Development of a Miniaturized Poschenrieder CDMS ion trap for increased charge accuracy and throughput

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The authors declare no competing financial interest.

Institutes

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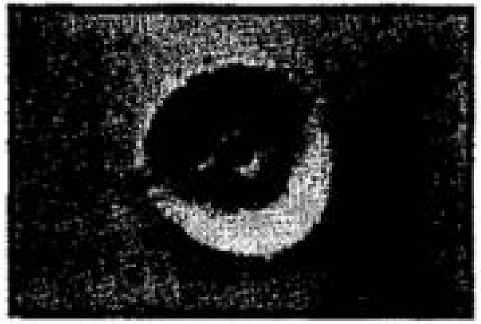
Introduction to charge detection mass spectrometry

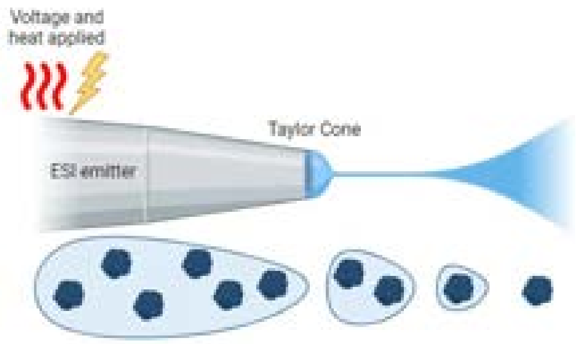


First developed in the 1960s

Measuring of dust particles masses that cause impact craters on satellites

CDMS field expanded by addition of ESI

Allows native, multiply-charged ions to be analysed

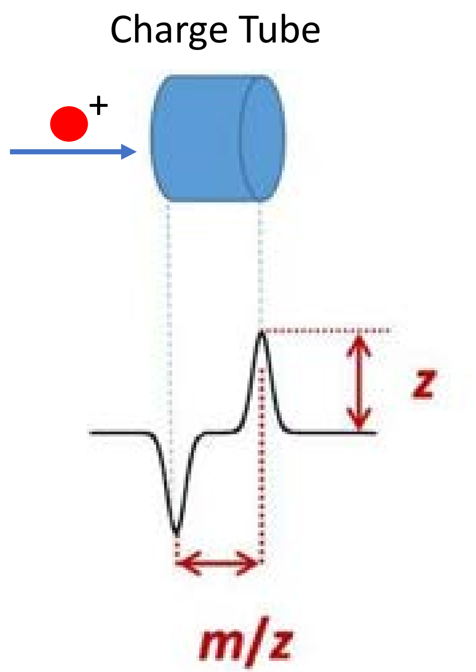


Principle:

Ions traverse through a cylindrical conductor and induce a charge on the surface

The time of flight gives *m/z* and the amplitude gives *z*, therefore *m* can be determined

Increasing number of detectors and number of oscillations improves the detection limit, this leads to the utilisation of electrostatic ion traps with FFT detection.



Overview

- Electrospray of very large species such as virus molecules yields a continuum of possible charge states meaning that conventional mass analysers that only detect m/z ratios fail to give distinct spectral peaks providing little useful analytical data.

- CDMS overcomes this limitation by injecting individual (or small populations) of ions and measuring both m/z and z, the product of these two parameters allow true mass (m) measurements. Mass resolution depends on both m/z resolution and charge accuracy.

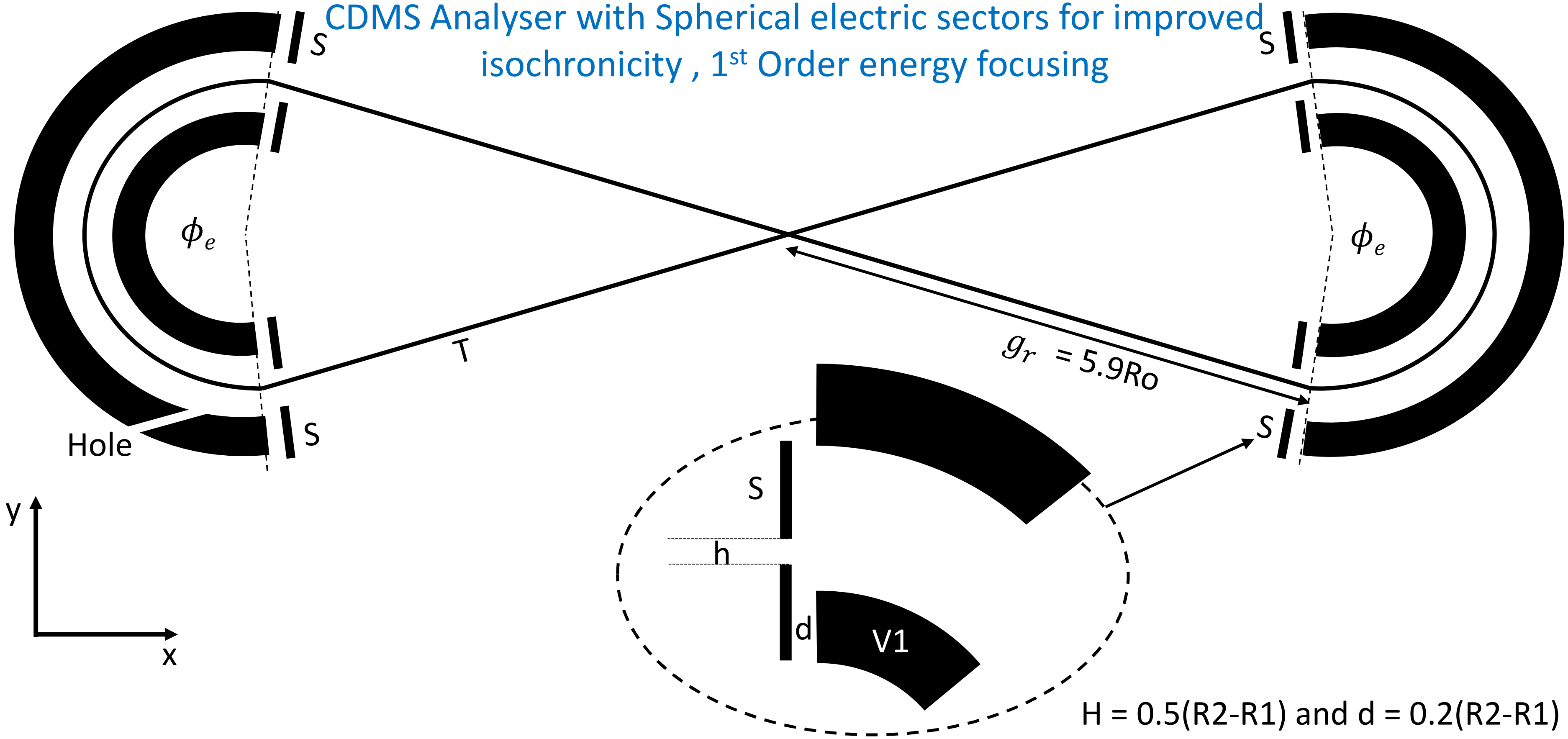
- Existing dedicated CDMS instruments based on Linear Ion Trap (ELIT) have high charge accuracy MegaDalton & Evan Williams group), but relatively small ion volume may lead to space charge limitations.

- The Orbitrap has been adapted to perform CDMS measurements, but the ion optical configuration limits charge (z) accuracy due to unpredictable radial excursions within the trap. This is mitigated by the STORI technique.

- A dual spherical electric sector ion trap configuration is described, this is based on the work of Poschenrieder [1972] with additional elements to allow for CDMS measurements, most importantly the addition Charge Tubes and a central lens.

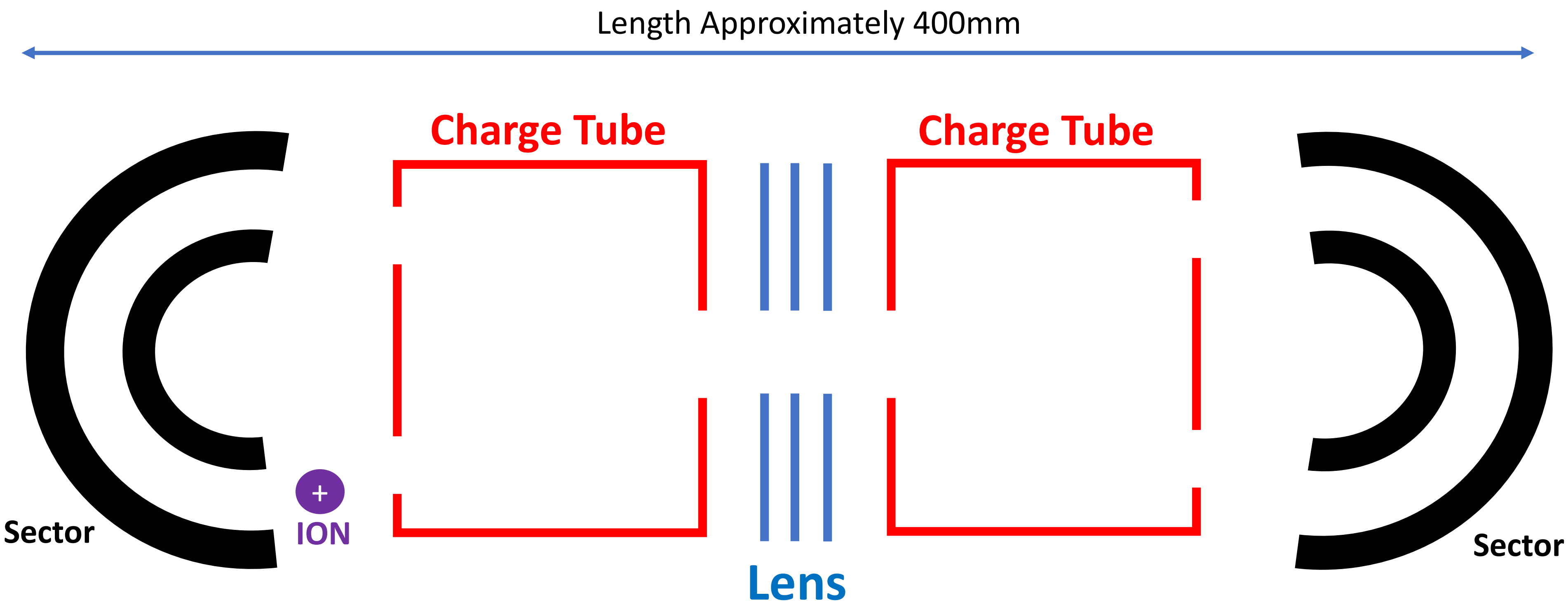
Geometry, 300eV/q ion energy

CDMS Analyser with Spherical electric sectors for improved isochronicity , 1st Order energy focusing



X-Y section of ϕ_e = 199.2° analyser with grounded shunts to control fringe fields

Principle of Operation Animation (MkI size shown)



Signal

First Prototype with MKI Analyser

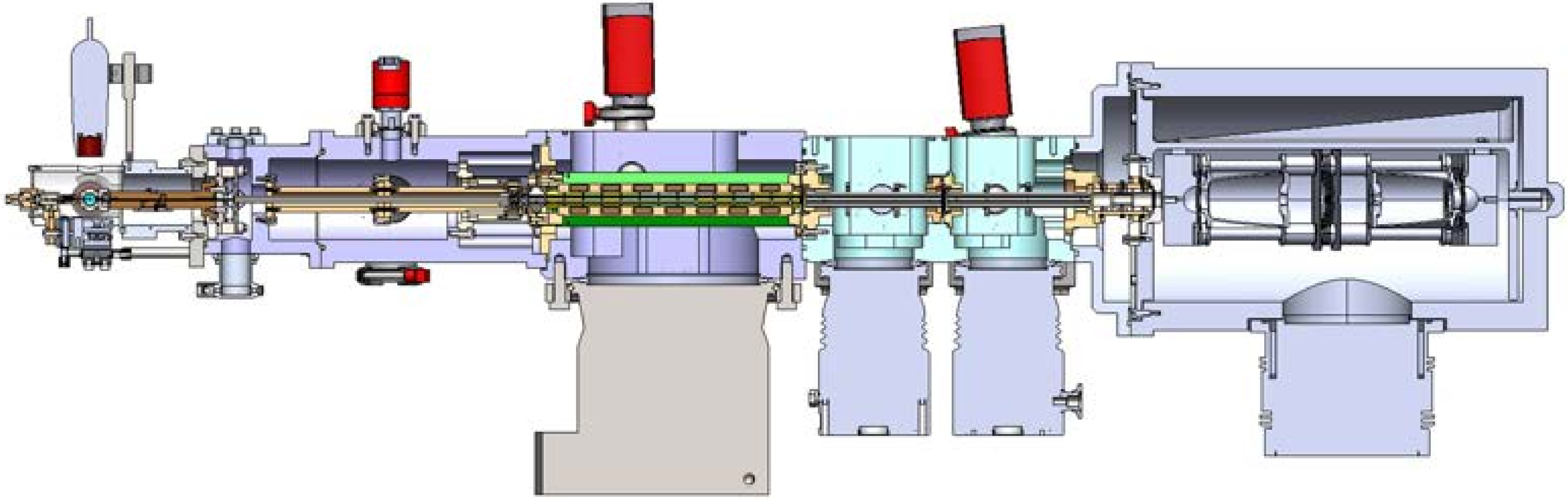
nESI/ESI source

Aerolens

Segmented Hexapole

Transfer Hexapoles

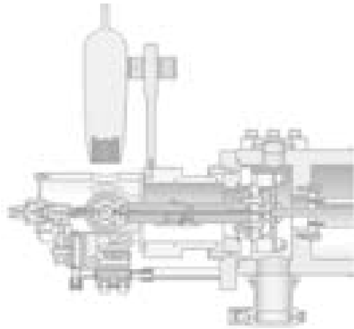
CDMS analyser

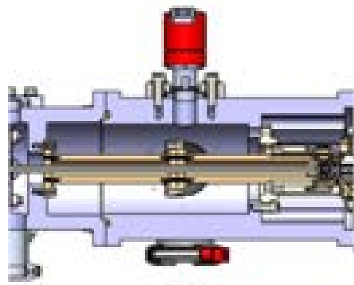


Fasmatech

TrueMass

Aerolens Principle (Fasmatech)

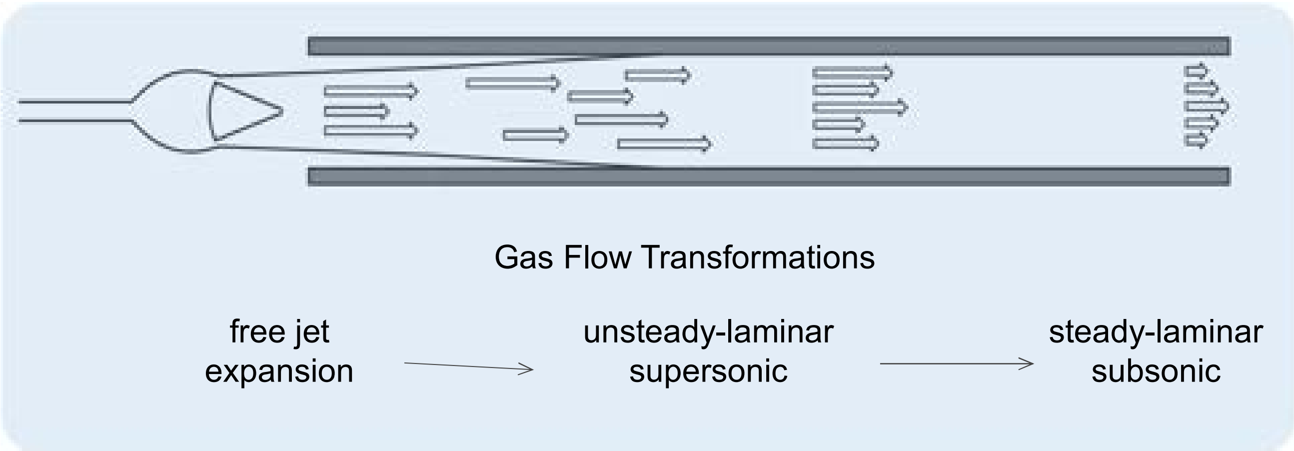




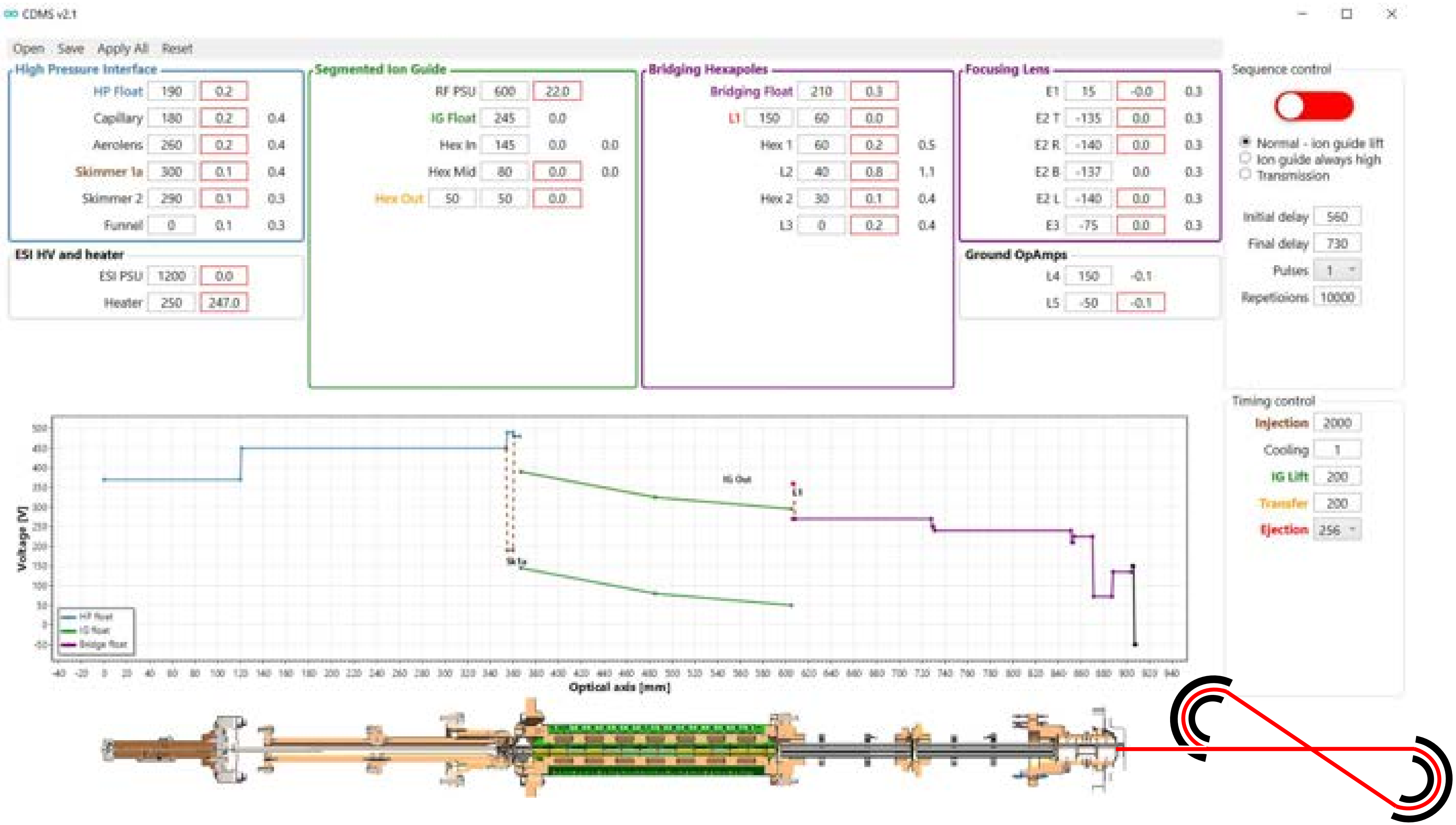
Both ESI and nanoESI sources available. The nanoESI inlet is used for the analysis of large biomolecules such as AAVs.

Charged particles generated by ESI or nanoESI are sampled from a heated capillary inlet and decelerated inside a laminarization flow tube at low pressure.

Ions are passed into an Aerolens where they are decelerated and attain a steady-laminar subsonic flow profile which minimises diffusion losses and efficiently transfers Megadalton species to a hexapole ion trap.



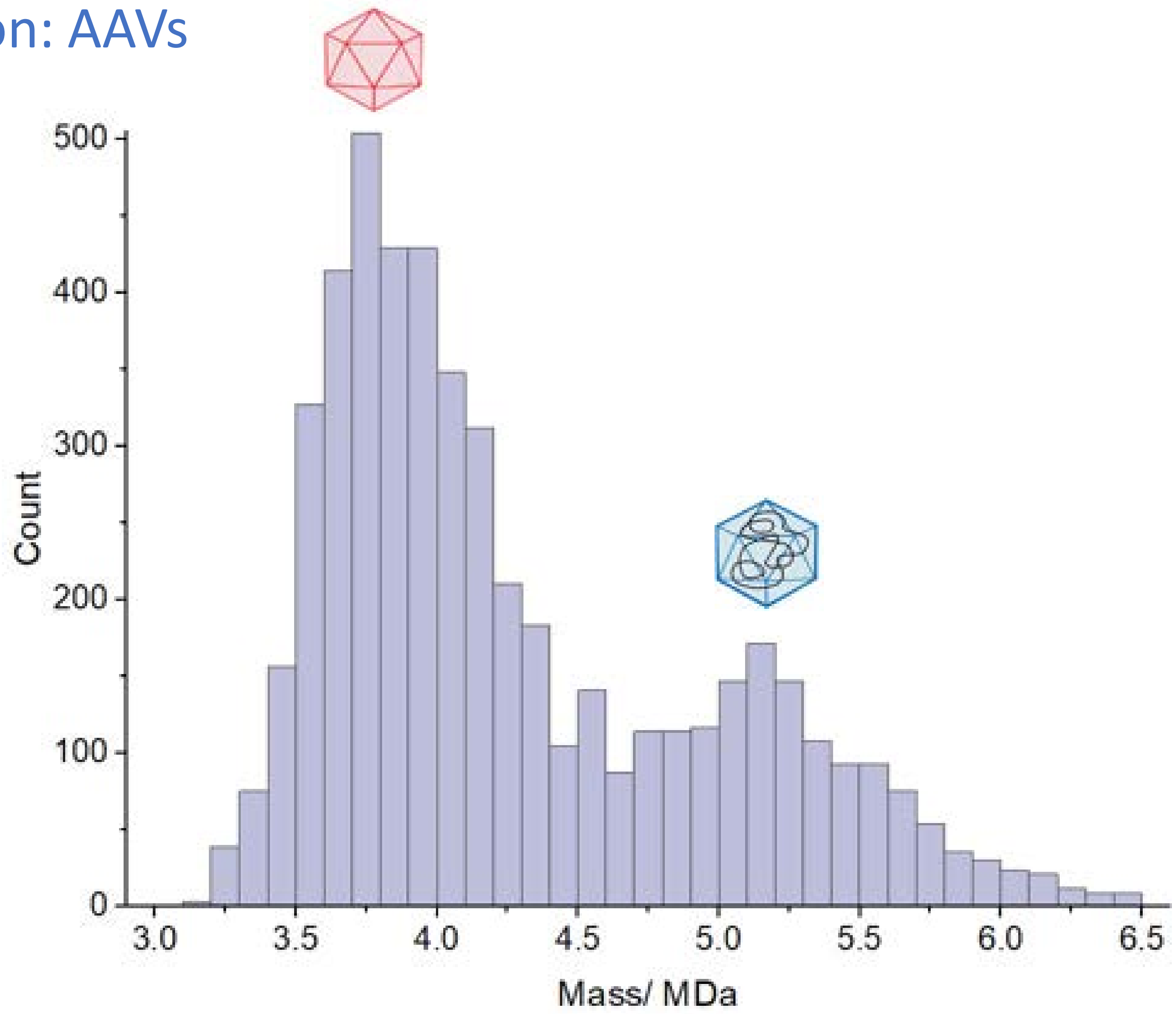
Fasmatech Software interface



Performance Validation: AAVs

Mass histogram of AAV sample 1e^13 VP/mL

CDMS-mode m/z-domain spectrum converted into a mass histogram by scaling the intensity axis to charge (charge calibration gain factor) and multiplying each feature by respective m/z.

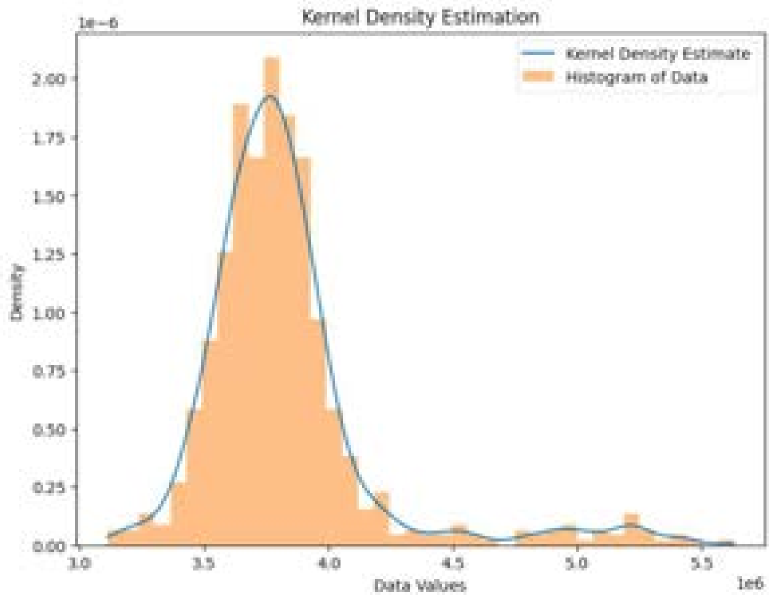


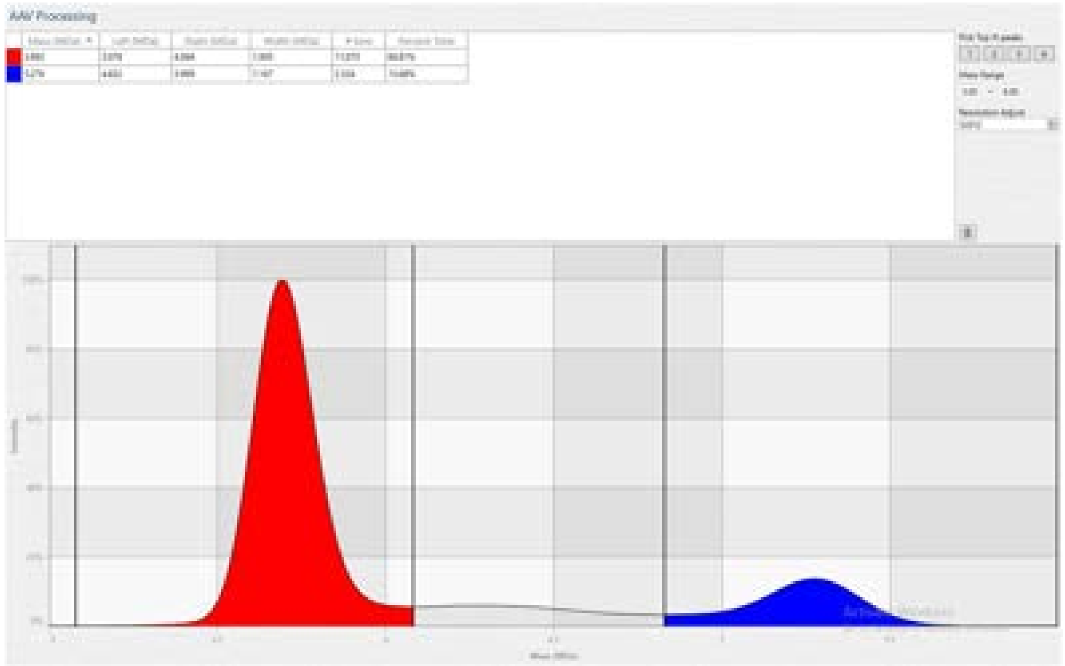
康龙化成 PHARMARON

MANCHESTER 1824
The University of Manchester

Performance Validation, AAV:

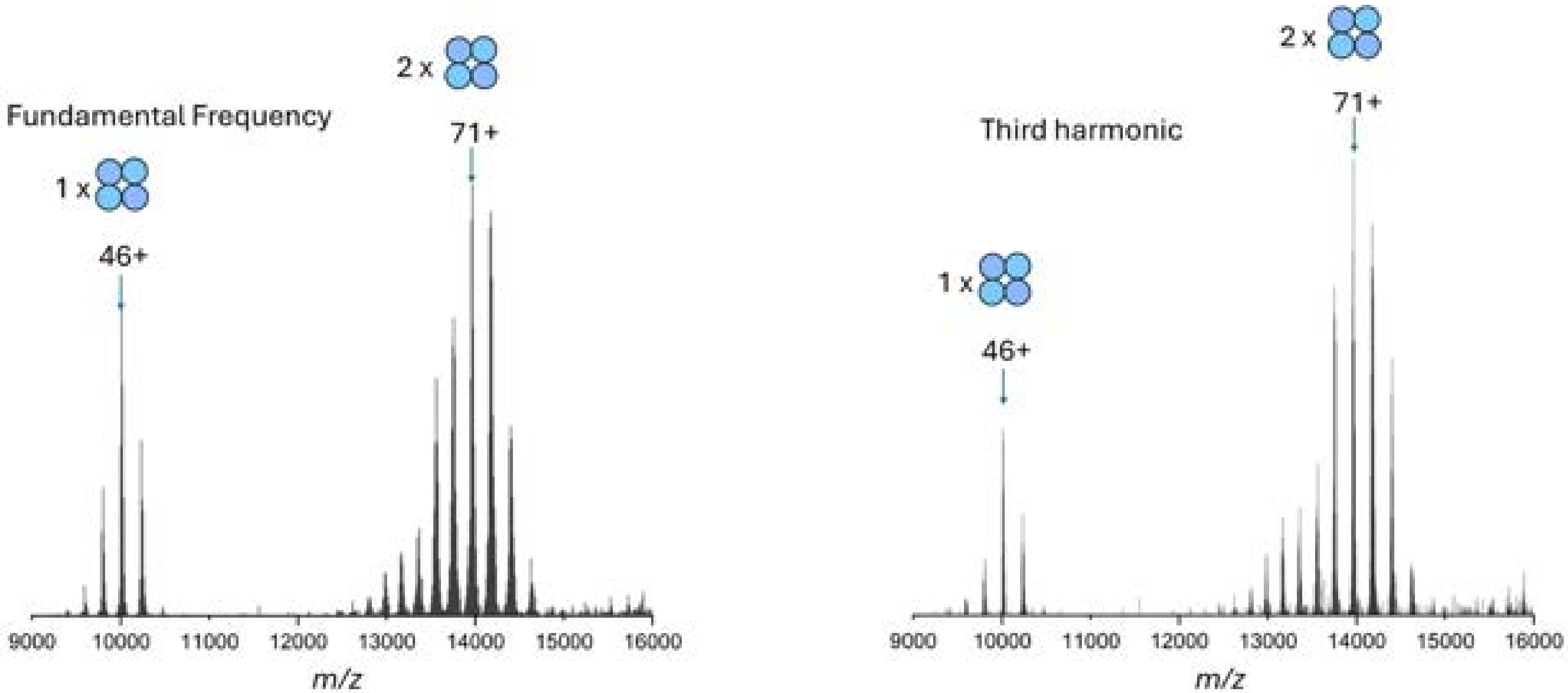
Comparison with Q Exactive UHMR in CDMS mode





Resolution within a factor of two of Orbitrap DMT on MkI

Performance Validation Beta-galactosidase (Spectroswiss Booster)



This result shows the Utility of the TrueMass instrument for Native non CDMS studies (ensemble mode)

Spectroswiss

New data acquisition and processing system

Signal Capture

- High Gain Preamp 400mV/MeV (Si)
- 16-bit resolution Digitisation (Picoscope 4262)

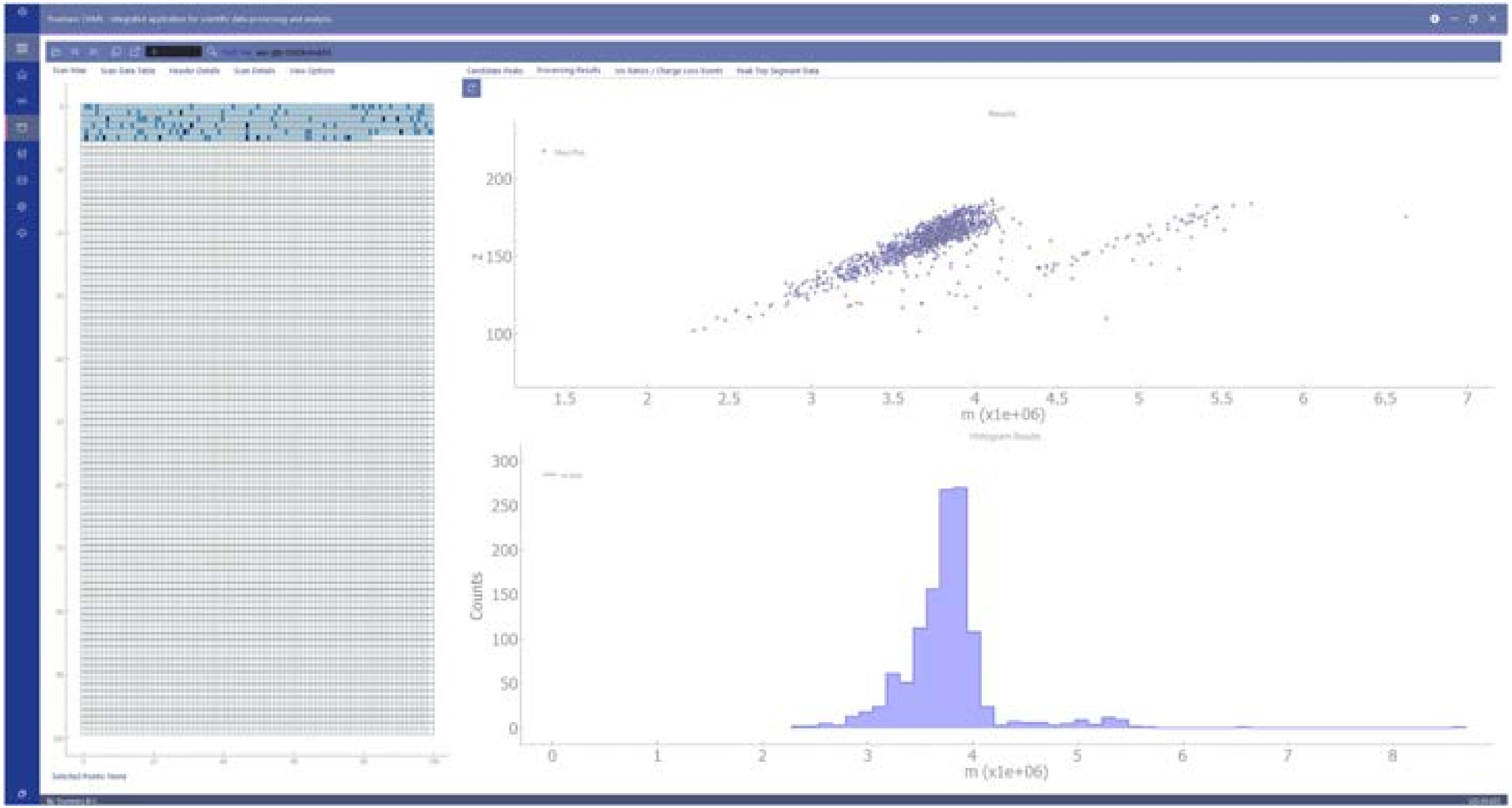
CAEN 1422 preamp

Software

- Data is steamed from Picoscope “scan by scan”
- FFT is generated by TrueMass Software
- Spurious noise rejected by harmonic filtering
- Ions are then quantified according to lifetime
- Scatter plots and histogram populated in real time.

Picoscope 4262, Cost $1300

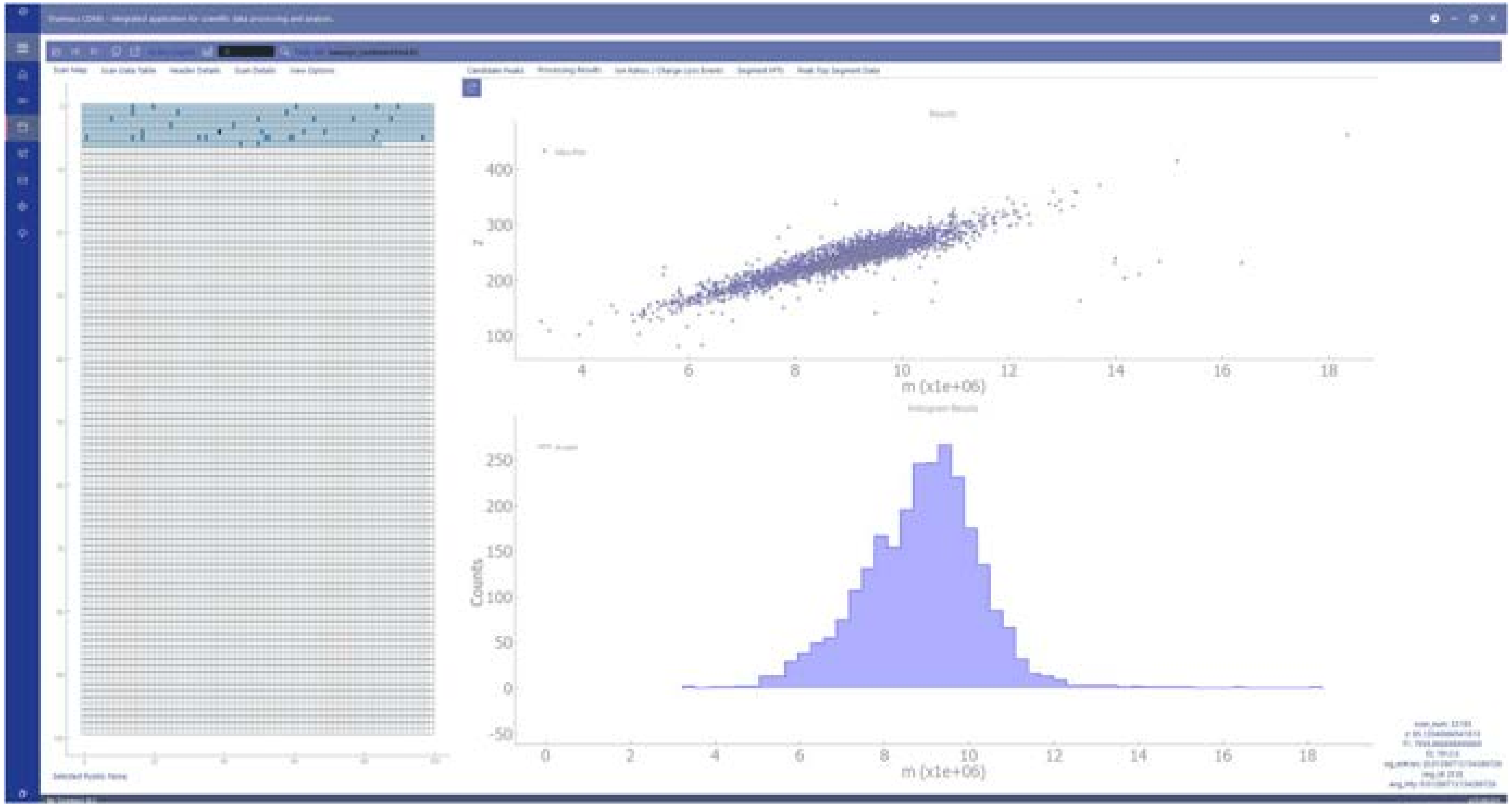
TrueMass Software showing AAV capsid result: Scatter Plot (M vs Z) and Mass Histogram



Real Time Acquisition

Real Time Acquisition, statistics have improved

TrueMass Software showing nano-syringe data:
Scatter Plot (M vs Z) and Mass Histogram

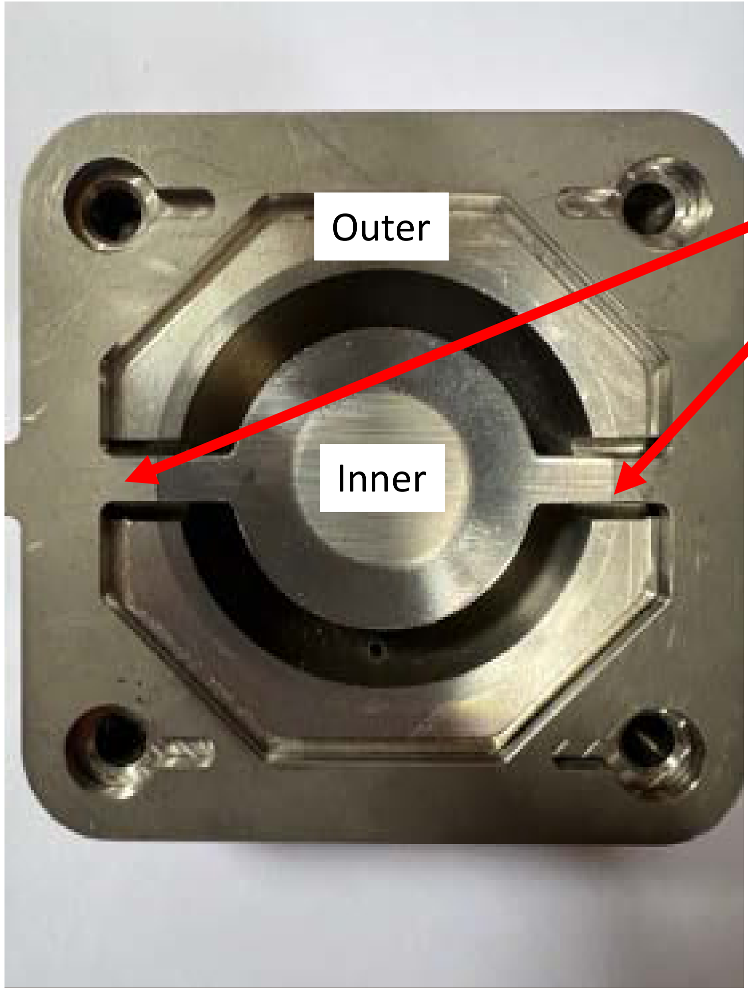


New Analyser Design

New Analyser design features

- Dimensionally shrunk from previous design by a factor of three
- Increase of frequency by factor of three lowers 1/f noise contribution
- Lower front-end noise due to reduced charge tube capacitance
- larger gap (aspect ratio) between hemispheres to compensate for smaller size
- Redesigned central lens using electrostatic quadrupole lens giving longer transient times (more round trips)
- Expected resolution improvement of a factor of ten over first prototype

Topology of MkI Hemispheres

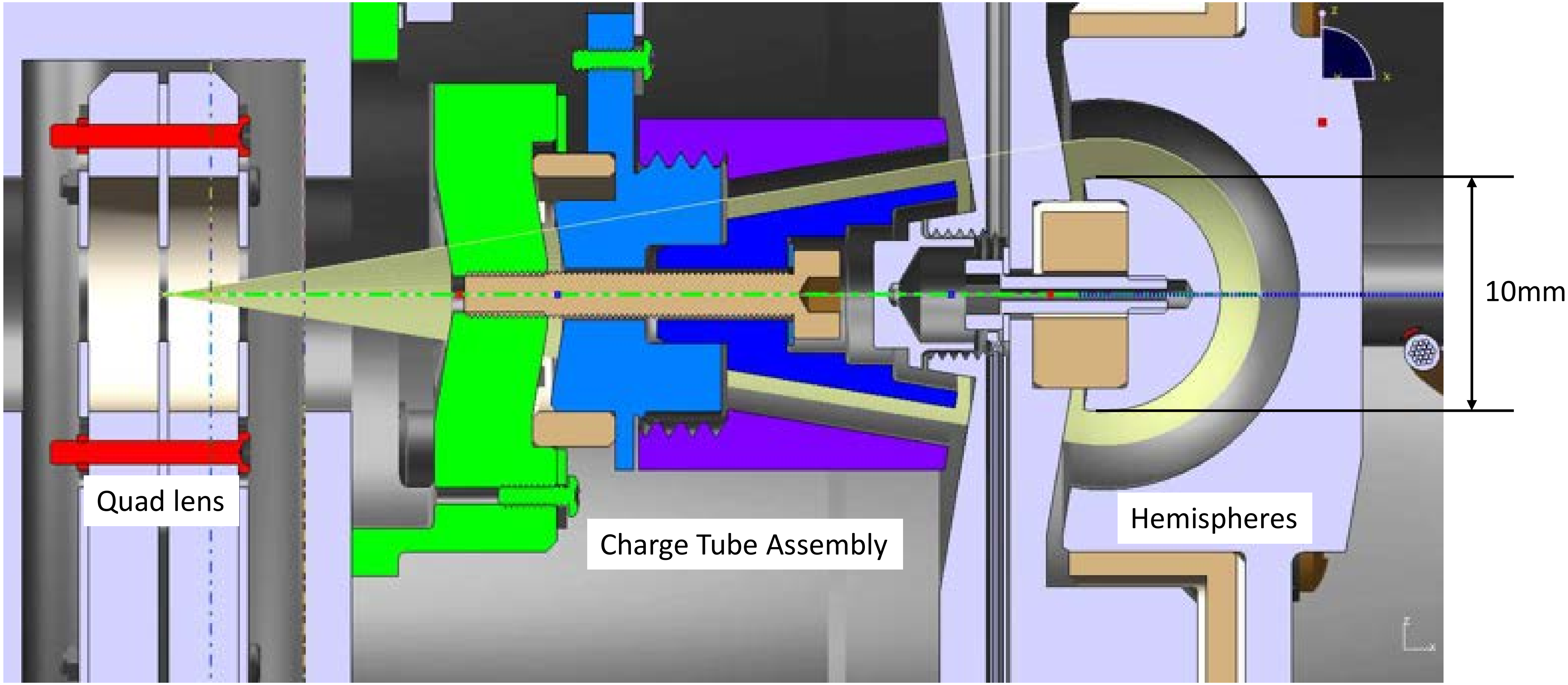


These supports distort the ideal fields between hemispheres

- The relative gap between hemispheres needed to be increased for MkII to improve the absolute phase space acceptance of the reduced scale analyser

- The solution for MkII is to mount the inner hemispheres inboard via a FFR region optical component.

Cross section of one half of new analyser design
Inner hemisphere mounted via shunt

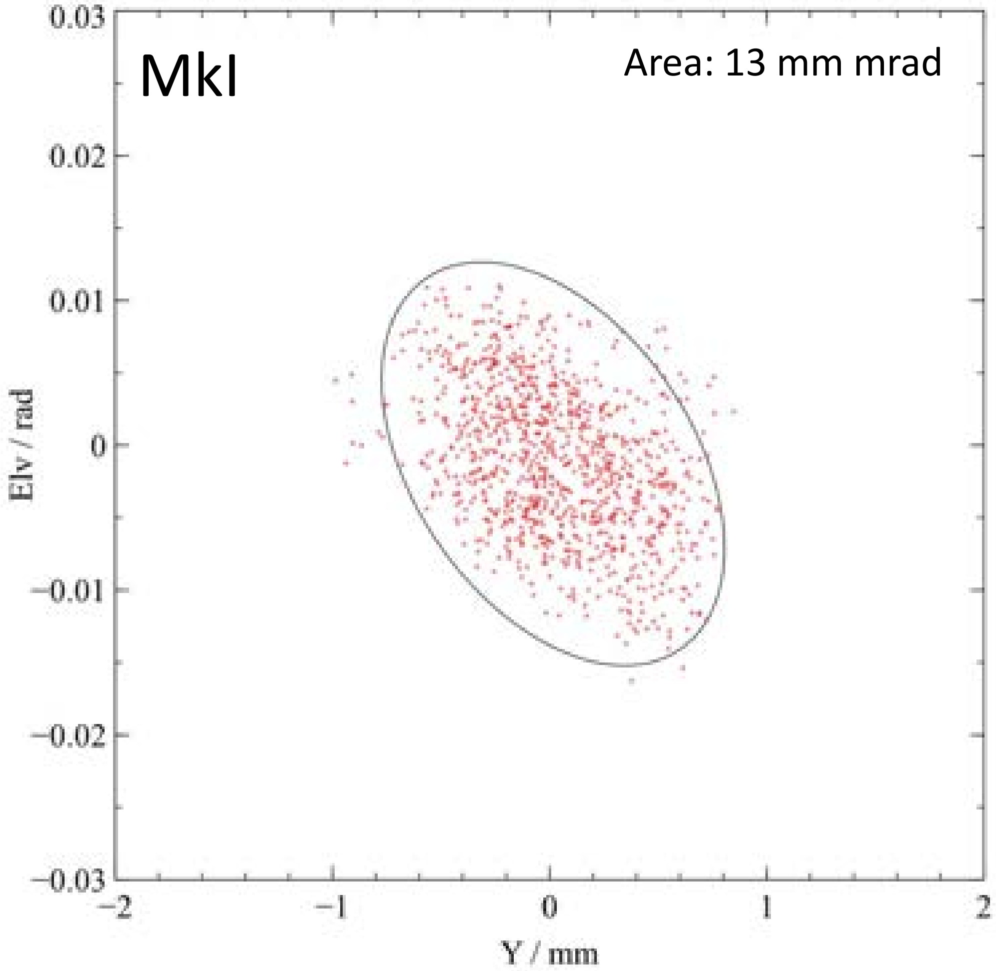


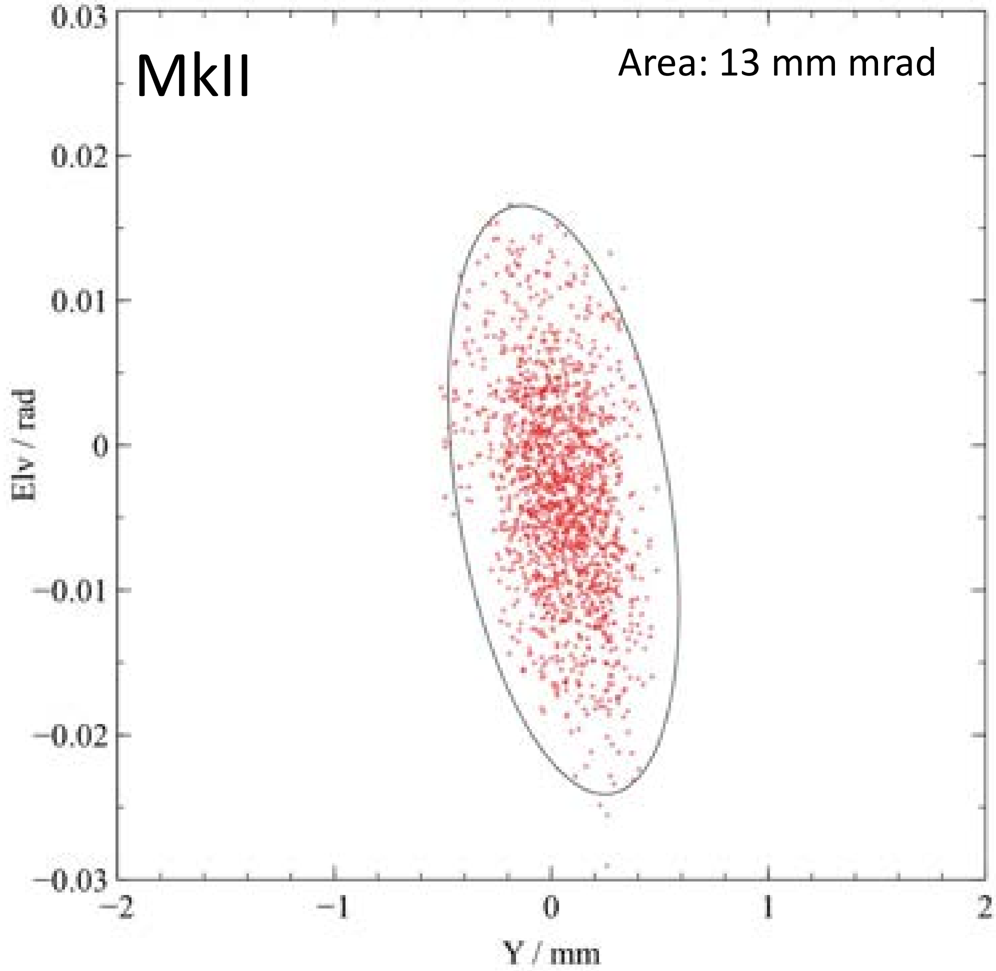
Analyser size

Phase space considerations

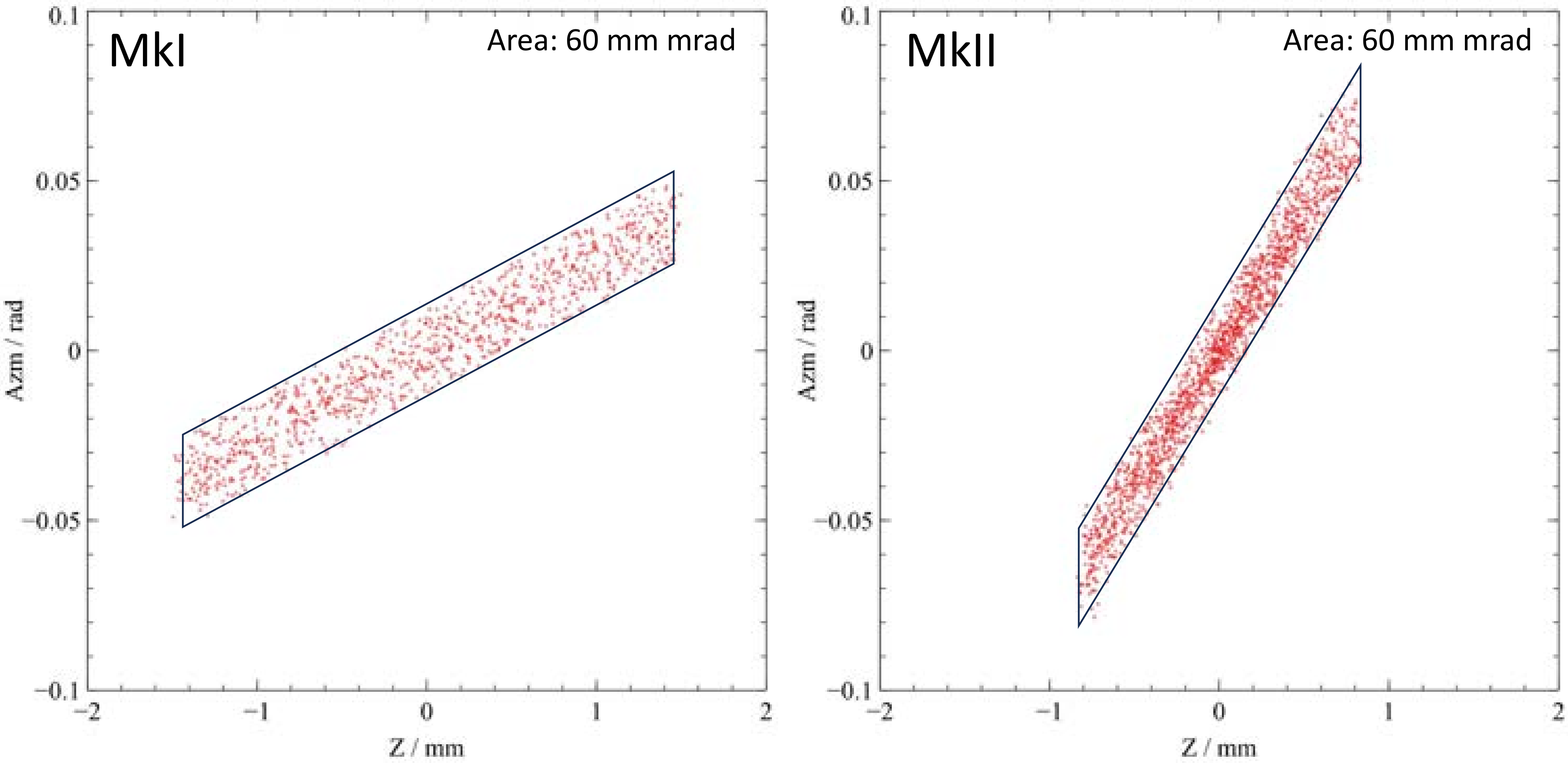
- Comparison of original and 1/3 scale analyser
- For comparison purposes I set optimal voltages on the D.C. quad lens for both analysers
  - Note that original analyser has sub optimal central einzel lens design
- Motivation is to understand if the increased aspect ratio gap compensated for smaller analyser size in terms of acceptance
- Both configurations showed an energy acceptance of 10% in 300eV/q
- Acceptance in the plane transverse to the ion beam has been simulated

Phase space acceptance in Y direction





Phase space acceptance in Z direction



Potential for Tandem CDMS

Signal from eight ions centred around 9600m/z, each separated by 50m/z

Transient

Frequency

Simulation performed using SIMAX Software

Precursor ion Selection

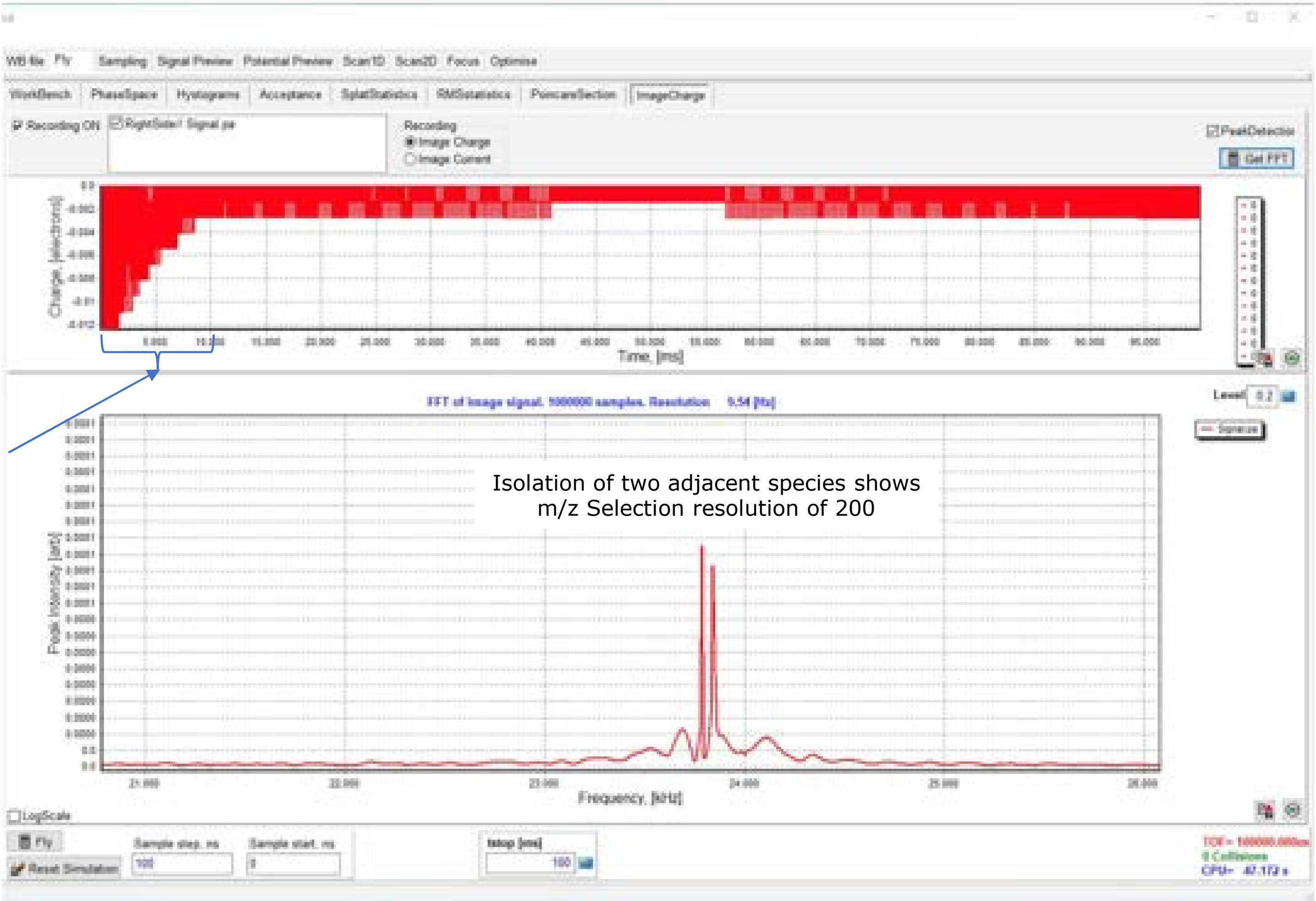
- Measure the true masses of ion population within a transient in real time
- Apply a Supplementary voltage at a high harmonic frequency of the fundamental ion of interest to the central lens
  - Typically, a square wave of 50 volts is applied
- Isolation of desired species takes around 10ms
- Selected ions may be ejected upstream to fragmentation device or Soft-landing Stage for EM

Isolation of two adjacent ions demonstrating precursor resolution of 200

Transient

Note that filtering of unwanted species takes only 10ms!

Frequency



Summary

- Results from MkI protype led to a redesign of our CDMS analyser
- Turnkey real time acquisition and processing software
- Potential for Tandem CDMS measurements
- New Analyser installed, awaiting first results