Cryogenic Detectors for Macromolecule Mass Spectrometer Applications

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Applications (1)

- **Genomics**
  - DNA Sequencing
  - Genotyping

Goal: with CryoDetectors sensitivity and 10 Da mass resolution for DNA fragments upto 1000 base length (300 kDa)

- **Proteomics**

DNA codes for proteins. But in most eucaryotic cells, proteins are posttranslational modified ⇨ biological and medical relevance

- protein identification
- protein characterisation (post translational modification)

Mass Spectrometry (1): Basics

Mass Spectrometry :

"analytical method to determine the distribution of molecules according to their **mass/charge** ratio"

Principle of Operation: separate molecules in vacuum

Steps of Operation:

- launch molecules: from sample into vacuum (laser)
- ionize molecules
- accelerate molecules
- separate molecule
- detect molecules (cryodetectors)

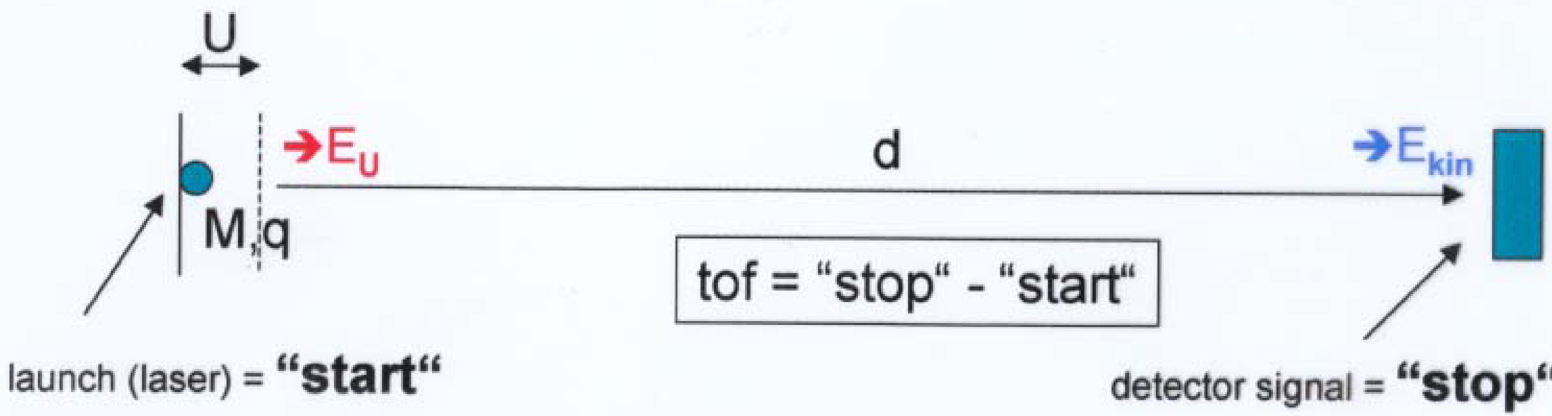
Time-of-flight Mass Spectrometry

separation according to velocity of molecules

acceleration energy: $E_U = q\,U$ (no mass term !)

kinetic energy: $E_{kin} = 1/2\ M\ v^2$

$$E_U = E_{kin} \Rightarrow v = \sqrt{\frac{2qU}{M}} \Rightarrow tof = d\sqrt{\frac{M}{2qU}} \Rightarrow \boxed{tof \approx \sqrt{\frac{M}{q}}}$$



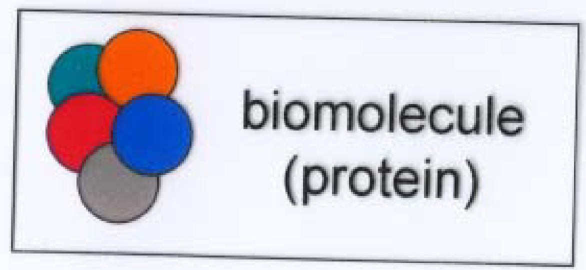
Mass Spectrometry (5): MALDI (1)

Laser illumination is an **ideal** launch mechanism:

- high energy density
- precise timing (nsec)
- precise spatial extension (10 μm)

however, when applied directly to molecule sample:

⇨ **disintegration** of biomolecule



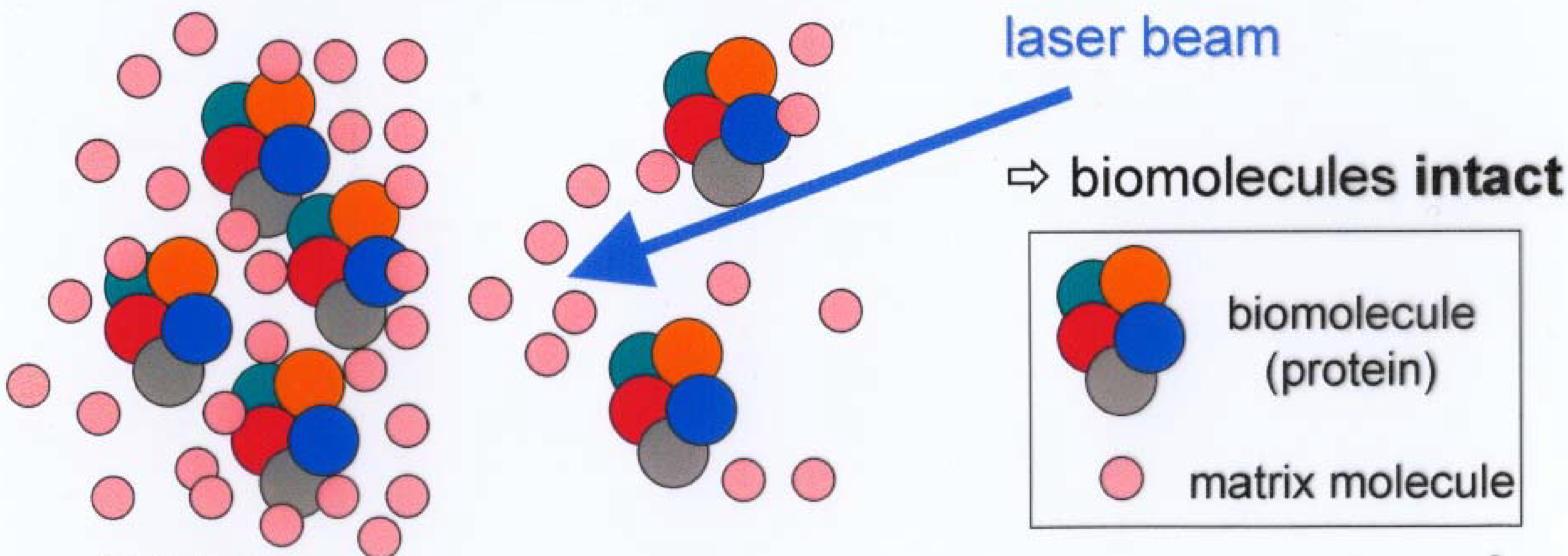
Mass Spectrometry (6): MALDI (2)

solution: Karas & Hillenkamp (1984)

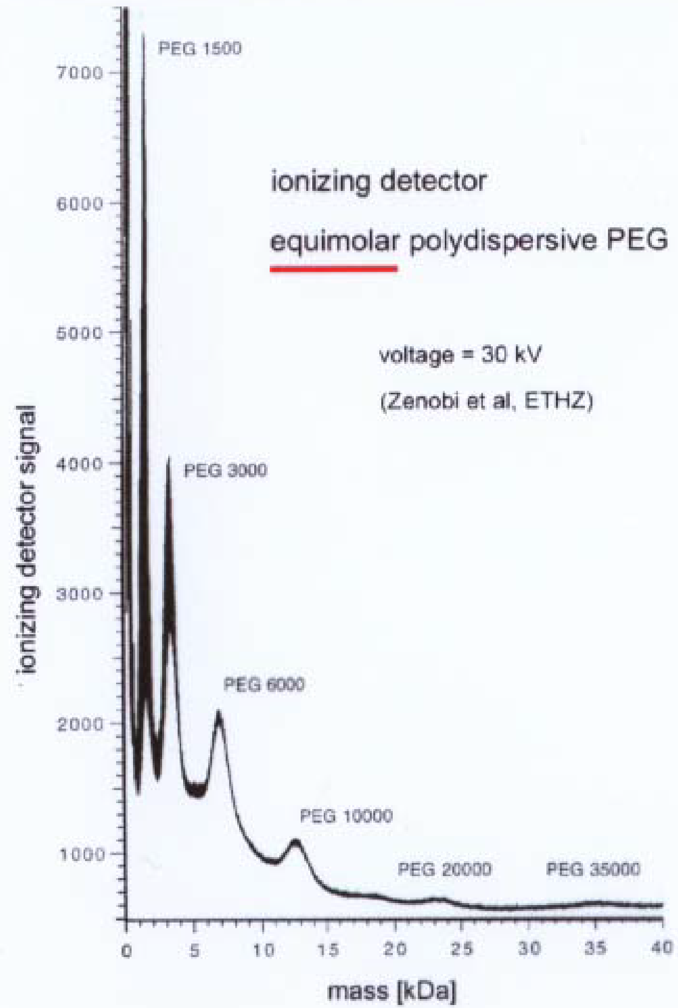
MALDI: Matrix Assisted Laser Depletion & Ionization

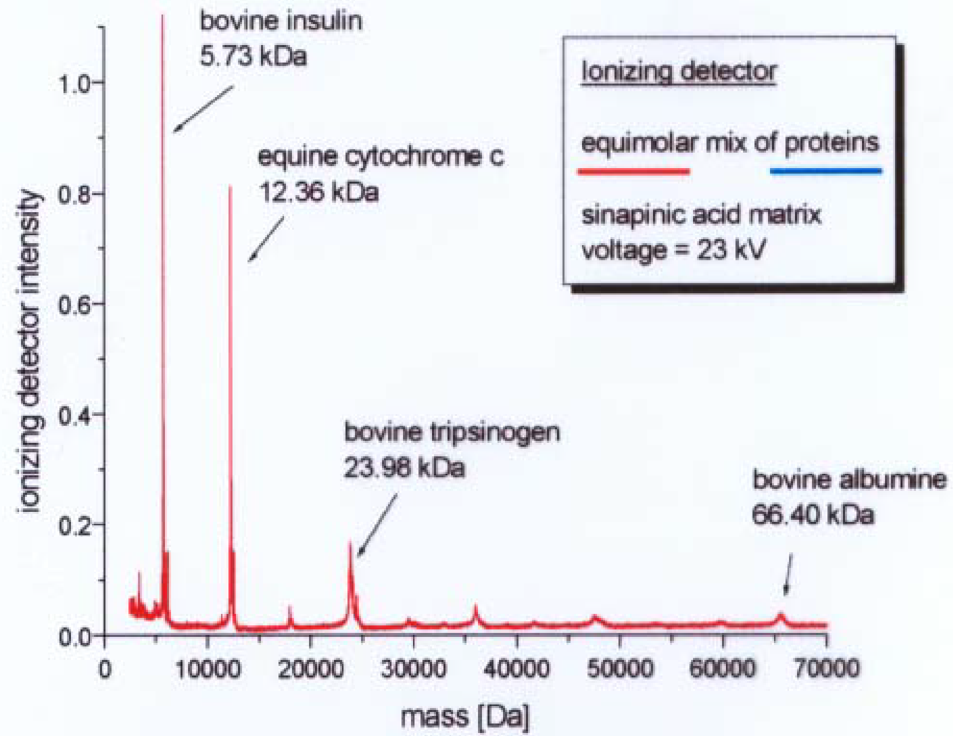
"biomolecules embeded in laser light sensitive matrix"

- laser energy absorbed by matrix
- "mechanical" momentum transfer of matrix molecules to the massive biomolecules



Decreasing Intensity with Increasing Mass

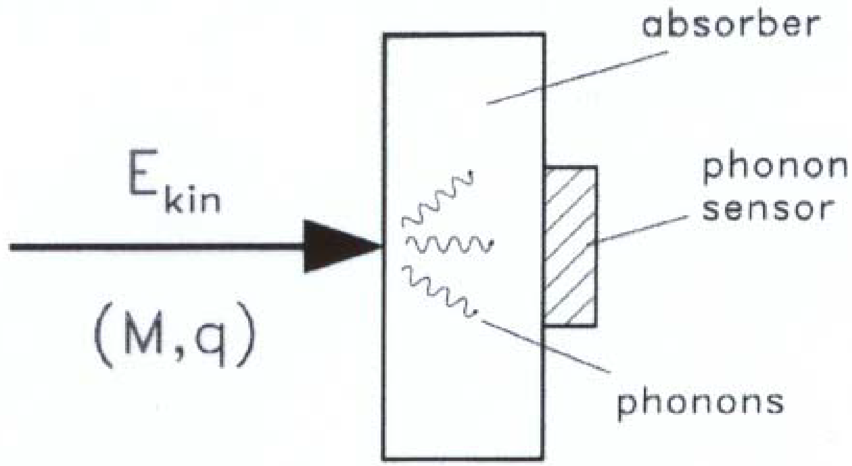


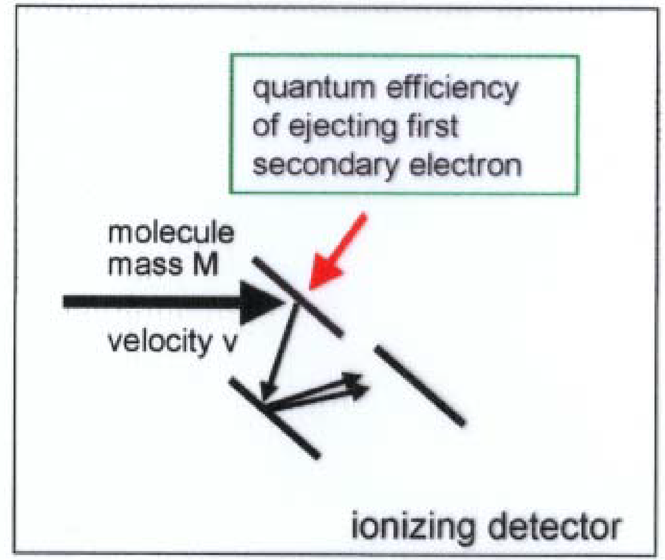


decrease of intensity:

- molecule launch ?
- ionization ?
- ion transmission ?
- detector sensitivity ?

Novel Detector for Mass Spectrometry: CryoDetectors



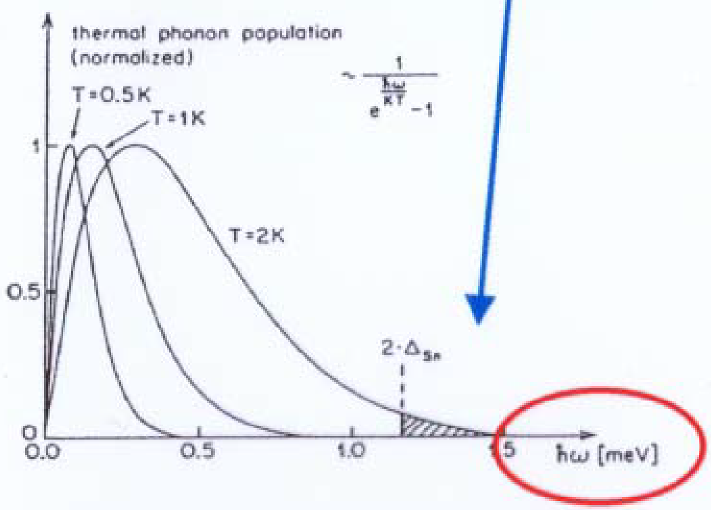


- **detector signal** = **"temperature"** rise owing to absorbed **kinetic energy** of particle
- low (thermal) phonon background requires **cryogenic operating temperatures** < 1 Kelvin

CryoDetectors (1): Principle

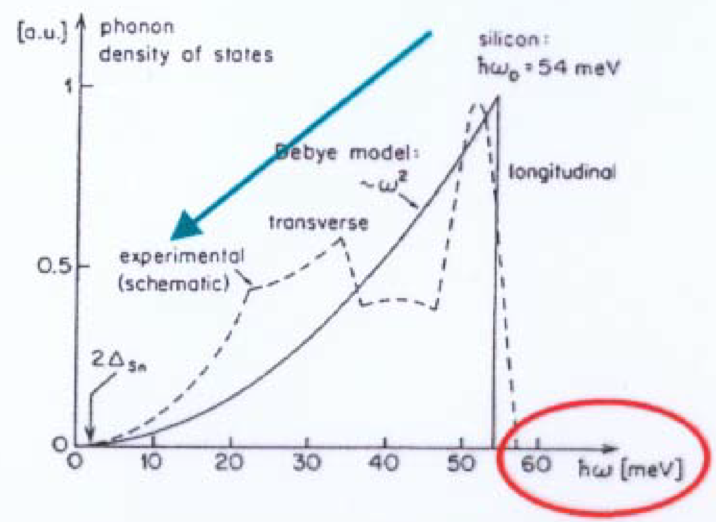
at temperatures below 1 K the primary excitations of materials (phonons, quasiparticles etc.) are of the order of ε = 1 meV

long relaxation life times



thermal phonon population

fast high energy phonon decay



(non) thermal phonon density of states

no charge creation by phonon excitation in semiconductors !

⇧

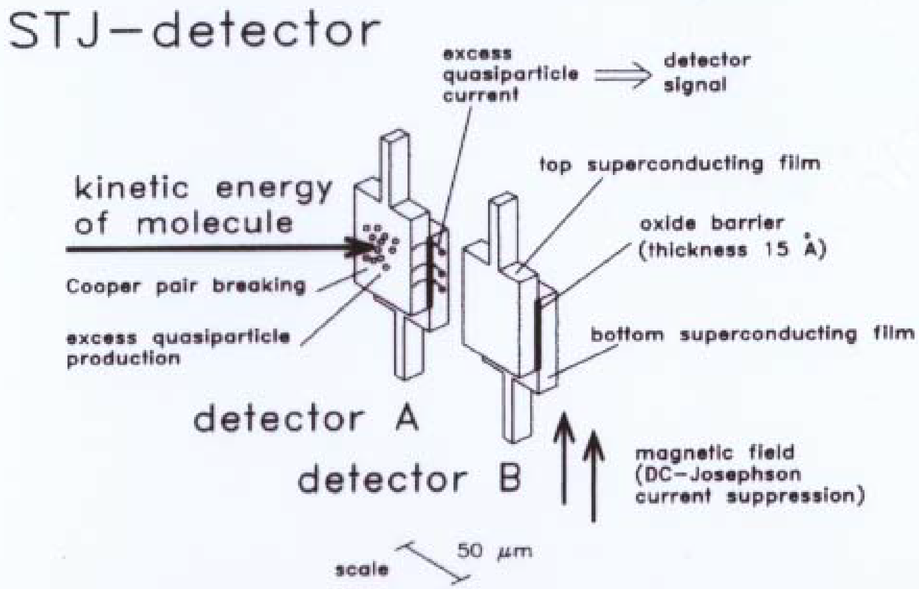
Δ_{semi}

↓

>> 1eV

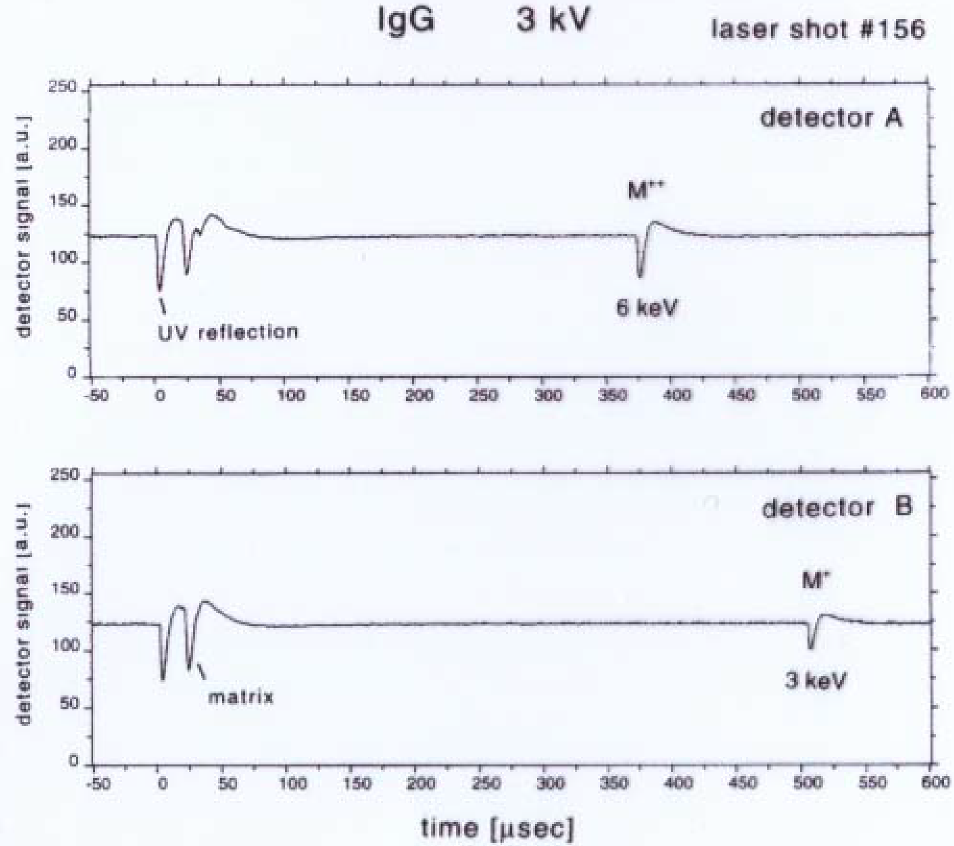
CryoDetector: First Results with Sn-Junctions

experimental results with
superconducting tunnel junctions:



first direct measurement of the total energy of a single biomolecule

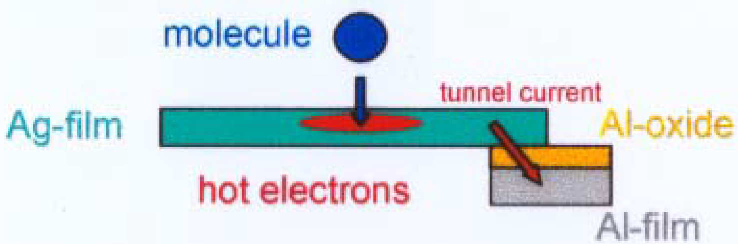
Immunoglobulin
IgG (130'000 Da) at 3 kV

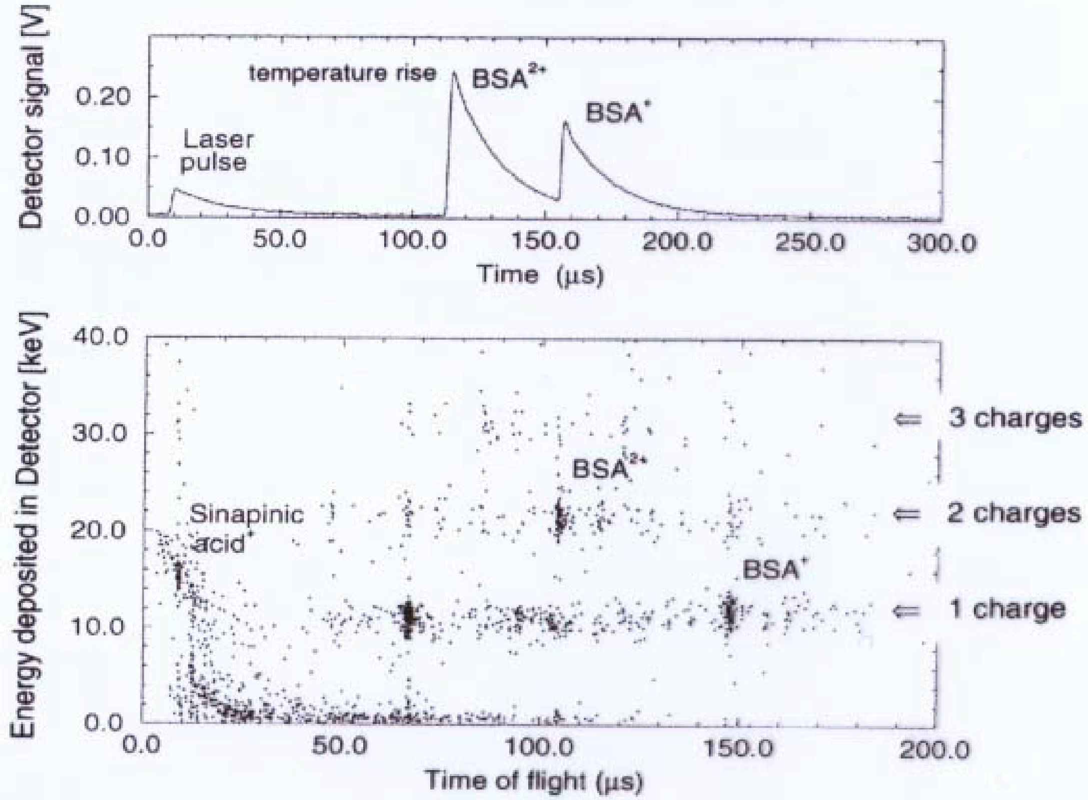


Microcalorimeter: Charge Deconvolution

collaboration:
- NIST (Boulder)
- Institut Physique, Neuchâtel
- GenSpec SA

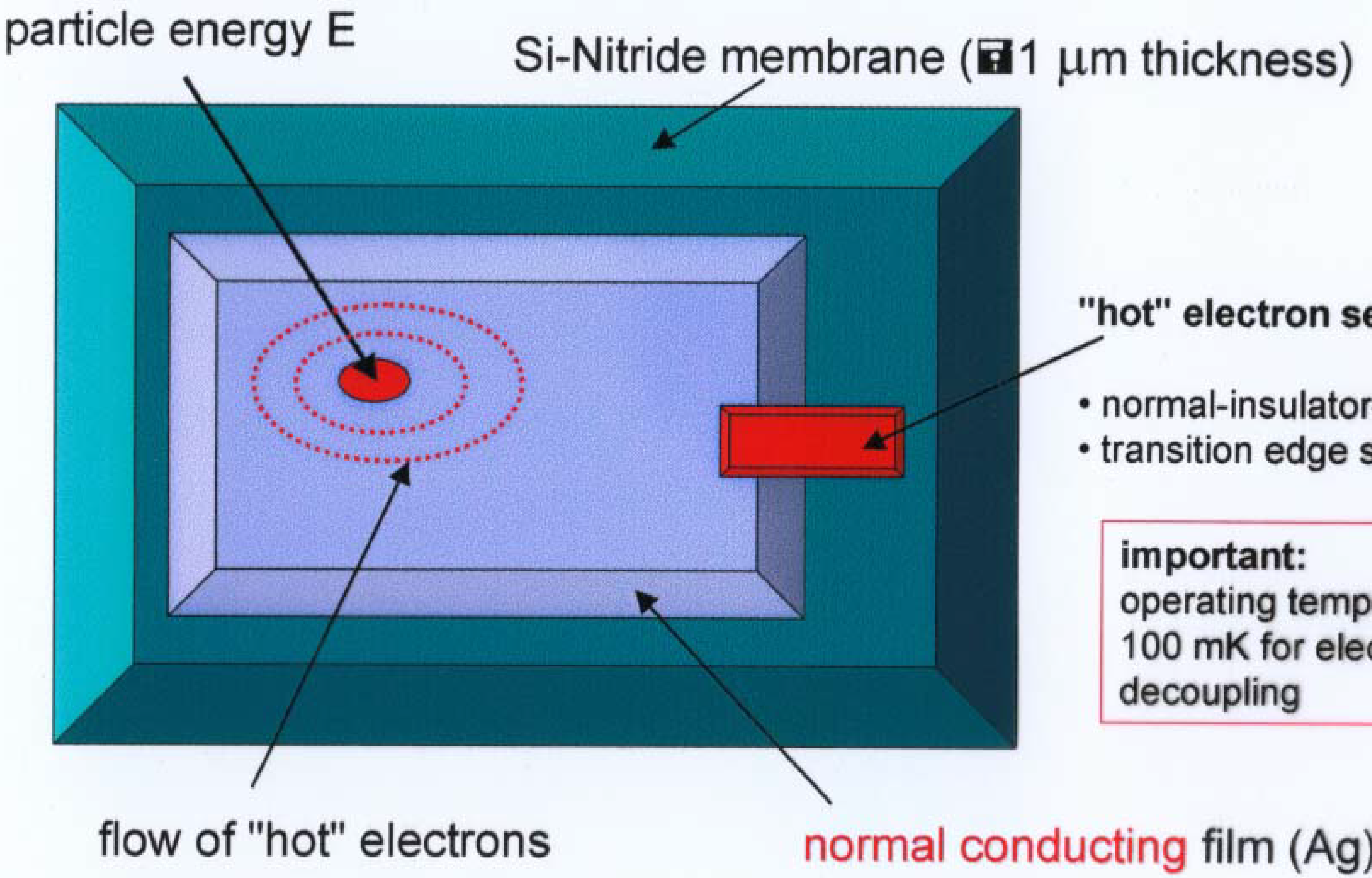
200 μm x 200 μm microcalorimeter operated at 100 mK





G.Hilton,J.M.Martinis,D.A.Wollmann,K.D.Irwin,L.L.Dulcie, D.Gerber,P.M.Gillevet & D.Twerenbold, *NATURE*, Vol 391, page 672, 12.February 1998

CryoDetectors (5): μ-calorimeter



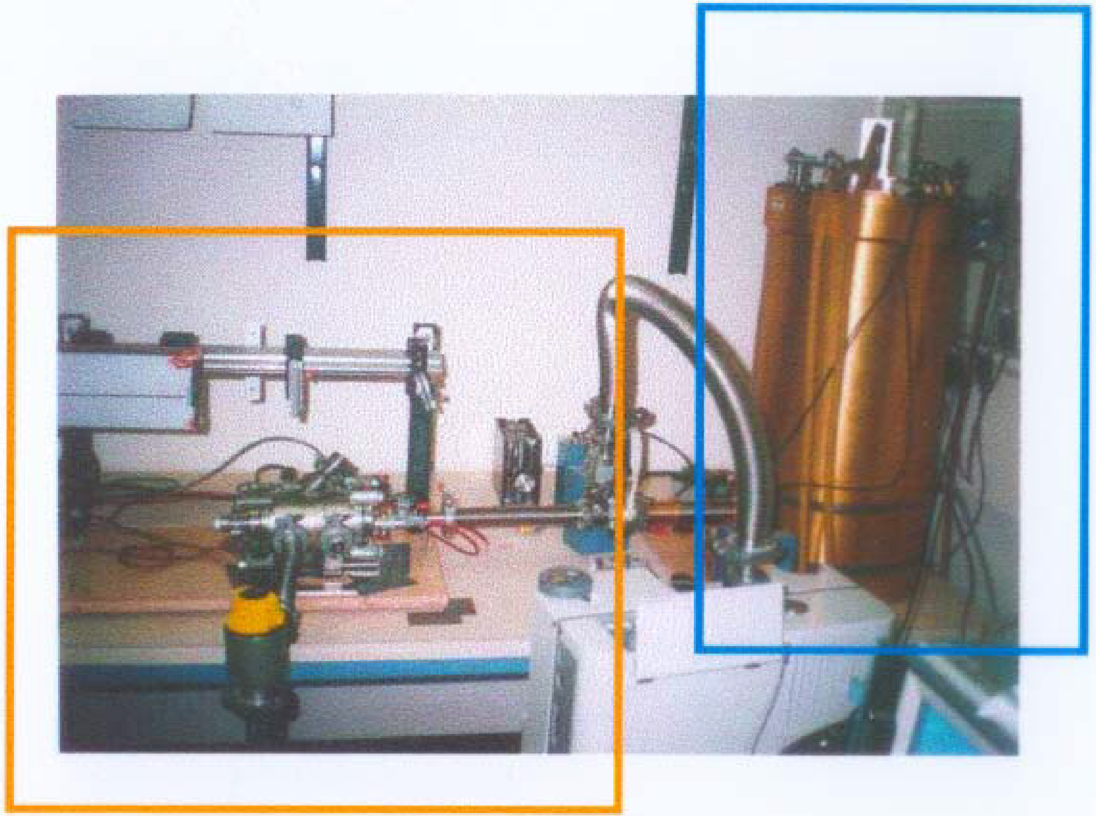
"hot" electron sensing device:

- normal-insulator-supra junction
- transition edge sensor

important:
operating temperature below 100 mK for electron-phonon decoupling

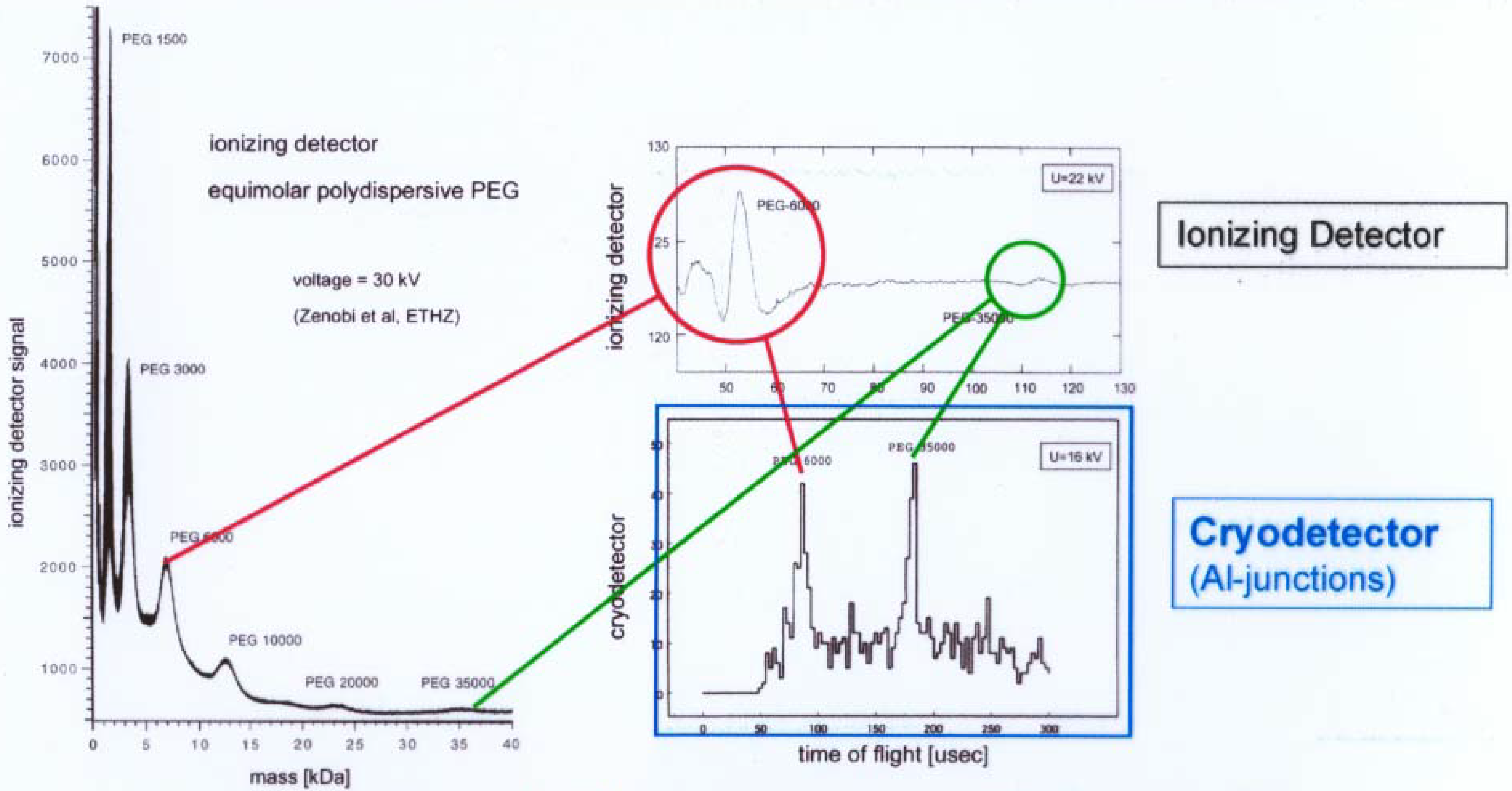
Microcalorimeter: Experimental Setup

MALDI
TOF
from
Neuchâtel



ADR
cryostat
from
NIST

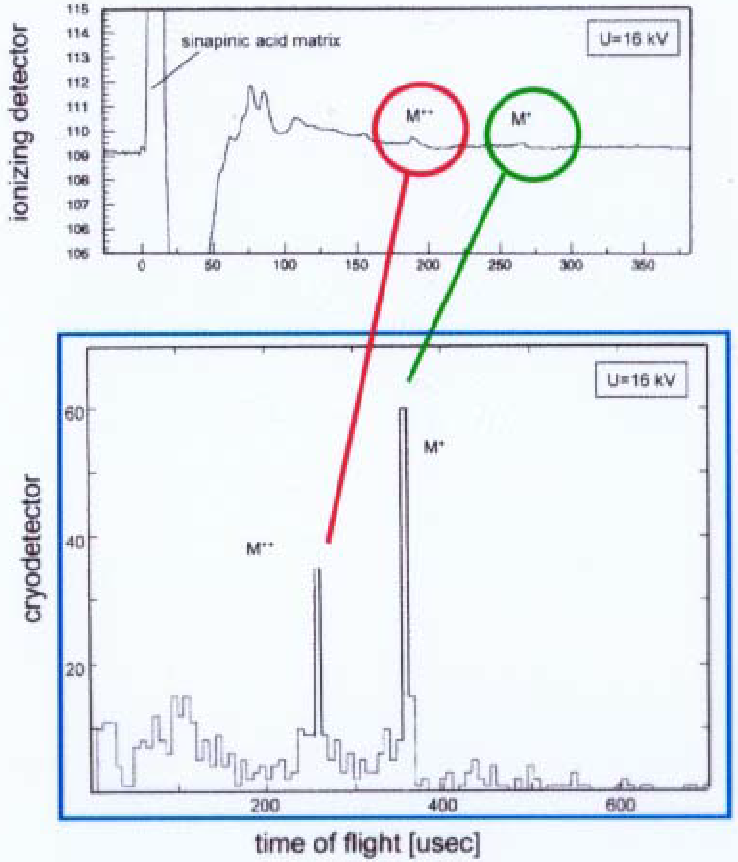
CryoDetector / Ionizing Detector: PEG



sample with equimolar concentration of PEG molecules

CryoDetector / Ionizing Detector: IgG

reversal of relative peak height M^+ to M^{++}

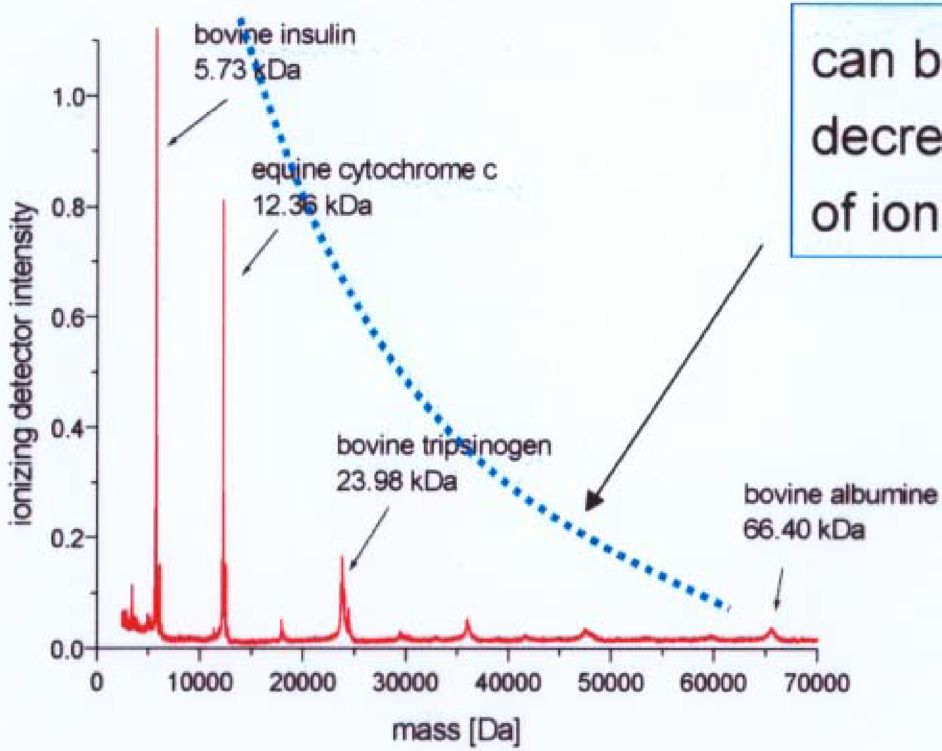


Ionizing Detector

Cryodetector
(Al-junctions)

Decreasing Intensity : Ionizing Detector Efficiency

equimolar mix of proteins

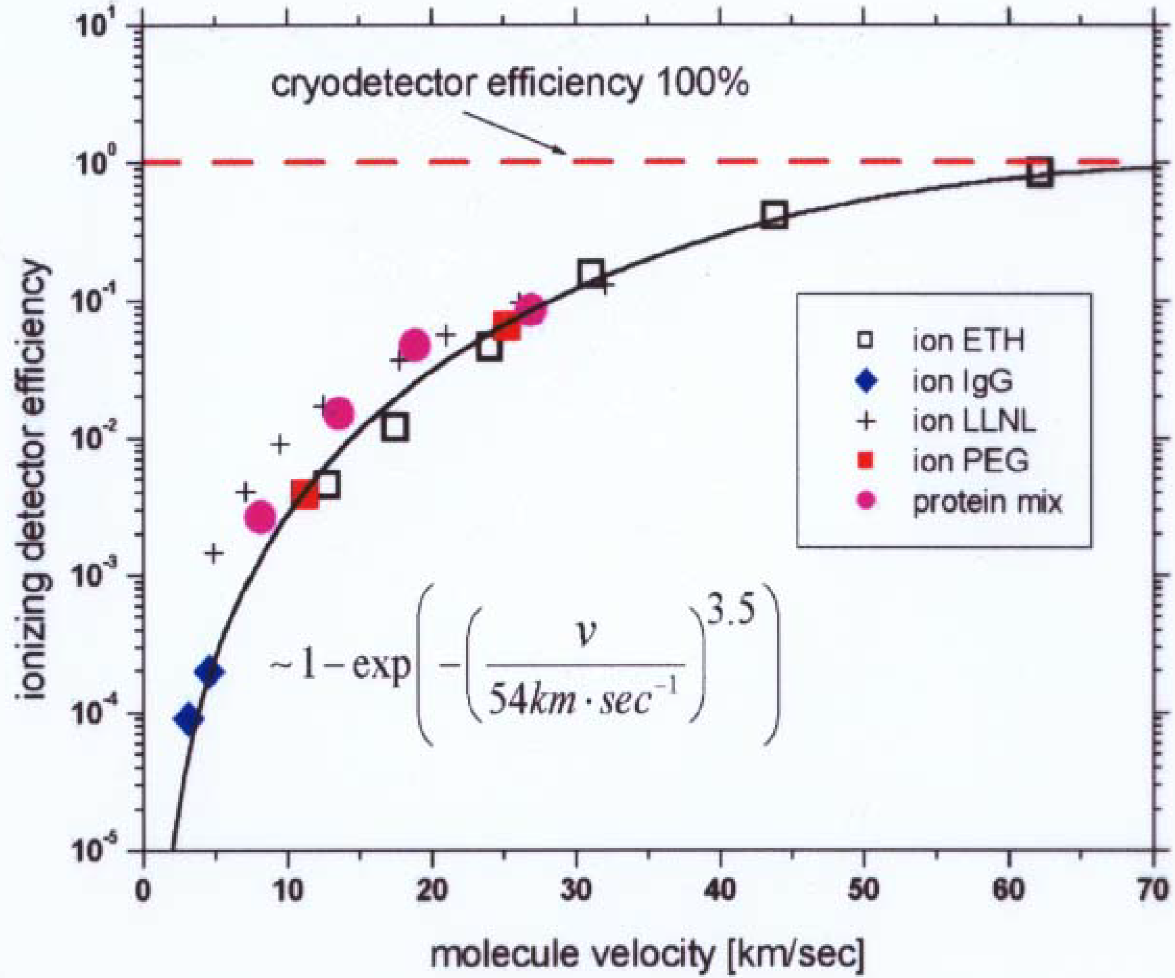


can be explained completely by decreasing detector efficiency of ionizing detector

in this experiment.

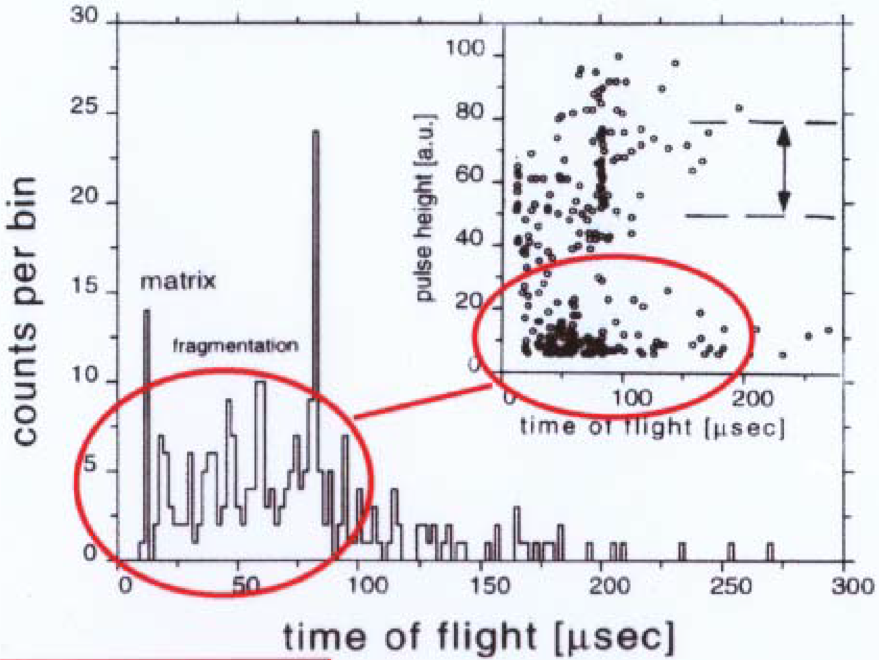
there are of course cases where heavier molecules are more metastable

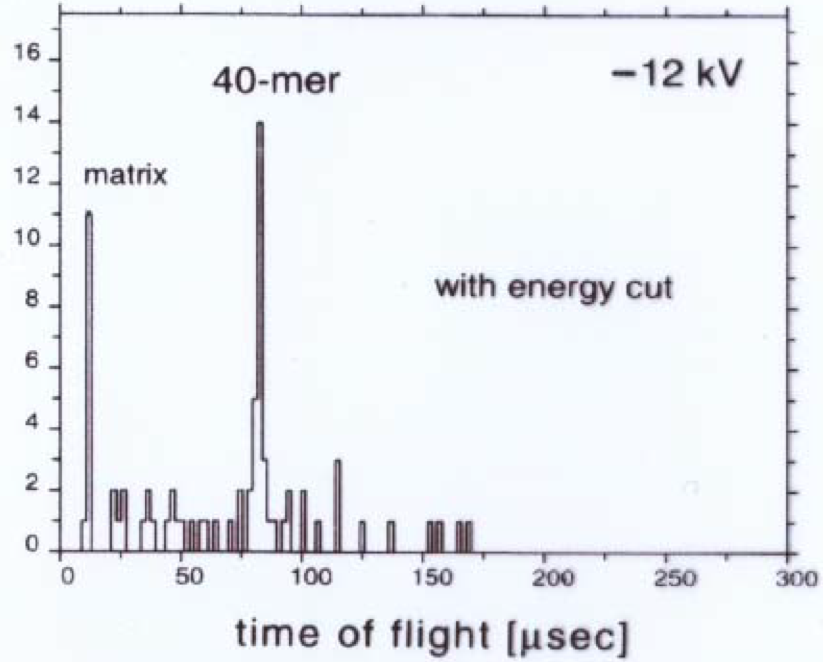
Comparison: Ionizing Detector vs Cryodetector



Improved Spectra through Pulse Analysis

DNA 40-mer oligonucleotide time-of-flight spectrum





fragmentation

all pulses

only pulses with 12 +/-2 keV pulseheight
(same data set)

CryoDetectors: Summary

- 100% intrinsic detection sensitivity on impact
- mass independent detection sensitivity
- direct determination of charged state
- increase signal-to-background of mass spectrum

Mass Spectrometry (4): Launch Methods

Various molecule launch methods:

- **MALDI** = Matrix Assisted Laser Depletion & Ionization
- ESI: Electrospray ionization
- FAB: Fast Atom Bombardment
- and others