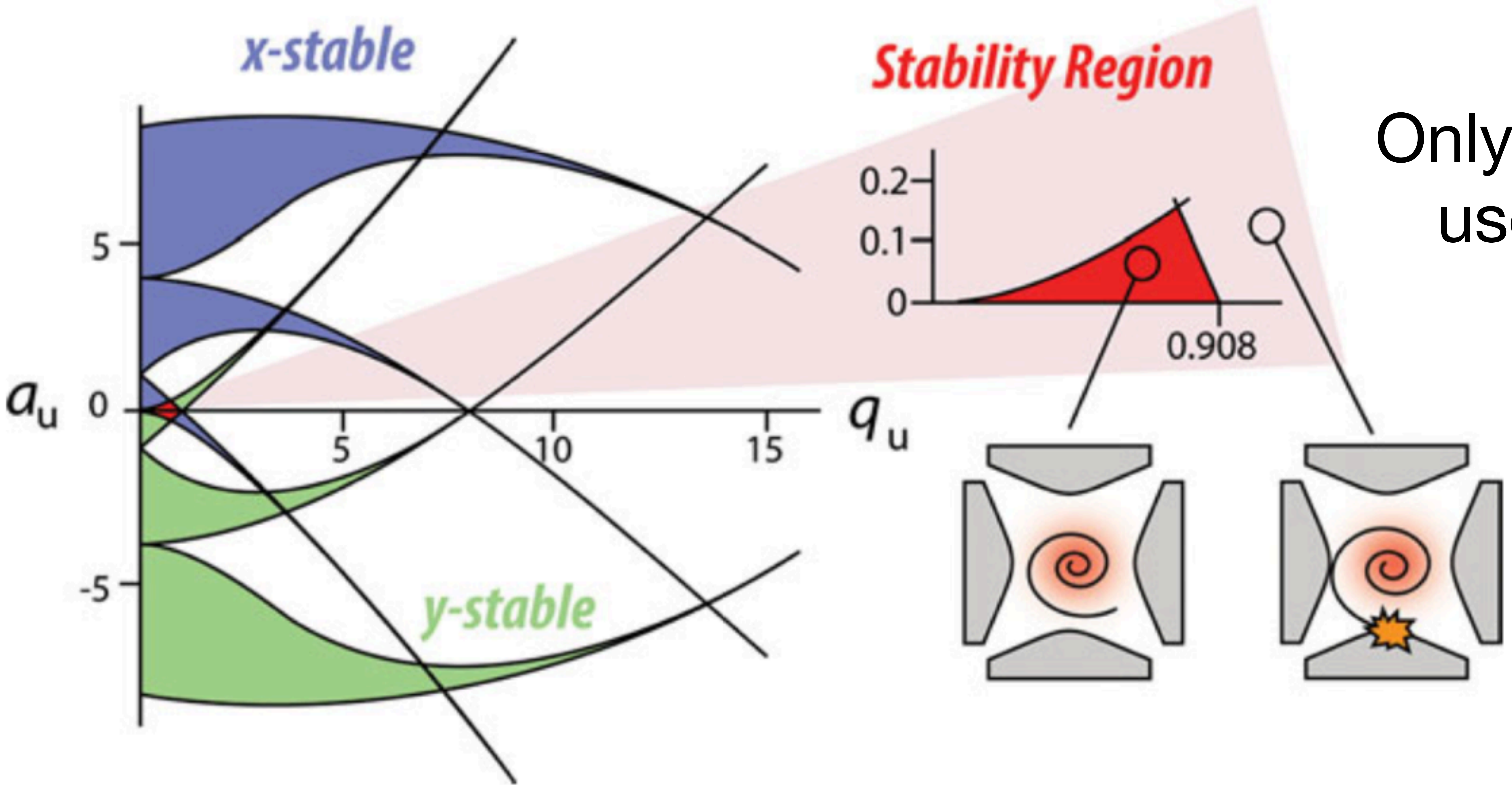
Define stable and unstable regions

Stability Diagram

Want values of U and V
such that
x and y $< r_0$

$$a_u = a_x = -a_y = \frac{8zeU}{m\omega^2 r_0^2}$$

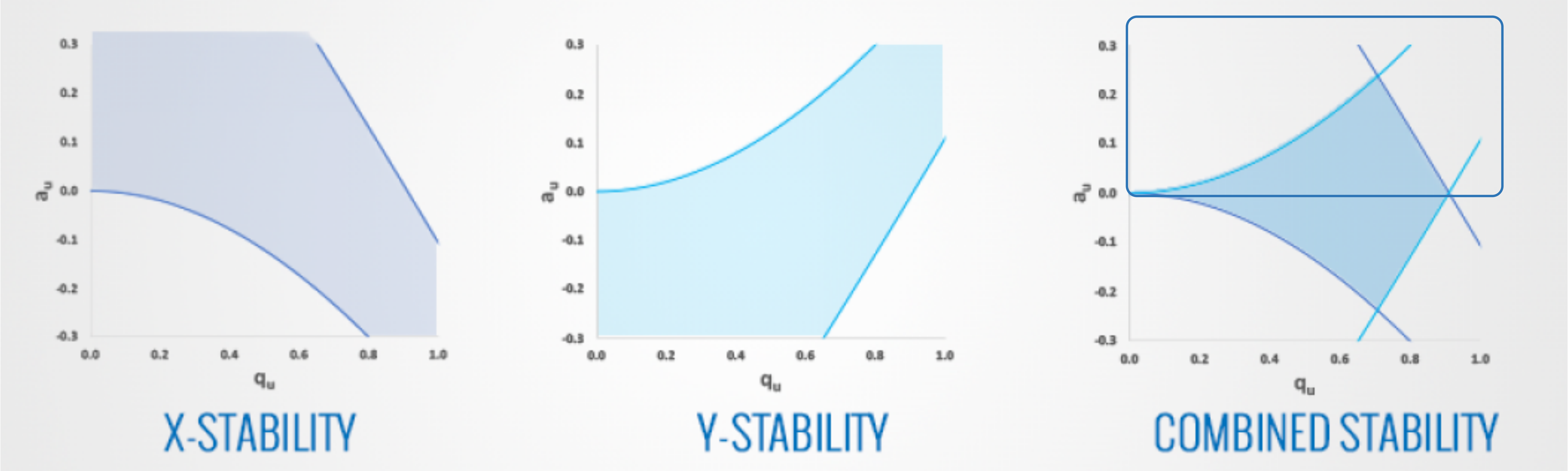
$$q_u = q_x = -q_y = \frac{4zeV}{m\omega^2 r_0^2}$$



Only this area is used in MS!

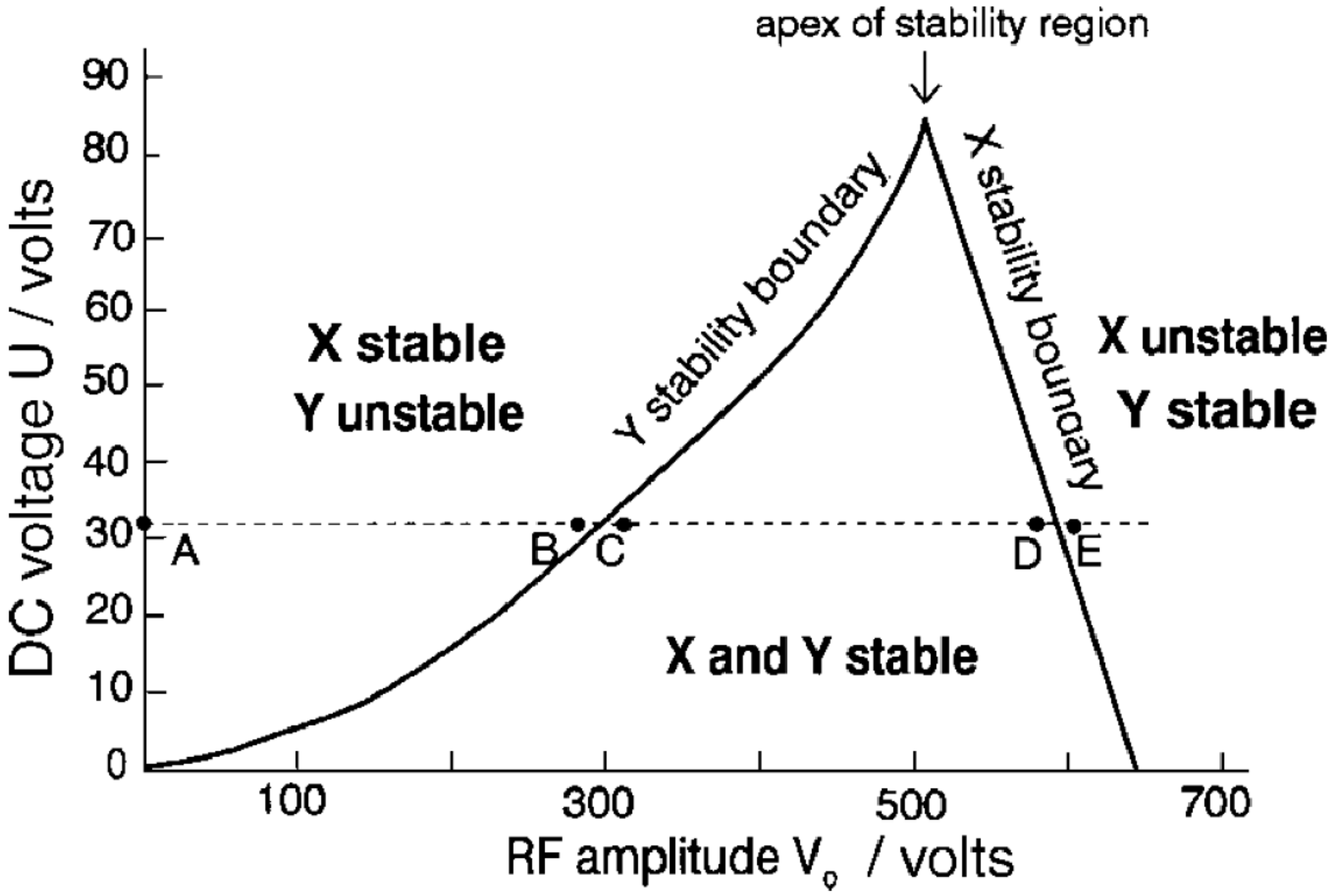
The overlay regions are where the ions have stable trajectories along both the x and y axes simultaneously.

Quadrupole stability



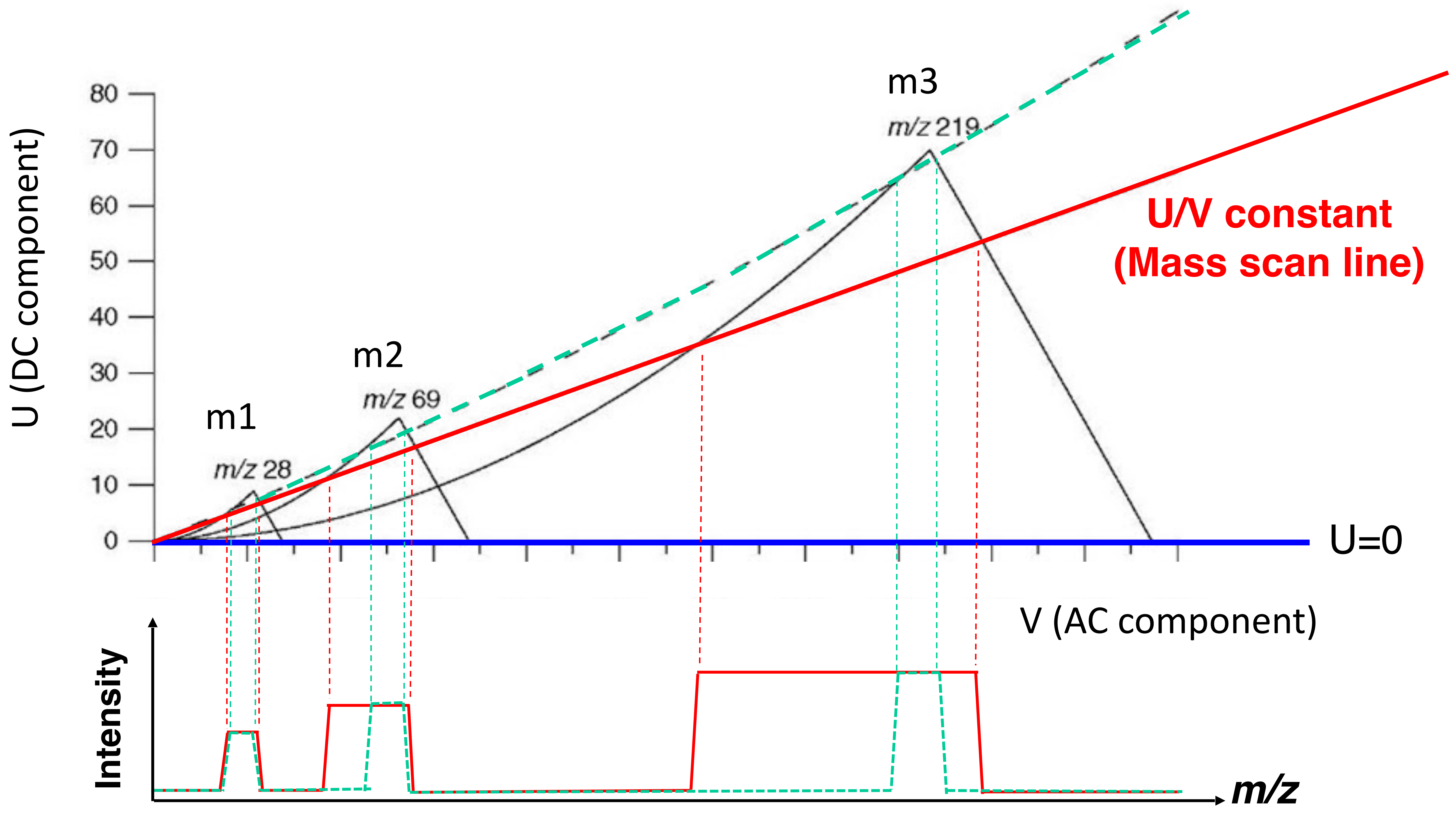
- Certain combinations of a and q (U and V at a fixed ω) provide stable trajectories
- To pass through the entire quadrupole length, ions must be stable in both dimensions
- U>0 ⟶ upper part of the diagram

Stability diagram in a quadrupole



In practice, quadrupoles are operated at fixed frequency but variable U and V.

Stability diagram in a quadrupole



a/q = 2U/V

- Frequency is fixed; U/V ratio is kept constant
- Scanning a U/V ratio line allows the successive detection of masses m1, m2, m3 when reaching stability area
- The higher the slope of U/V is, the better is the resolution
- If U=0, all the masses above m1 will have a stable trajectory

Clicker question

To operate a quadrupole in a scanning mode, where individual m/z values are transmitted one after the other (e.g., m/z = 100; 101; 102 …).

A. U is held constant, while V is scanned
B. V is held constant, while U is scanned
C. U and V are held constant, while ω is scanned
D. U and V are both changed
E. A or B

Clicker question

To operate a quadrupole in a scanning mode, where individual m/z values are transmitted one after the other (e.g., m/z = 100; 101; 102 …).

Clicker question

If a quadrupole is operated with a DC potential of 0 volts, what will be transmitted when the AC potential is scanned:

A. No ions will be transmitted
B. All ions will be transmitted (i.e., all masses)
C. Only the lightest masses will be transmitted.
D. Only the heaviest masses will be transmitted.

Clicker question

If a quadrupole is operated with a DC potential of 0 volts, what will be transmitted when the AC potential is scanned:

Clicker question

The mass resolution in a linear quadrupole:

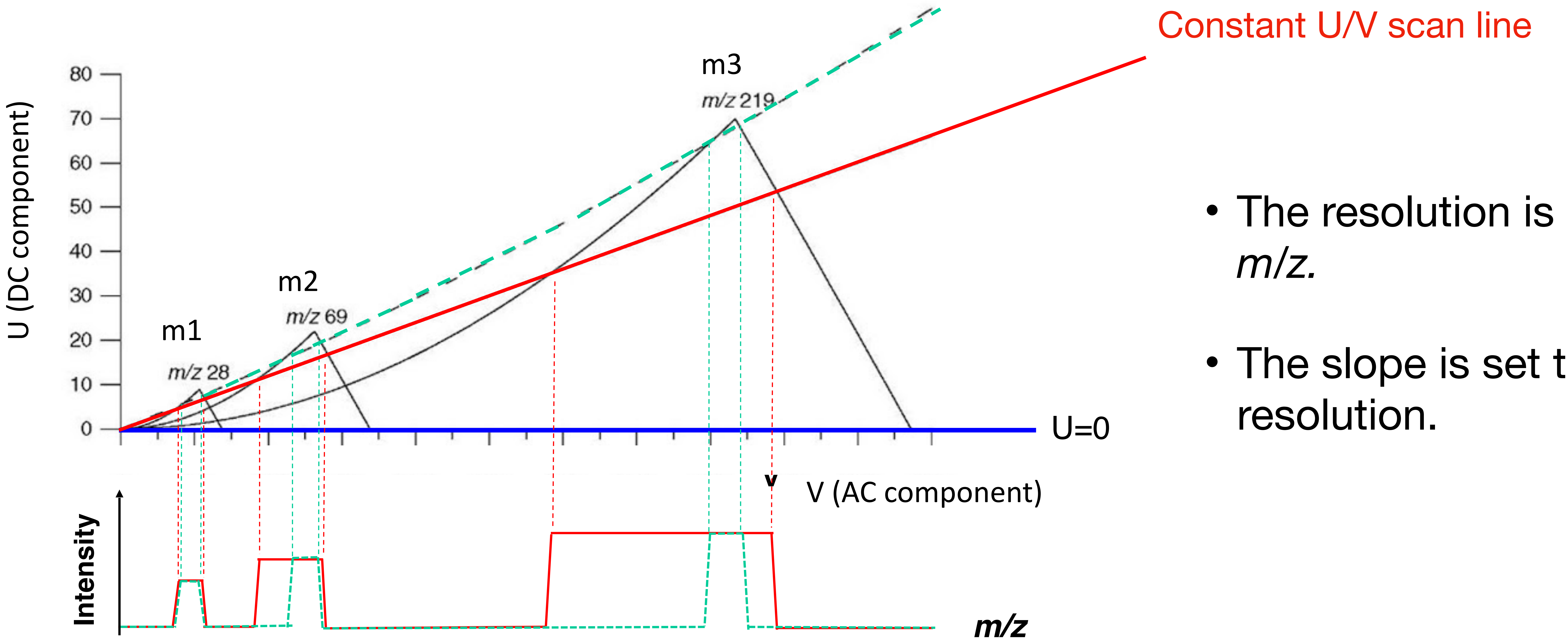
A. Increases with increasing mass
B. Decreases with increasing mass
C. Is independent of mass
D. Can increase or decrease depending upon the slope U/V

Clicker question

The mass resolution in a linear quadrupole:

Quadrupole resolution

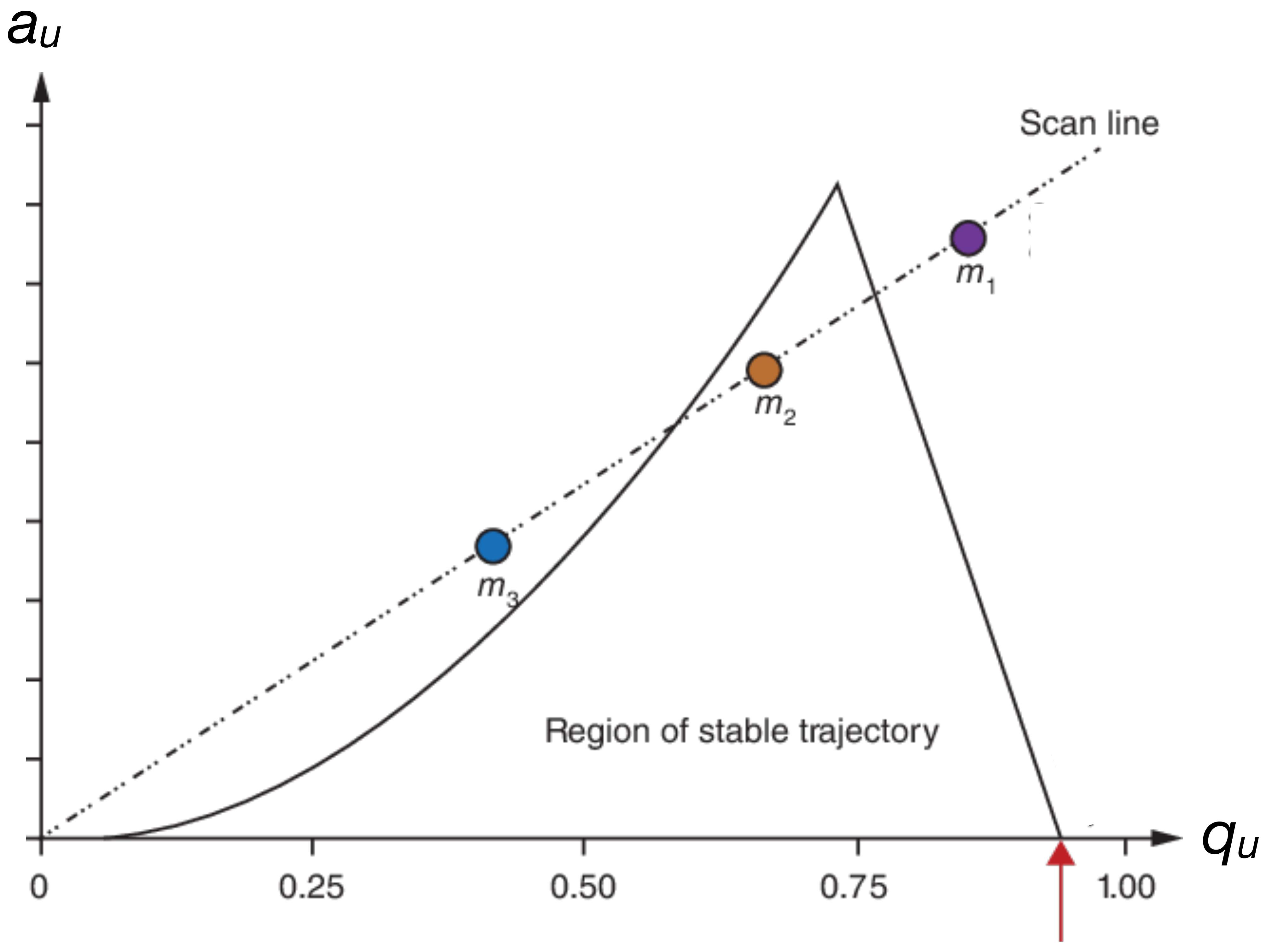
The ion pass range is determined by the intersection of the constant U/V scan line inside the stability region



- The resolution is not uniform with *m/z.*
- The slope is set to get the best resolution.

Clicker question

Given the quadrupole stability diagram below, indicate which statement is true.



q_u=0.908

stability limit

$$a_u = a_x = -a_y = \frac{8zeU}{m\omega^2 r_0^2}$$

$$q_u = q_x = -q_y = \frac{4zeV}{m\omega^2 r_0^2}$$

A. m_1 and m_3 will be unstable in both x and y directions

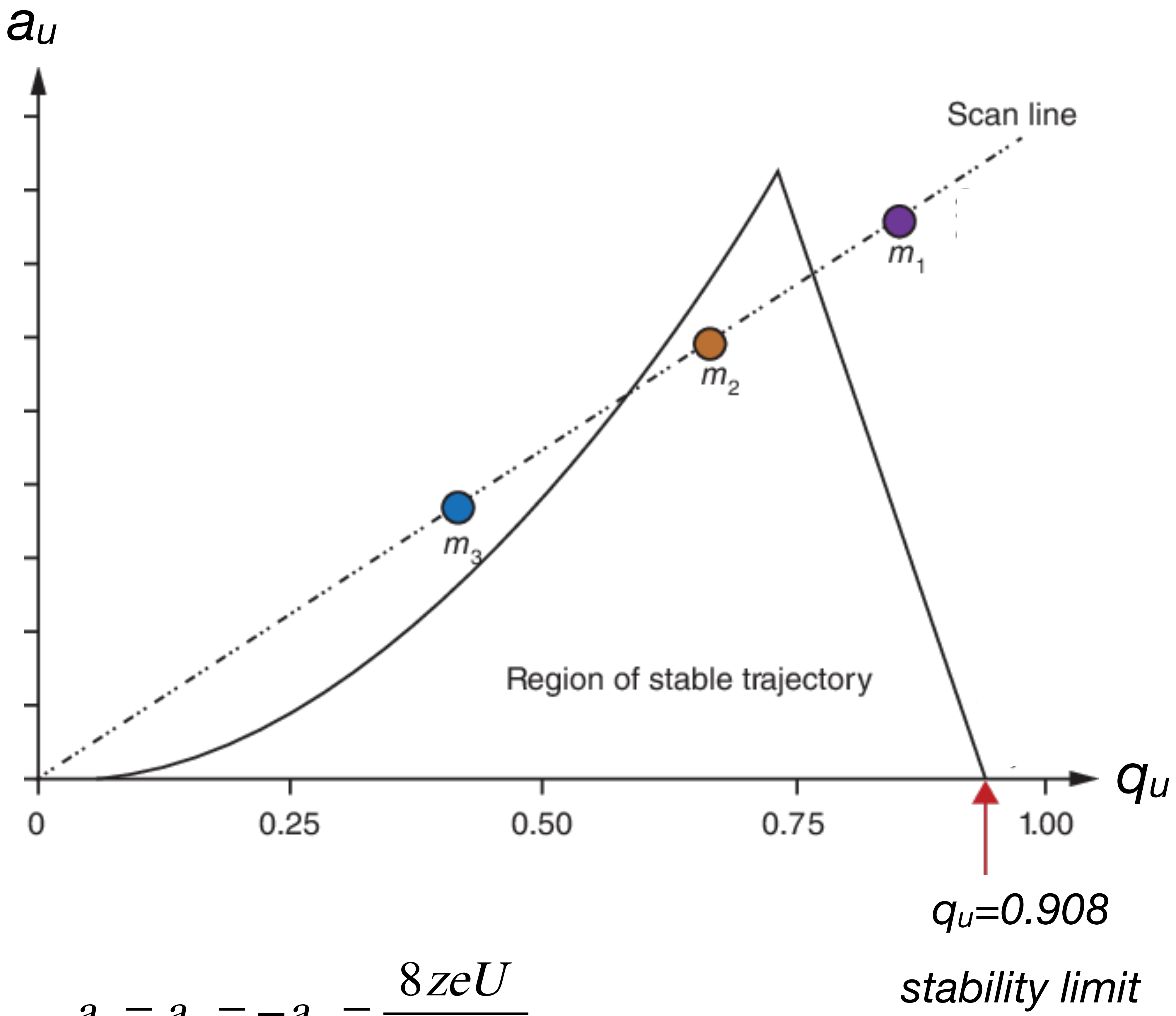
B. m_2 is less than m_3

C. m_1 is greater than m_2

D. Higher frequencies are needed for higher mass ions to have stable trajectories

Clicker question

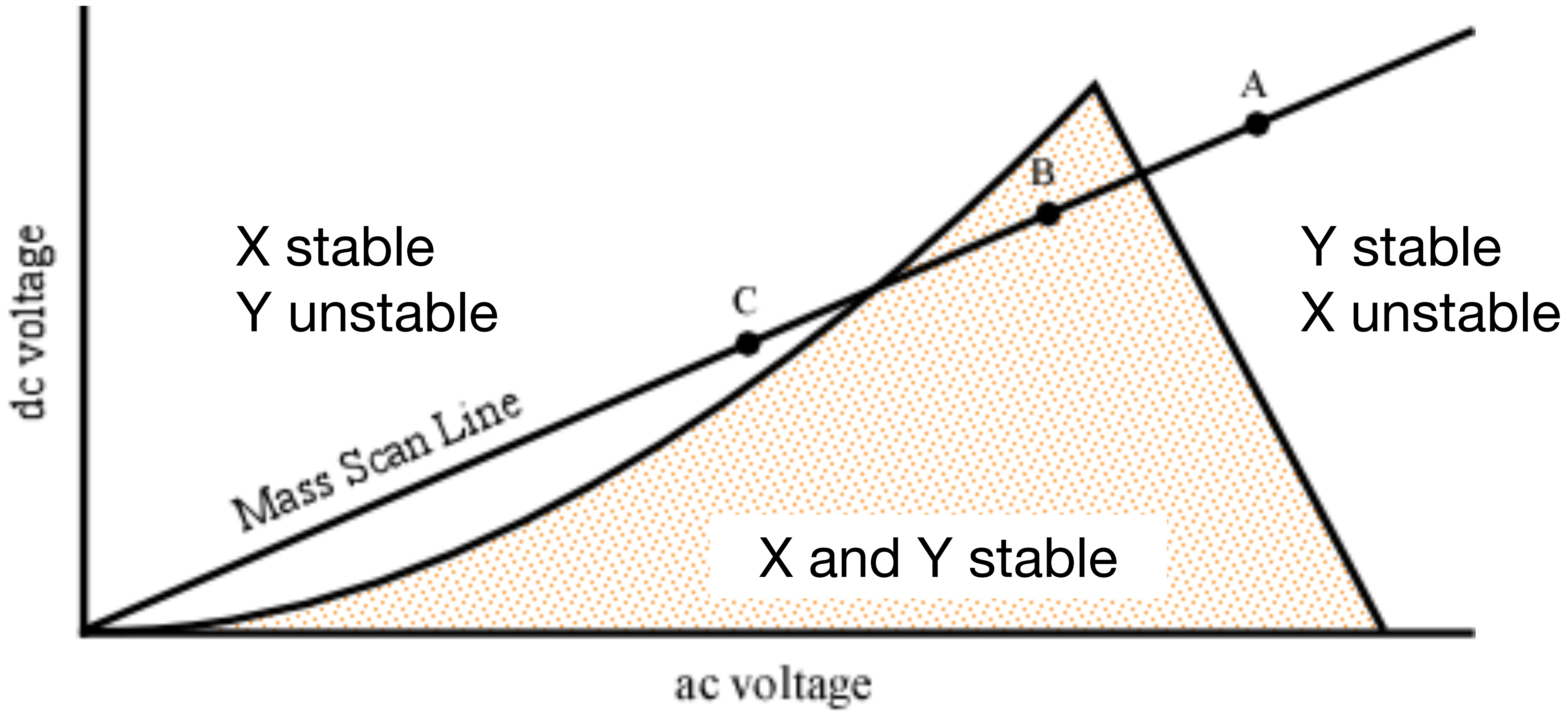
Given the quadrupole stability diagram below, indicate which statement is true.

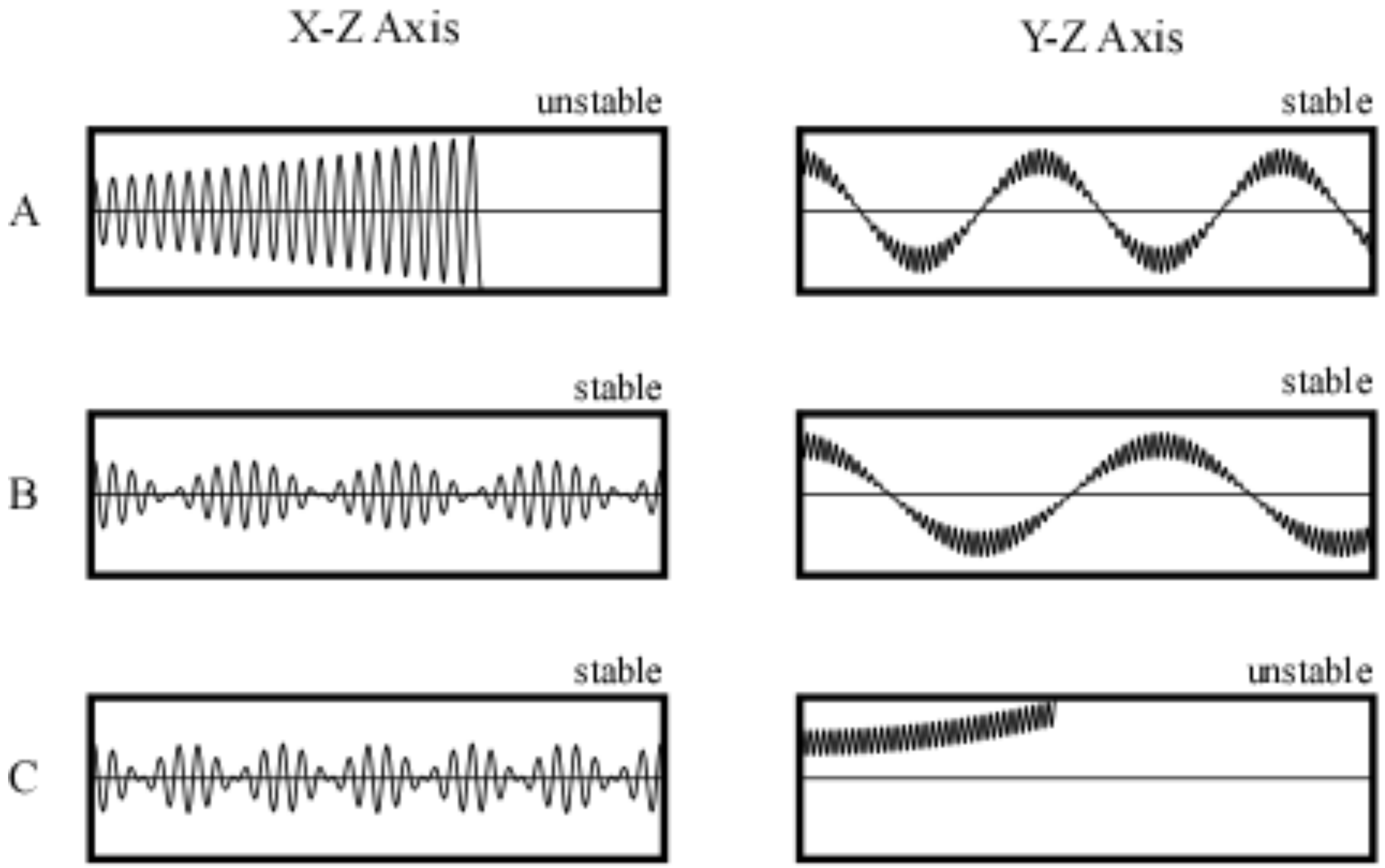


$$a_u = a_x = -a_y = \frac{8zeU}{m\omega^2 r_0^2}$$

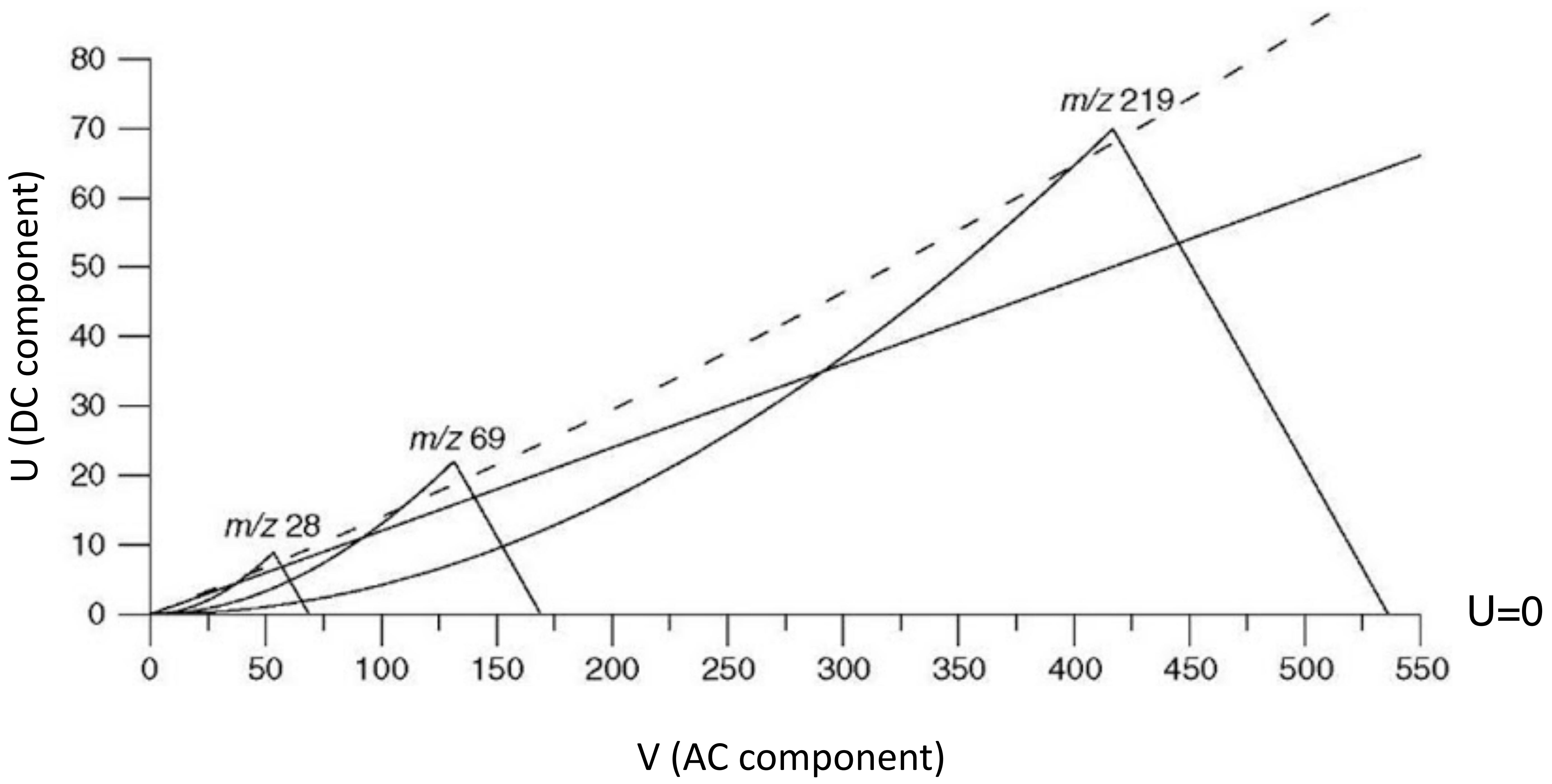
$$q_u = q_x = -q_y = \frac{4zeV}{m\omega^2 r_0^2}$$

Ion trajectories in a quadrupole





Digression: RF only multipoles



- If U=0, there is only RF potential applied
- In this case, all masses are transmitted
- RF only devices like this are used for guiding ions

Linear quadrupole MS

Advantages

- Small and lightweight: ~20 cm long
- Inexpensive
- Simple to operate
- Low accelerating voltage can accommodate high source pressures

Disadvantages

- Limited mass resolution and mass range
- Contamination of rods can degrade resolution and sensitivity