

Cryodetectors in Life Science Mass Spectrometry

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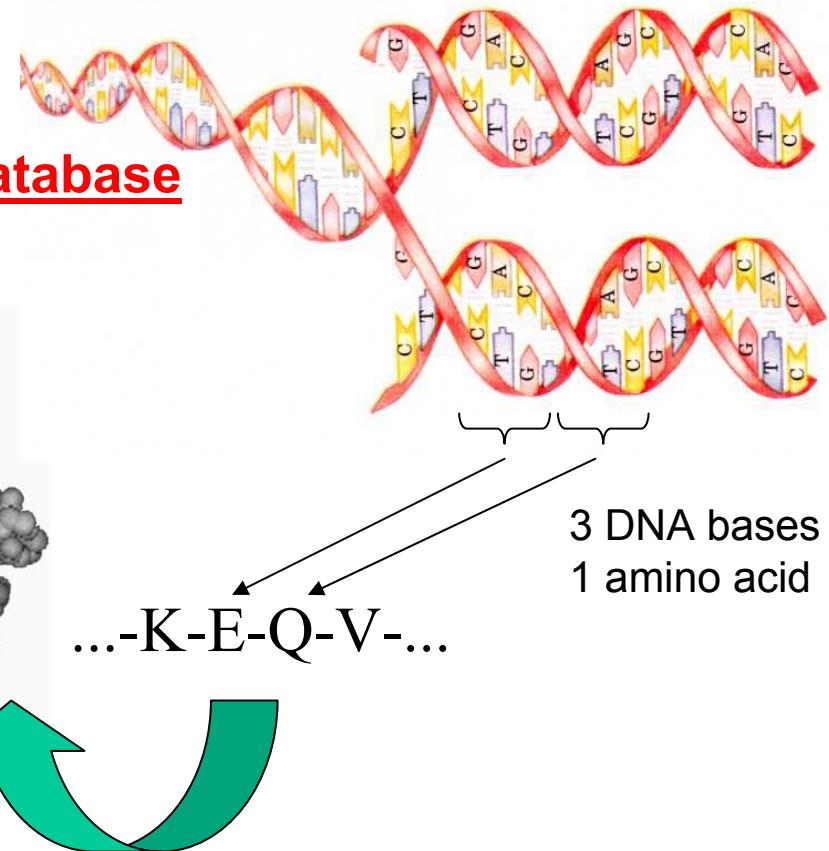
Contents

- Genomics, Proteomics
- Mass Spectrometry
- Cryodetectors in Mass Spectrometry
- Status and Applications
- Outlook

Genomics and Proteomics

Genomics:

- DNA base sequence in Genome **Database**



Proteomics:

- Protein amino acid sequence in Protein **Database**

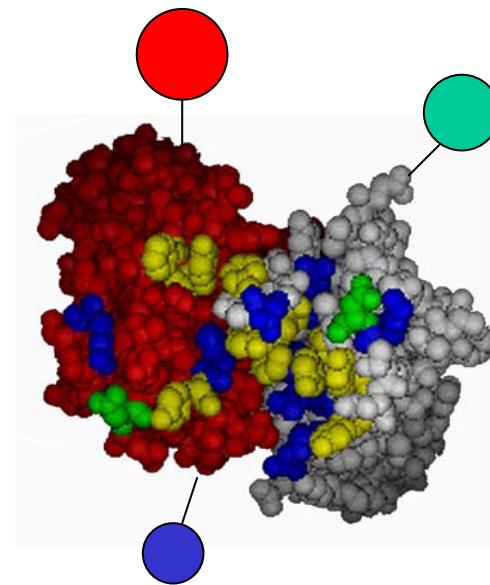
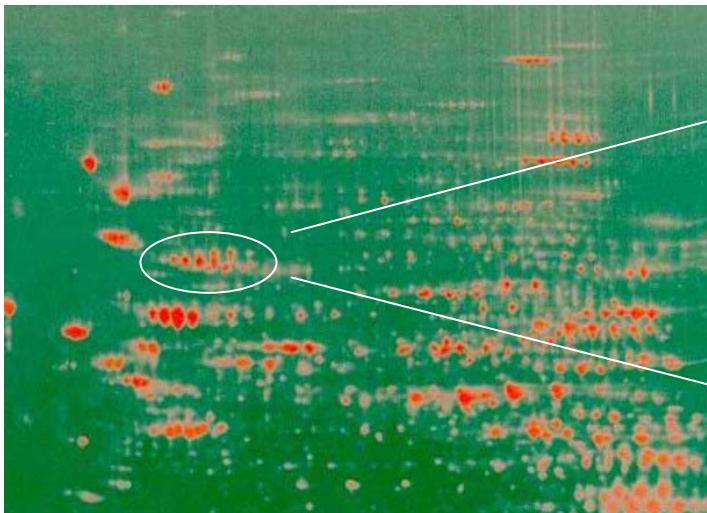
Proteomics: Reality is more complicated

2D-gel



iso-electrical point

apparent mass



in complex biological systems:
1 gene \Rightarrow 10 proteins



post-translational modifications:
(glycosylation, phosphorylation, ...)

Goal of Genomics and Proteomics

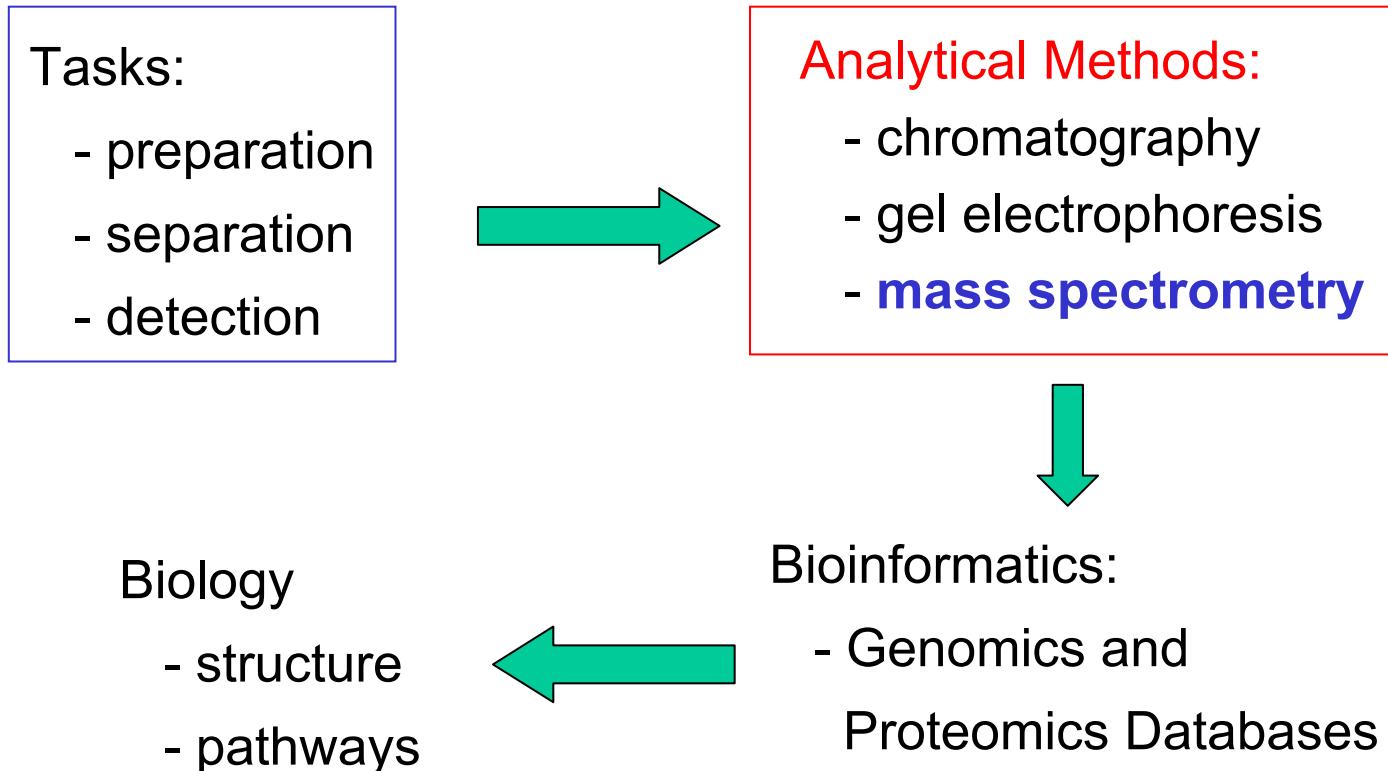
What do biologists want ?

("biologist" = molecular biologists, biochemists, protein chemists, real biologists, **pharmaceutical** drug discoverers)

- identify proteins:
 - ⇒ (partially) sequence primary structure and look up genomic and protein **databases**
- characterize proteins:
 - ⇒ analyze biologically relevant modifications
- look for protein complexes and networks:
 - ⇒ goal: **biological function (new drug!)**

Analytical Instrumentation in Life Sciences

ingredients: proteins, DNA, sugars, salts, fluids, ...
⇒ very complex mixtures

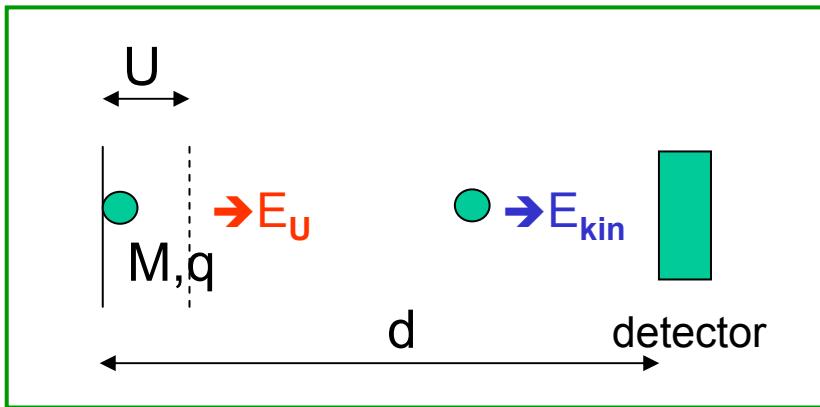


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Time-of-Flight Mass Spectrometry

TOF principle: separation according to velocity of molecules

⇒ accelerating molecules to energy: $E_U = q U$



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

$$E_U = E_{\text{kin}} \Rightarrow tof = d \sqrt{\frac{M}{2qU}}$$

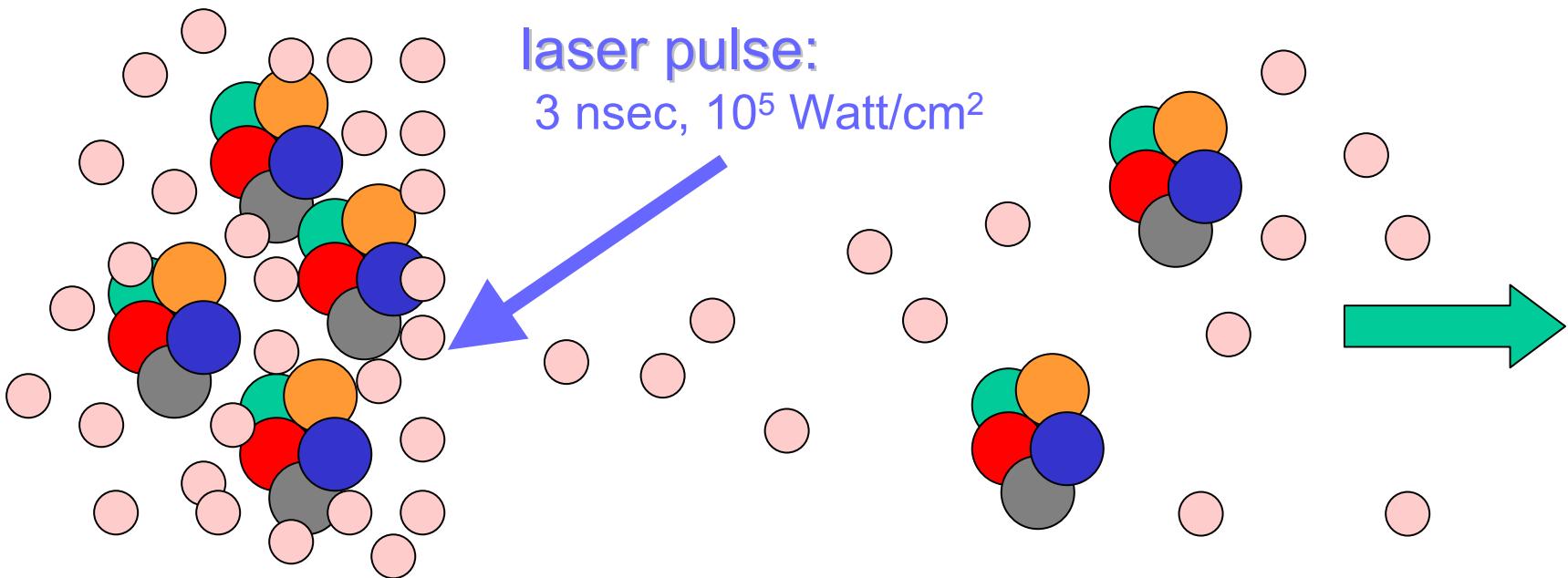
NOTE: energy of molecule: $E_U = q U$ (no mass term !)

MALDI Molecule Launch

MALDI: Matrix Assisted Laser Depletion & Ionization

biomolecules embedded in laser light sensitive matrix

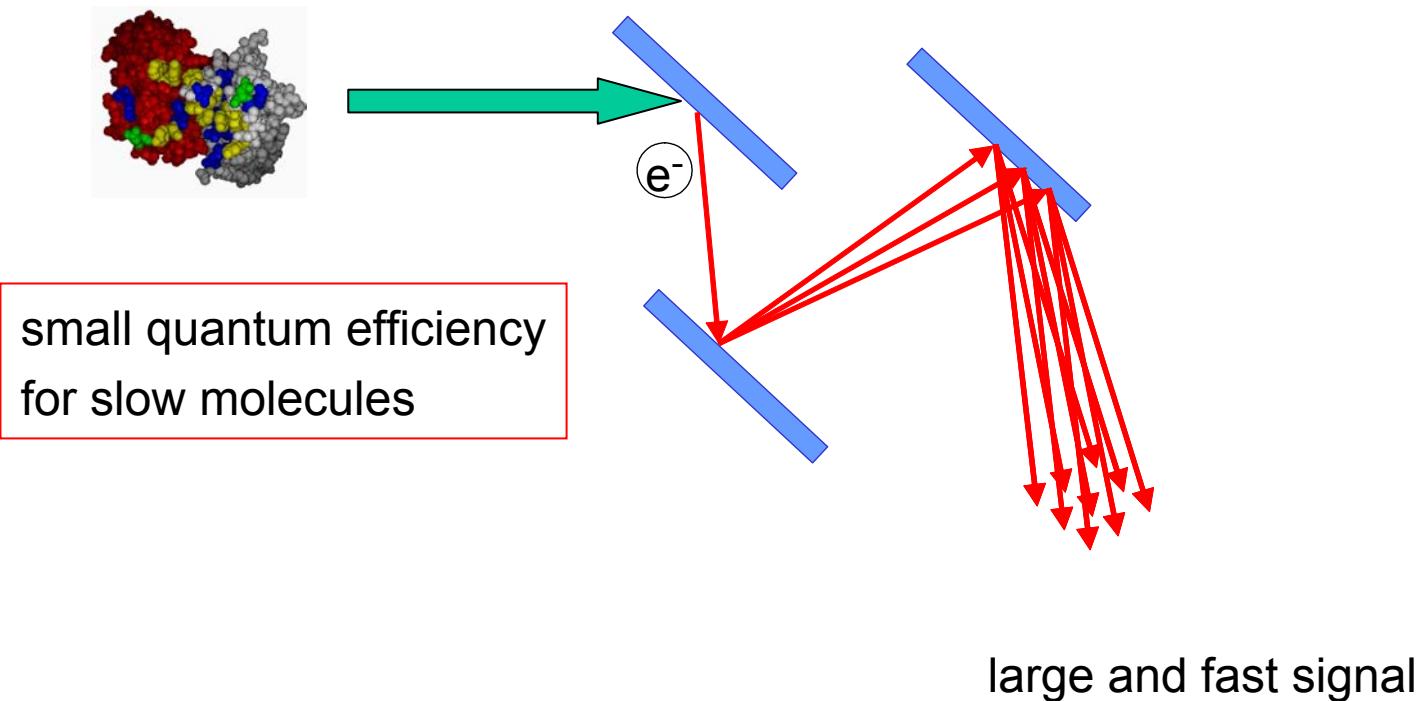
- laser energy absorbed by matrix
- “mechanical” momentum transfer of matrix molecules to the massive biomolecules



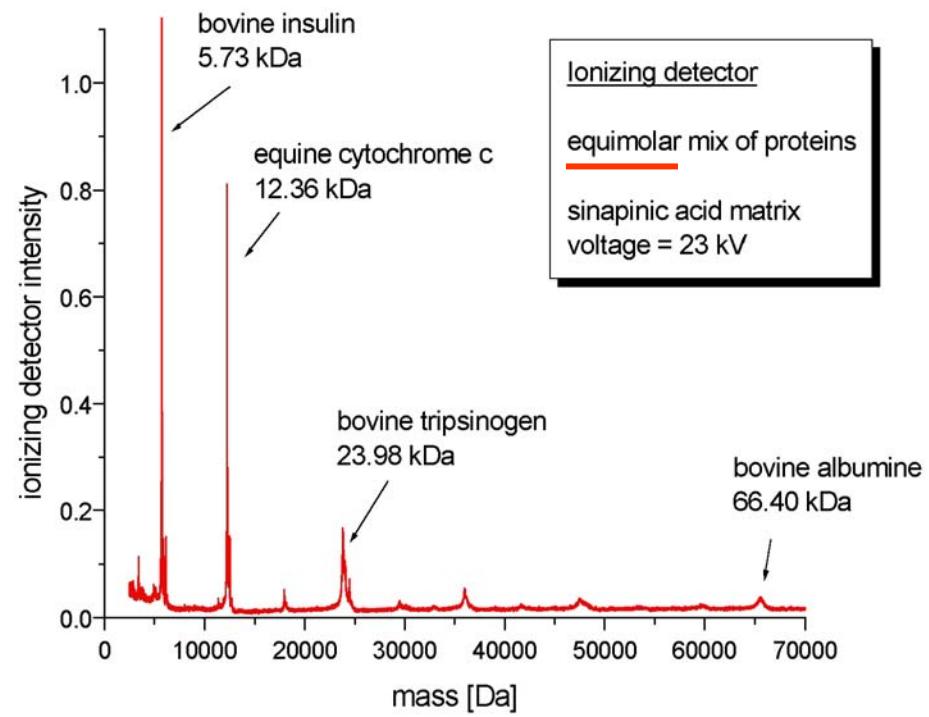
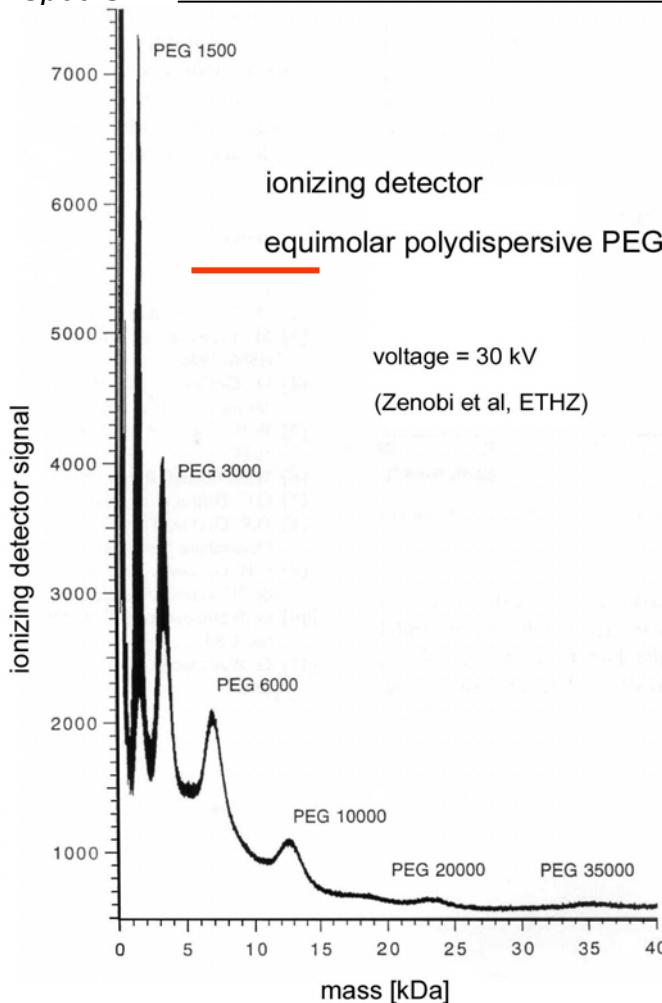
Standard Ionizing Detectors

Ionizing Detectors:

detection mechanism: emission of secondary electrons from surface



Ionizing Detector Problem: Efficiency



decrease of intensity:

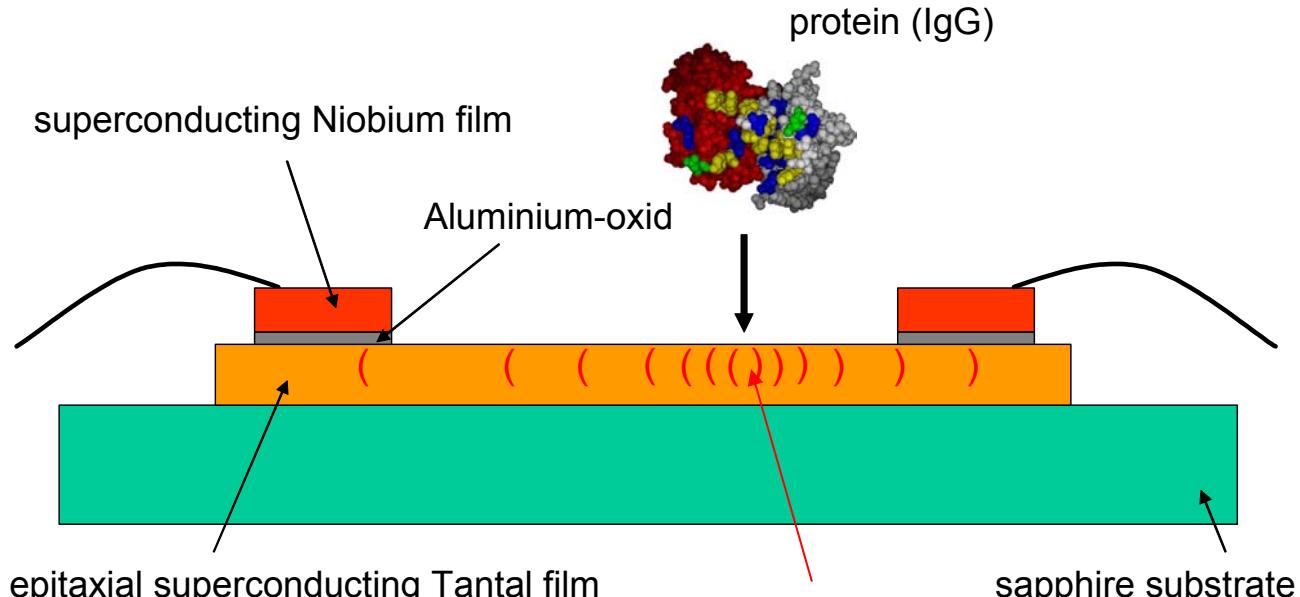
- molecule launch ?
- ionization ?
- ion transmission ?
- detector sensitivity ?

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Molecule Detection with Cryodetectors

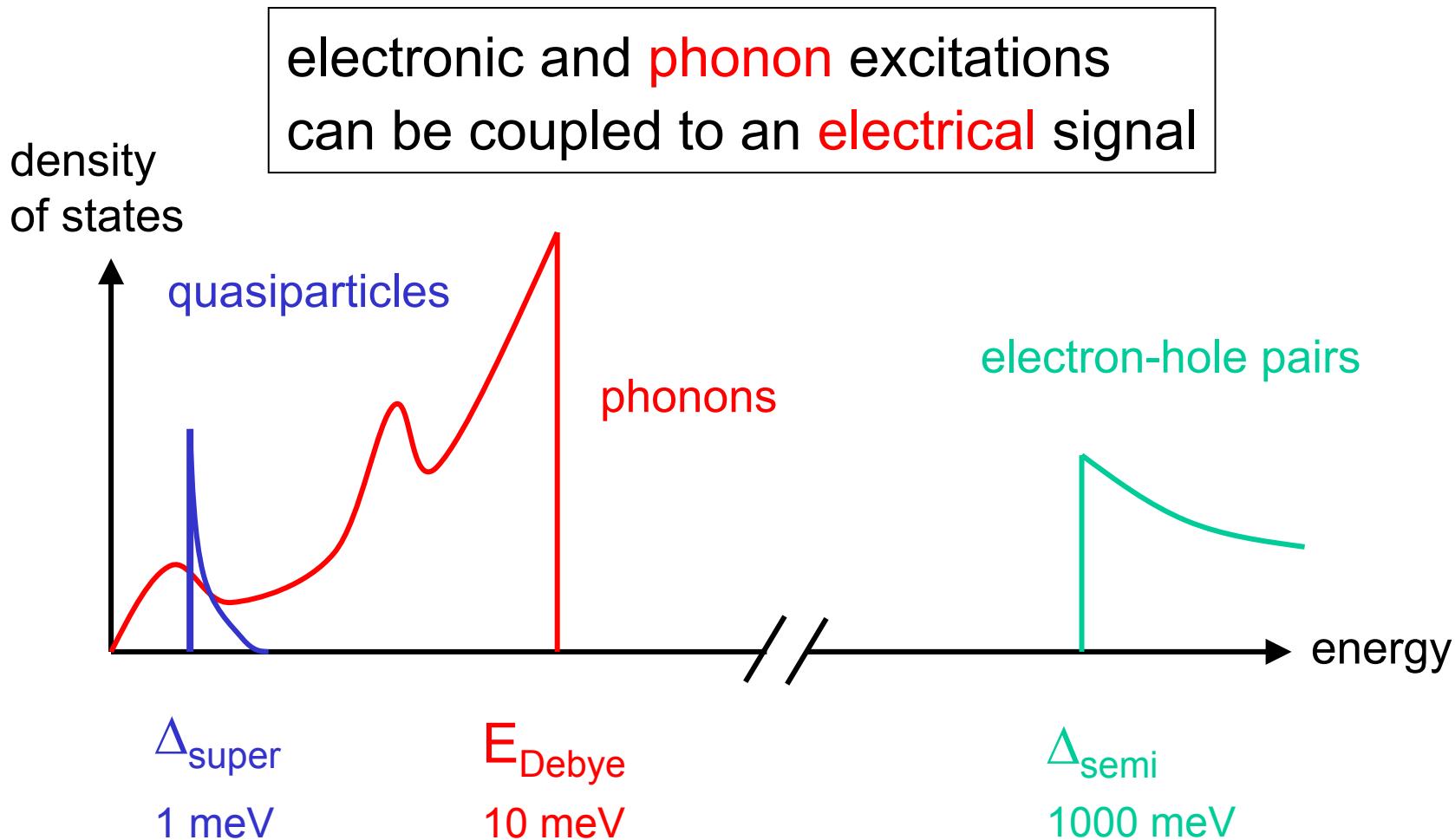
Cryogenic Particle Detectors:

detection mechanism: internal energy excitations (meV)



molecule impact energy deposition \Rightarrow excess quasiparticles

Fundamentals of Calorimetric Detection



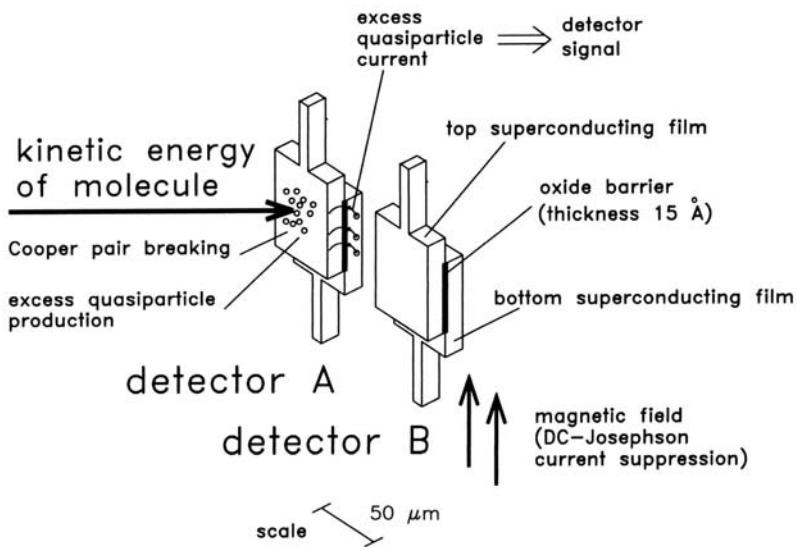
History of Cryodetectors in Mass Spectrometry

- Neuchâtel 1996
 - Sn-junctions
 - **proof: basic principle**
- Lawrence Livermore/ Lawrence Berkeley 1996
 - Nb-junctions
 - **proof: detector sensitivity 1000 times larger**
- NIST Boulder / Neuchâtel 1997
 - microcalorimeter
 - **proof: charge deconvolution**

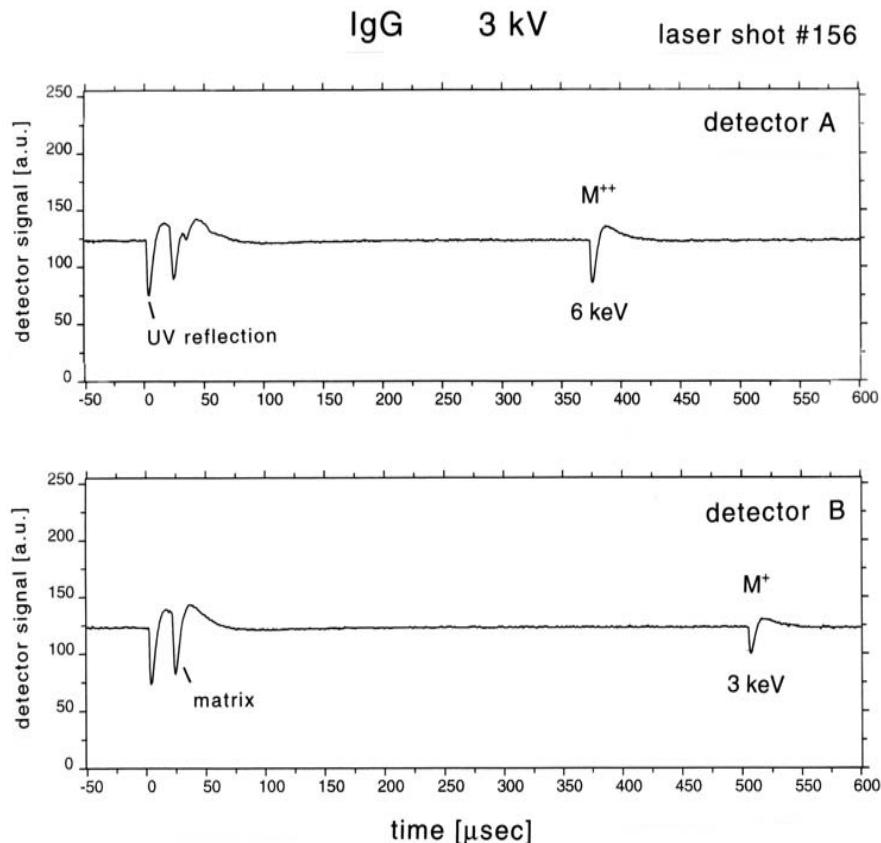
First Results: STJ

Neuchâtel (1996)

50 μm x 50 μm
Sn-STJ detector
operated at 300 mK



mass IgG = 150'000 Da (antibody)

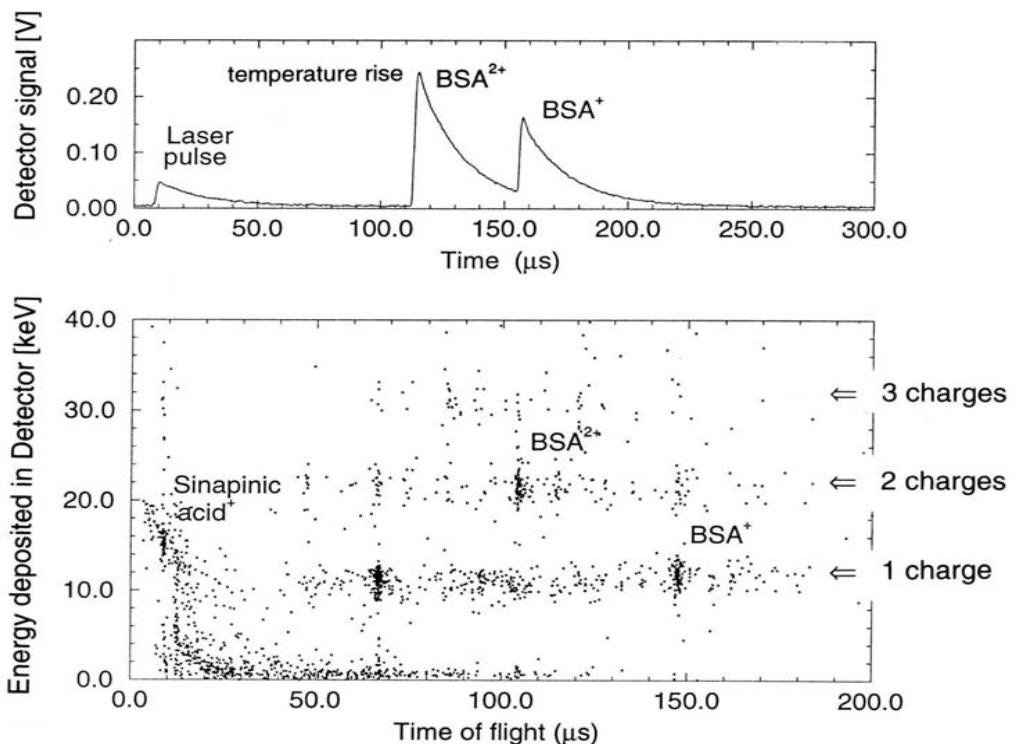
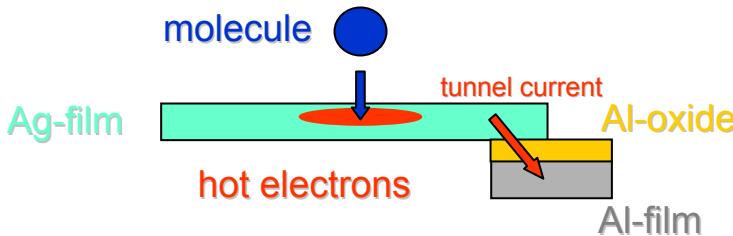


Microcalorimeter

collaboration (1998)

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

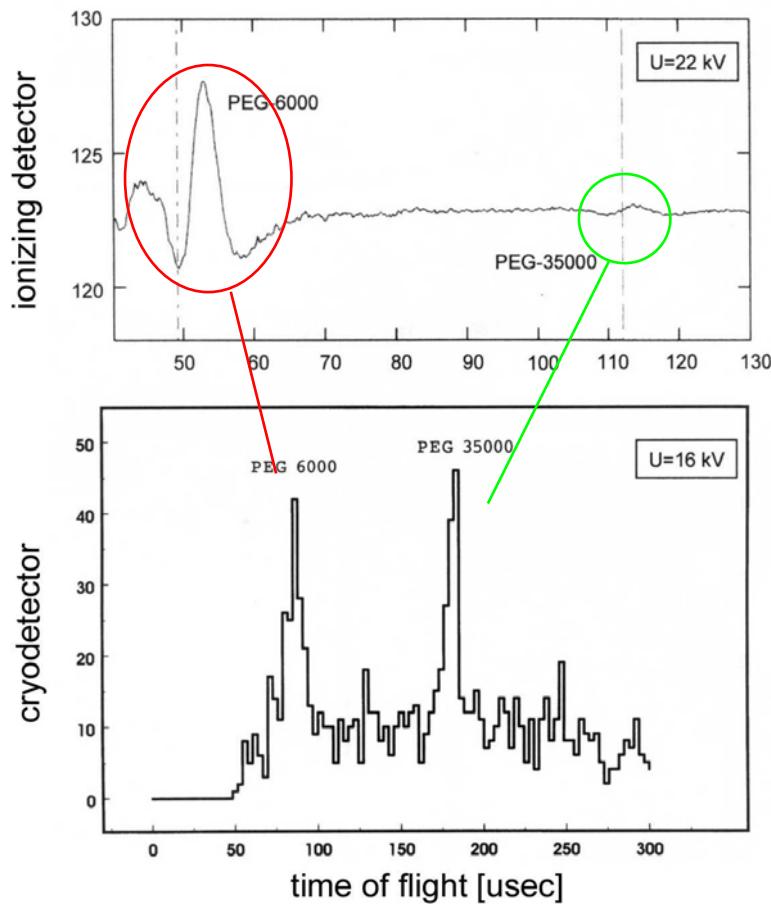
200 $\mu\text{m} \times 200 \mu\text{m}$
microcalorimeter
operated at 100 mK



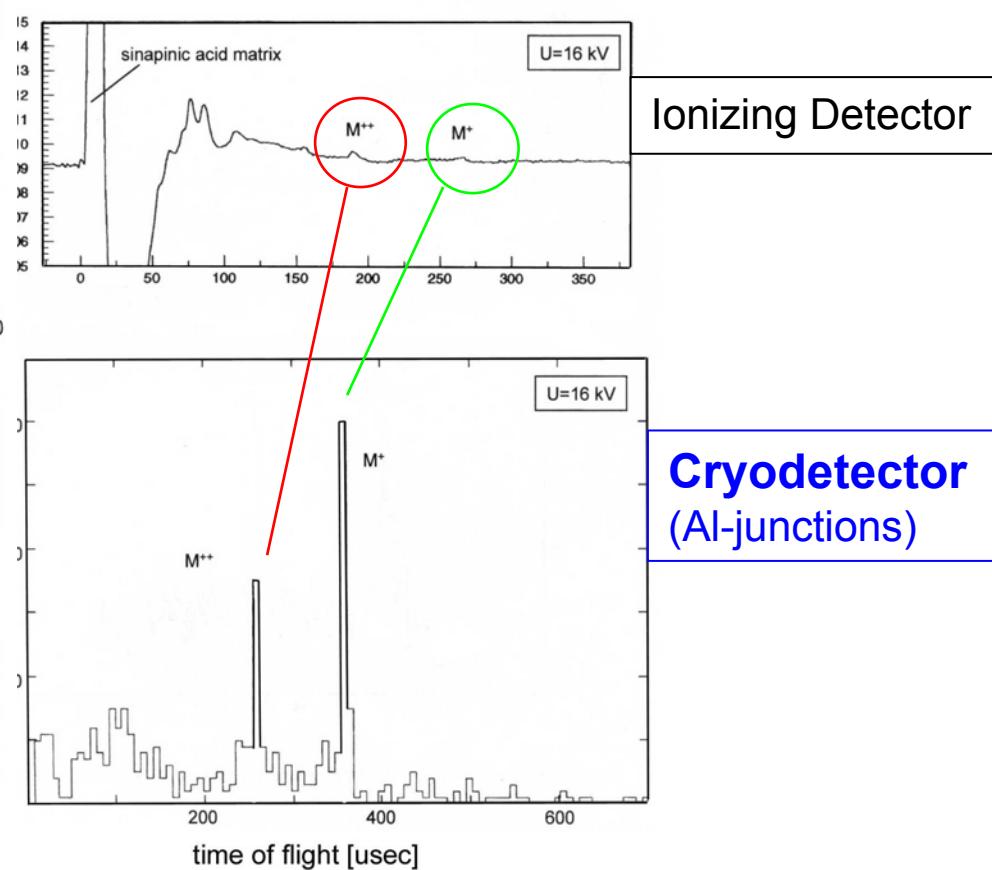
G.Hilton,J.M.Martinis,D.A.Wollmann,K.D.Irwin,L.L.Dulcie, D.Gerber,P.M.Gillevet & D.Twerenbold, Nature, Vol 391, page 672, 12.February 1998

Cryodetector versus Ionizing Detector

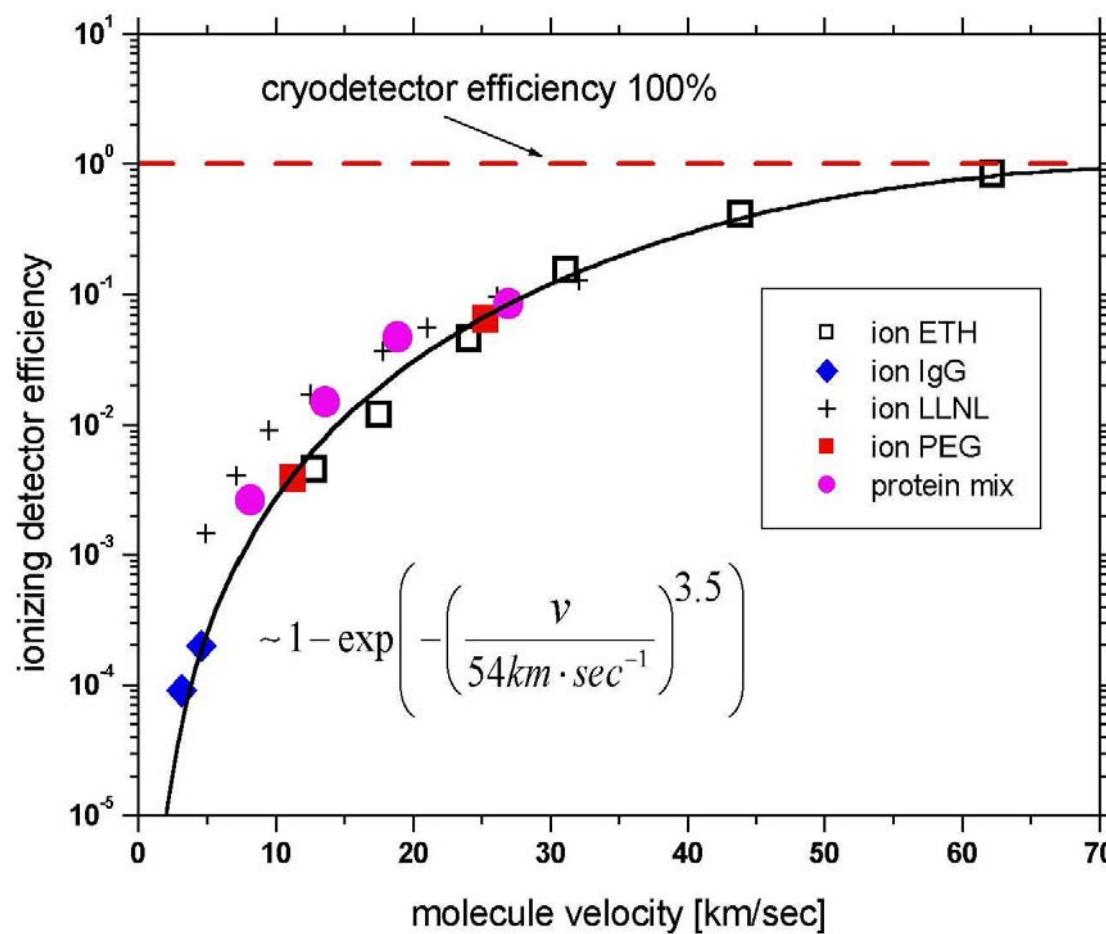
equimolar PEG sample:



IgG sample:

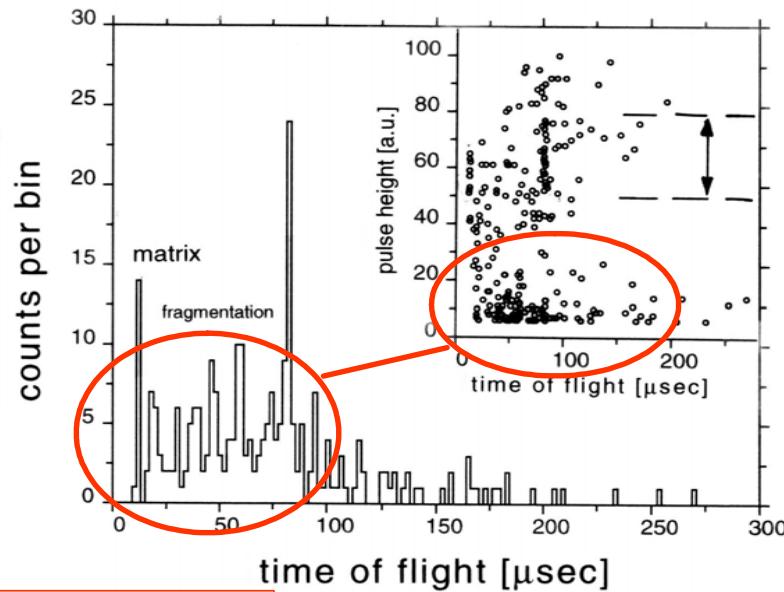


Cryodetector versus Ionizing Detector



Energy as additional information

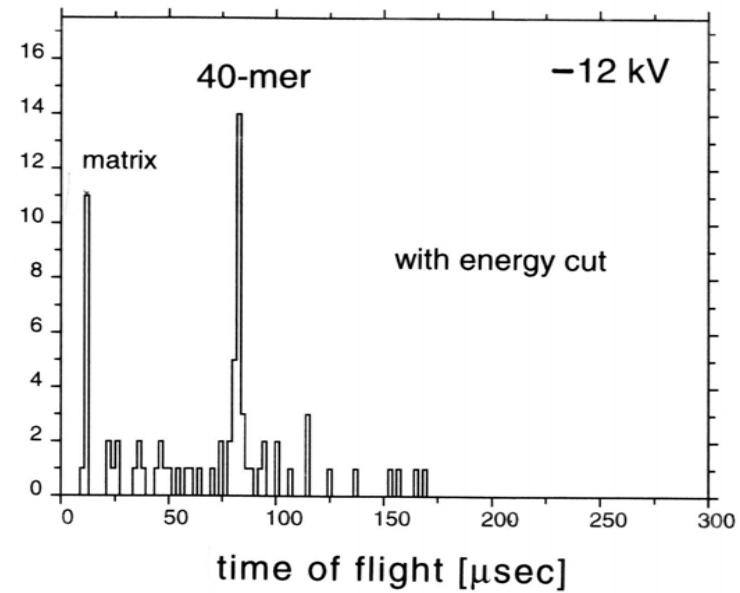
DNA 40-mer oligonucleotide time-of-flight spectrum



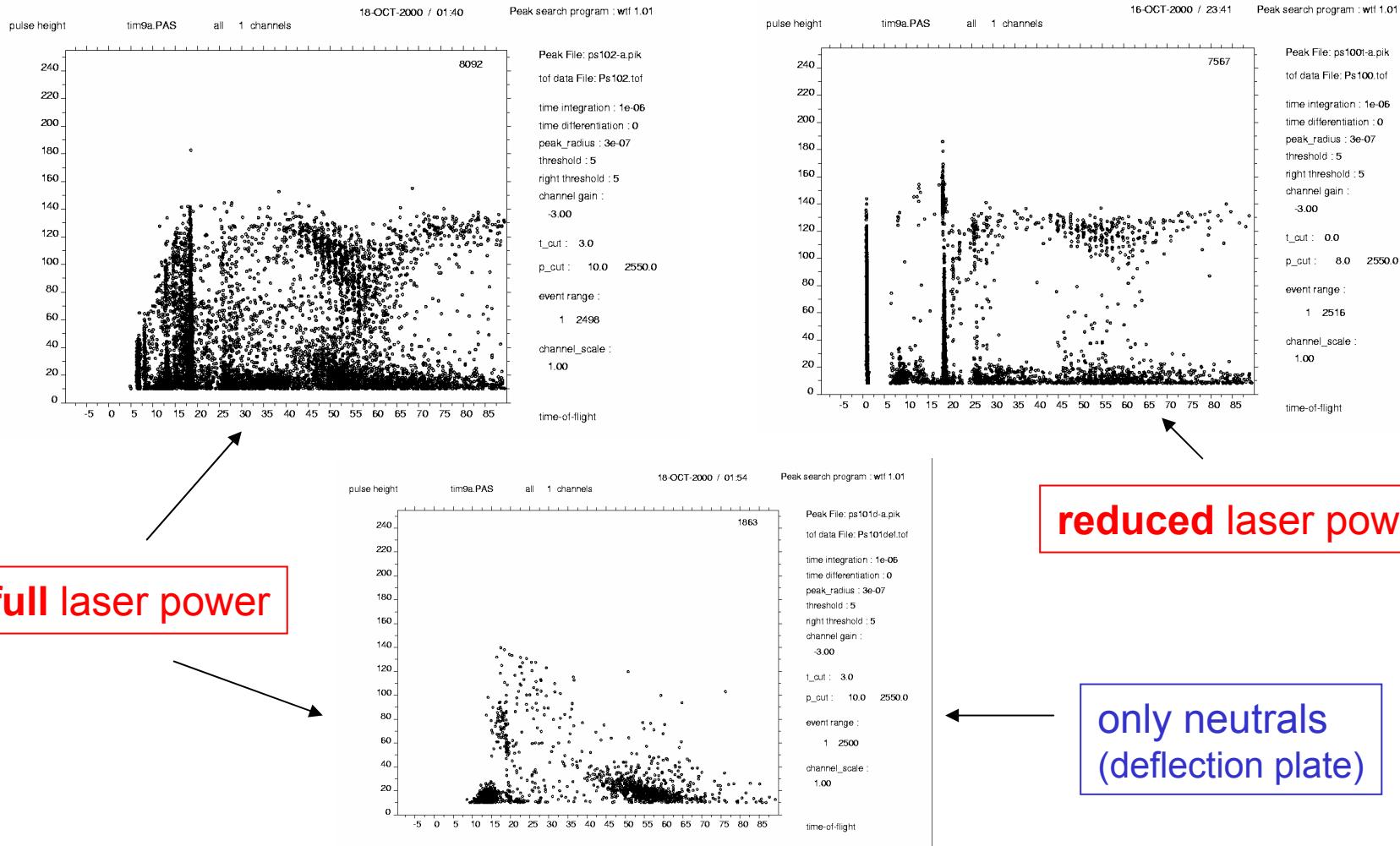
fragmentation

all pulses

only pulses with 12 ± 2 keV pulseheight
(same data set)



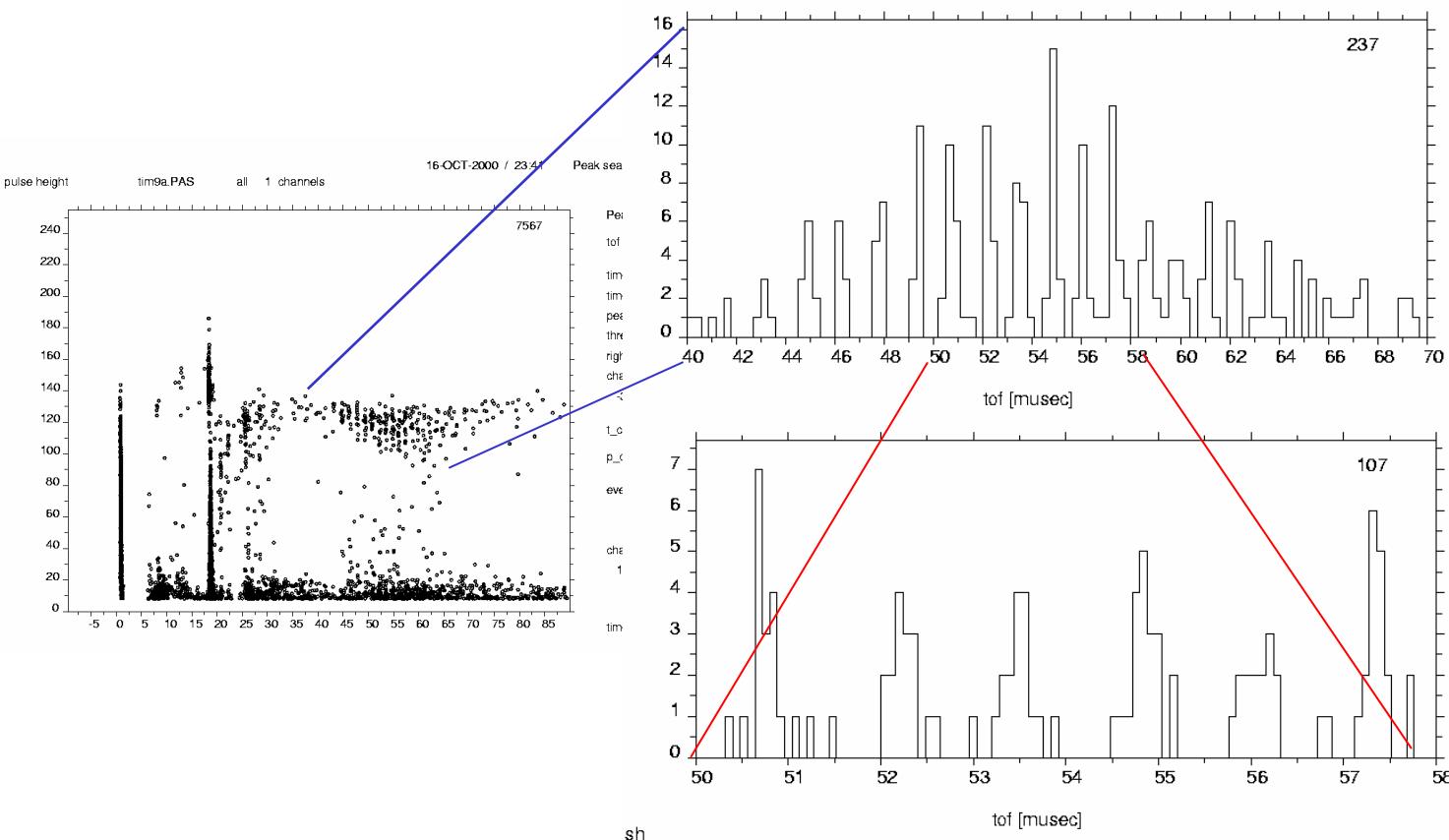
Polystyrene 2000: laser power



Polystyrene 2000

tof9a.PAS all 1 channels 17-OCT-2000 / 17:56

Peak search program : wtf 1.01



Peak File: ps100t-a.pik

tof data File: Ps100.tof

time integration : 1e-06

time differentiation : 0

peak_radius : 3e-07

threshold : 5

right threshold : 5

channel gain :

-3.00

t_cut : 5.0

p_cut : 80.0 150.0

event range :

1 2516

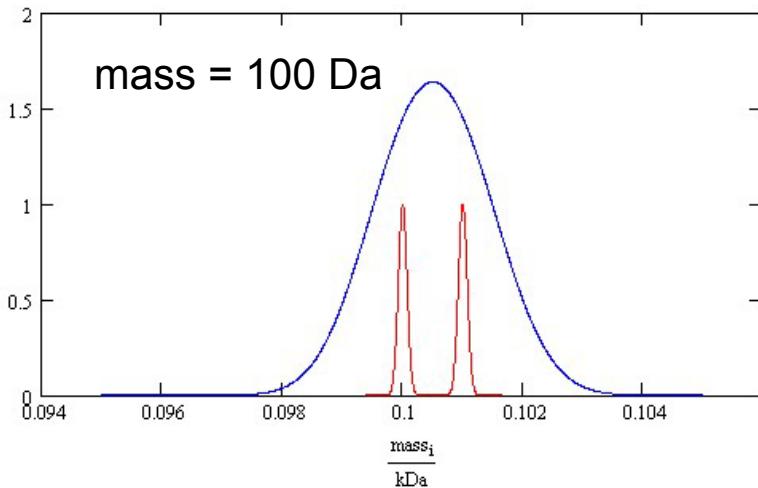
channel_scale :

1.00

nbin_pulse : 100

nbin_time : 100

Mass Resolution



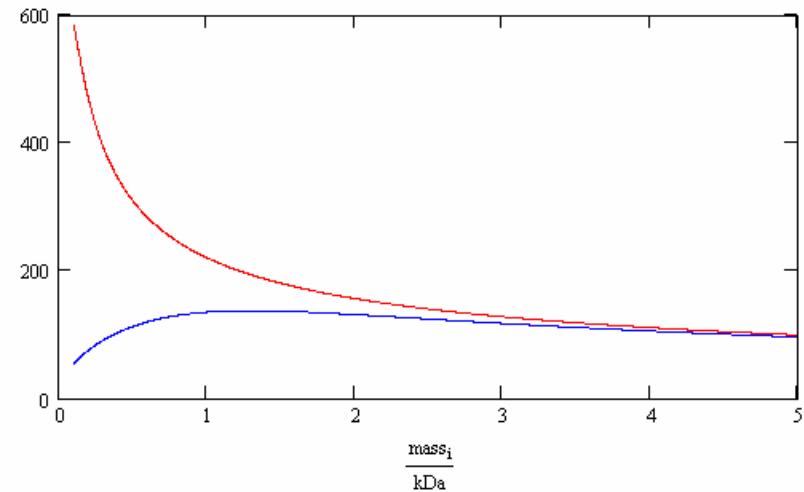
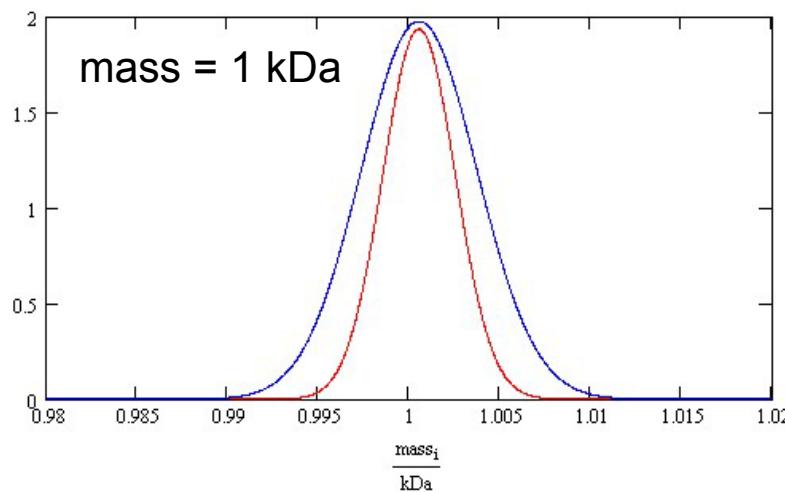
detector time resolution:

 $\Delta t = 10 \text{ nsec}$

 $\Delta t = 100 \text{ nsec}$

initial velocity dispersion:

$$\Delta v_0 = 100 \text{ m/sec}$$



Summary: Cryodetectors for MS

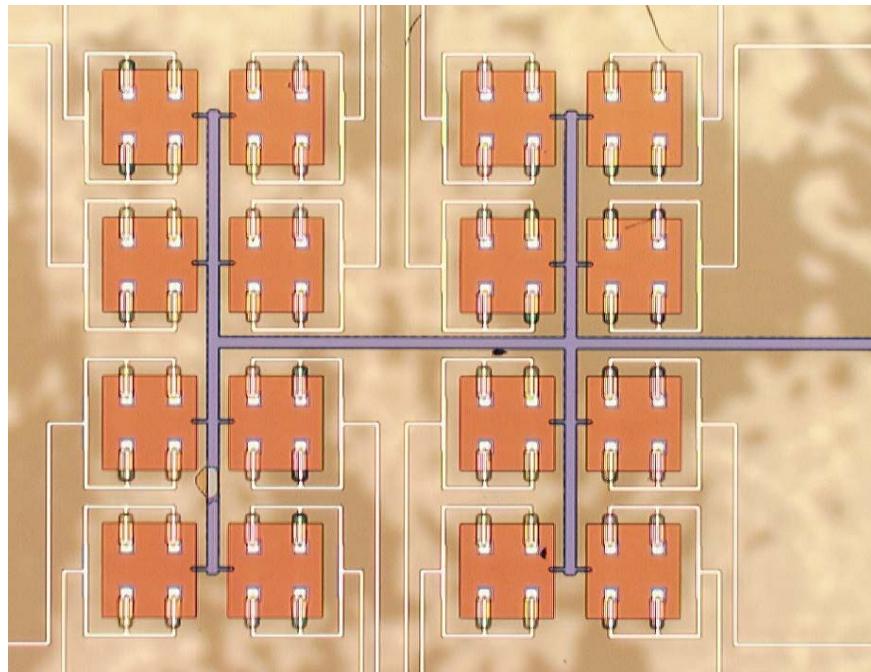
- pro:
 - mass **independent** detection sensitivity
 - high sensitivity for very **large** molecules
 - pulse height proportional to molecule **energy**
⇒ clean up mass spectrum
- contra:
 - **slow** signal (100 nsec)
⇒ low mass resolution at small mass molecules
 - total **overall** sensitivity is still small
⇒ small size of detectors

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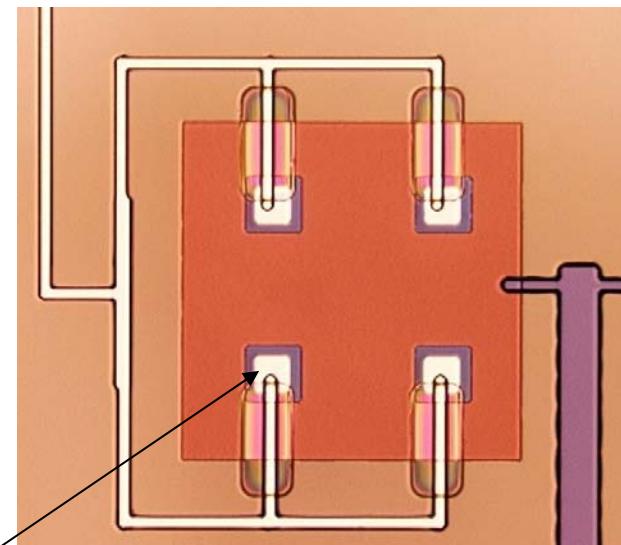
Requirements for Cryodetectors

- no high energy resolution required !
- robust with respect to temperature fluctuations
 ⇒ "molecules cannot go through thin windows"
- large area cryodetector (array technology)
- stable operation

PSI epi Ta STJ Detectors for Molecules



fabricated at
Paul Scherrer Institut



30 μm x 30 μm

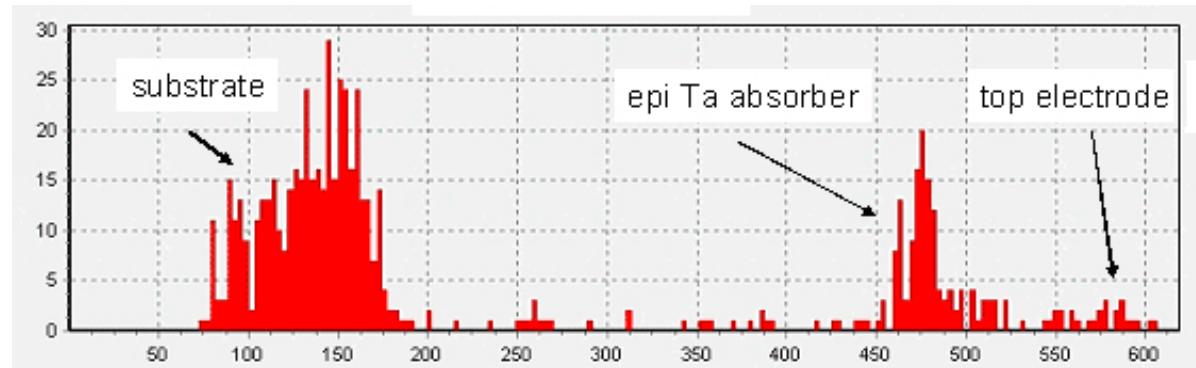
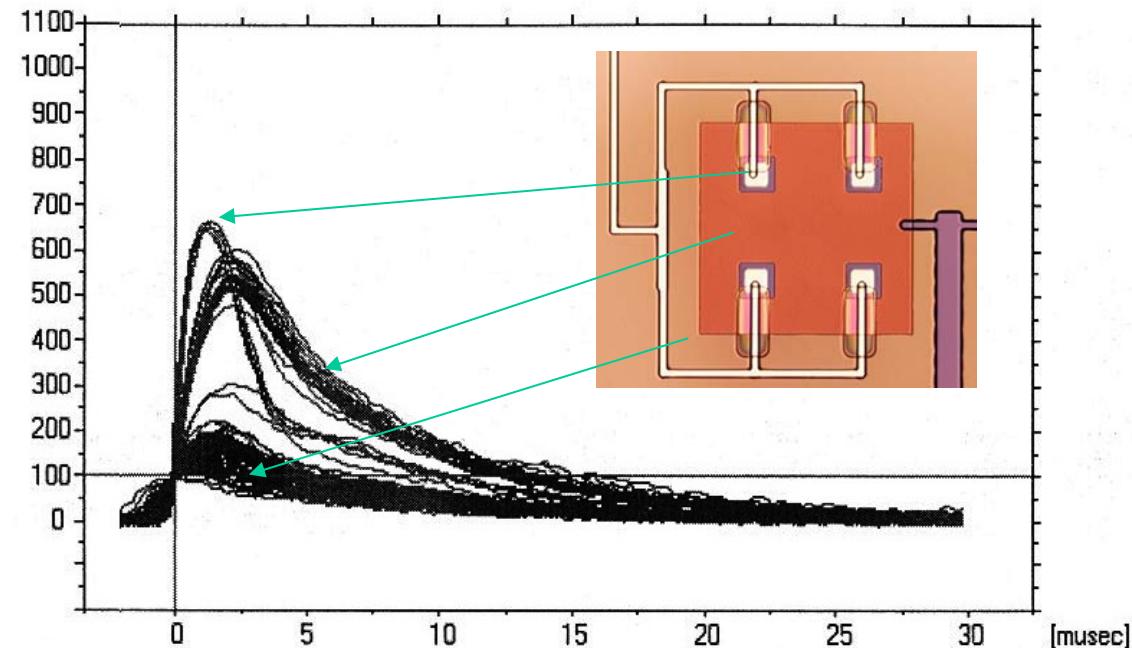
180 μm
epi Ta

Yale Voltage Biased Current Preamplifier

6 keV x-rays

$T_{\text{base}} = 0.32 \text{ K}$

$T_{\text{STJ}} \approx 0.6 \text{ K}$



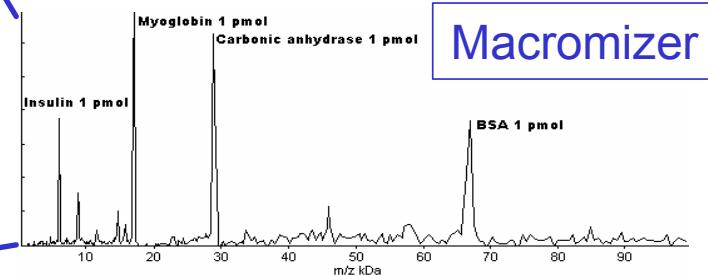
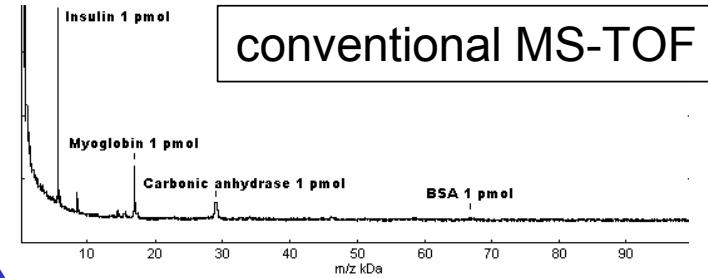
Requirements for an Instrument

- Instrument should be "biologist" friendly (= fool proof)
 ⇒ **cryogenfree** cryostat
- stable operation of cryodetectors (simple electronics)
- everything software controlled

Results with first Commercial Instrument

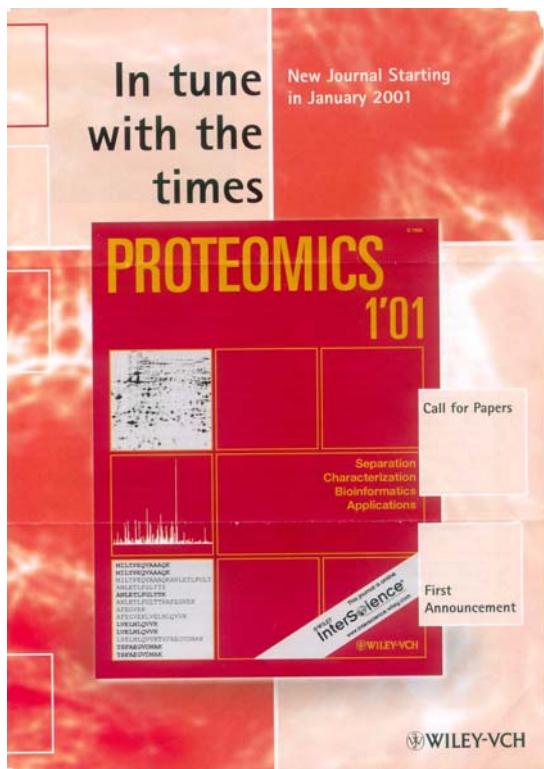


- Comet Analytics, Flamatt, Switzerland
- Product: Macromizer



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Life Science Community Reaction



- pro:
 - fascinated to see single molecules
 - mass independent detection
 - high sensitivity for very large molecules
- contra:
 - low mass resolution at small mass molecules
 - total sensitivity (small detectors)
- promising applications
 - protein complexes
 - glycobiology
 - biomarker discovery

Cryodetector Improvements

The Life Science User's wish list:

- large area detector \Rightarrow **1 cm²**
- fast detector response \Rightarrow **1 nsec**
- "high" operating temperature \Rightarrow **5 Kelvin**