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(To be published in Rapid Communications in Mass Spectrometry)

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Running title: A Faraday Cup Detector for High Mass Ions]

Abstract:

A detector has been developed, which collects and amplifies the electric charge of an incoming bunch of ions, for use in matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry The detector has a time-of-flight resolution of about 50ns and a noise level of 750 electrons rms. It has been tested in a Finnegan LaserMAT spectrometer with a number of samples which were expected to give reliable results in MALDI time-of-flight spectrometry. Clear mass peaks have been observed from samples with masses above 300kDa.

INTRODUCTION

The detection of heavy ions is a significant problem in matrix-assisted, laser desorption-ionisation time-of-flight mass spectrometry, which can produce singly-charged ions of several hundred kDa [1, 2]. Practical considerations limit the accelerating voltage to a few tens of kV and the efficiency of conventional detectors, such as secondary electron multipliers or microchannel plates, becomes very small for velocities below about 10^4 ms^{-1}, corresponding to a singly-charged 38 kDa ion with an energy of 20 kV.

In view of the need to detect very heavy ions with high efficiency it is natural to consider the use of a simple electrode to collect and measure the incoming electric charge directly. In what follows we will call such a detector a 'Faraday cup'.

A Faraday cup has been developed which has a time resolution of about 50 nS and a noise level, for the detection of an ion charge produced by a single laser pulse, of 750 ± 110 electrons rms.

EXPERIMENTAL DETAILS

Design considerations

An ion approaching a conducting plate connected to an external circuit causes a current I(t) to flow in the circuit, as charge of the same sign as that on the ion is repelled from the plate. Q, the charge on the ion, is related to I(t) by $Q = \int I(t)dt$. In order to reduce the duration of the current pulse it is necessary to shield the collector from the approaching ion with a fine mesh grid. In the

present detector an electroformed stainless-steel mesh with a transparency of 90% was placed about 0.4 mm in front of the collector, which was simply a 30 mm-diameter aluminium disc.

The signal was amplified by a low-noise, charge-sensitive preamplifier, followed by a shaping amplifier. The preamplifier was an *eV Products*, eV5093, JFET-input hybrid preamplifier [3], which has an integrating capacitance of 0.47pF and a feedback resistance 1 GΩ. The rise time with a 2 pF source capacitance is specified to be 60 ns. The noise performance is quoted by the manufacturer to be 150 electrons rms, with C_{source} = 0 pF and amplifier shaping time constants (rise and fall times) of 1.5 μs. The noise slope is 1.4 e^- /pF. The output pulse from the preamplifier with a delta function charge input is therefore expected to have a risetime of about 60 ns, an exponential decay, with a time constant of about 470 μs, and an amplitude of 0.35Q μV, where Q is the input charge in electrons. In the Faraday cup detector the risetime is degraded by the input capacitance of about 10 pF, and by the intrinsic risetime of the charge pulse, corresponding to the transit time between grid and collector, which may be as long as 250 ns for a 20 kV singly-charged 1 MDa ion. When a charge pulse a few ns in duration was applied to the Faraday cup detector the rise time of the preamplifier output pulse was observed to be of the order of 100 ns, the fall time was 270 μs and the conversion gain was measured to be (0.50 ± 0.05) μV per electron.

The output from such a preamplifier connected to Faraday cup installed in a MALDI time of flight mass spectrometer is, in general, a series of steps each followed by a portion of an exponential decay. Since the maximum time of flight expected in the spectrometer is of the order of 300μs, the ion signal comprises an ascending staircase with relatively little decay on each step. In principle, the preamplifier signal could be buffered to an ADC and digitised

directly, maximising the information in the recorded signal and enabling it to be filtered off-line. However, the laser pulse produces a large number of low-mass matrix ions, which give rise to a large charge signal at short times of flight. This must not saturate the preamplifier, (or if it does the preamplifier must recover rapidly from saturation). In addition, the signals of interest comprise relatively small steps on a large DC signal and have limited precision when digitised. As a result of these considerations the preamplifier pulse was differentiated and shaped by a main amplifier before being digitised.

The shaping amplifier was designed and its performance modelled extensively using the PSPICE [4] simulation routine. The choice of low- and high-frequency cut-offs for the shaping amplifier was a compromise between a number of requirements. Minimising the noise implies minimising the bandwidth. On the other hand, the rise time must be sufficiently short to obtain the best possible mass resolution. The differentiation time constant must be short enough to allow the amplifier to recover rapidly after an overload, but should, ideally, be longer than the rise time of the slowest charge pulse to be detected by the system. With a 0.4 mm gap between mesh and collector, a 20 kV, 1 MDa singly-charged ion will produce a charge pulse that rises linearly from the baseline to its maximum value in about 200 ns. In practice, due to the marked velocity spread associated with ions produced by MALDI, a bunch of 20 keV, 1 MDa ions will be spread out appreciably after a flight path of 0.6 m, with the result that the rise time of the corresponding charge signal may be longer than 1 μs. It is also useful to incorporate pole zero compensation, in order to minimise long pulse tails, which contribute to baseline fluctuations and make the observation of small signals unreliable.

The time constants selected for the final amplifier design resulted in an amplifier output pulse, in response to a short charge pulse injected into the preamplifier, with a rise time of 100 ns, (10 - 90%), and a fall time of 0.7 μs. Figure 1 shows the output pulse from the amplifier when a short charge pulse containing just under 10^5 electrons was injected into the Faraday cup. The output pulse amplitude is 0.32 V; the overall charge/voltage conversion gain is 3.4 μV per electron. Figure 2 shows the output signal when a pulse containing 8000 electrons was injected and illustrates the effect of system noise when the signal/noise ratio is 10:1. In principle, if the noise is uncorrelated from one laser pulse to the next, the signal/noise ratio may be improved by superimposing time spectra from several successive laser pulses. Superimposing ten laser pulses should, in principle, reduce the noise by a factor of $\sqrt{10}$, to about 250 electrons rms, with the result that a signal/noise ratio of 10:1 should be obtained with a sample that, on average, produces only 250 electron charges per laser pulse.

Detector bench tests

The detector was tested by injecting a known charge on to the collector plate, by applying a small voltage step to one terminal of a 2.2 pF capacitor whose other terminal was attached to the collector plate. Initially, the amplifier output pulse was viewed on a digital oscilloscope in order to measure the gain and linearity. The system was linear, with no detectable variation in output pulse shape, for input charges up to 0.4×10^6 electrons. The output of the amplifier was connected to the input of an EG&G Spectrum 2k ACE ADC card plugged into an IBM PC clone, running Maestro II pulse height analysis software [5]. Pulse height spectra were obtained with a variety of step voltage inputs to the preamplifier, from 5 mV (corresponding to an input signal of

about 7 x 10^4 electrons), to 30 mV. The full width at half maximum, FWHM, of each spectrum was determined and, as expected, was found to be independent of the input signal amplitude. The average value of the FWHM was 1.05 ± 0.10 channels, and the corresponding rms noise was inferred to be 0.45 ± 0.04 channels, assuming Gaussian-shaped peaks. The input signal for each measurement was converted to electrons, enabling the ADC channel number to be calibrated in terms of electrons, and the rms noise evaluated in electrons, see Figure 3. The result for the rms noise referred to the preamplifier input was 750 ± 110 electrons, where the error is dominated by the uncertainty in the value of the 2.2 pF capacitor.

Performance in MALDI Time-of-Flight Mass Spectrometry

The complete detector was installed in a Finnigan LaserMAT time-of-flight mass spectrometer. Initially, large spurious signals were observed from switched mode power supplies and the turbomolecular pump, but with careful supply line decoupling and shielding this was reduced substantially, but not completely eliminated, with the result that the amplifier output still contained sharp noise spikes at the 1000-electron level. The pulse of low-mass matrix ions initially swamped the later heavy ion signals, but was substantially reduced by biasing the grid by a few volts relative to the collector plate. Both positive and negative biases reduced the duration of the matrix peak, presumably by sweeping away secondary electrons and negative and positive ions produced by primary ion impact, but too large a negative bias resulted in the appearance of a large negative overshoot on the matrix signal. The most natural explanation for this effect is the repulsion back to the detector plate of low energy negative ions, which are known to be produced efficiently by primary ions, but it could also be due to the ejection

of electrons from the grid by positive secondaries. The detector was operated with the grid biased at +3.5 V relative to the collector, which effectively suppressed the matrix signal without producing a negative overshoot.

The detector was tested with a variety of samples, which were expected to give reliable results in MALDI time-of-flight spectrometry - bovine insulin, (5.7 kDa), myoglobin (17 kDa), bovine serum albumen (BSA, 66.4 kDa), soluble complement receptor (SCR1, 245 kDa), and fibrinogen L (330 kDa). No effort was made to optimise the analyte/matrix ratio in order to improve the spectra, although this is one of the keys to obtaining good mass spectra from massive ions [2], but for each analyte the laser power was adjusted to obtain the best signal/noise ratio.

Measurements were made of sensitivity and pulse shape with all available samples. Figure 4 shows a typical measurement with BSA. The matrix signal dominates at low masses, and five high-mass peaks are observed, corresponding to the singly-charged monomer and dimer together with multiply-charged species. Expanding the vertical scale and truncating the spectrum at a mass of 10 kDa shows the high-mass peaks in greater detail, see figure 5. The vertical scale corresponds to about 4500 electrons per division. As a result of averaging ten laser pulses the intrinsic amplifier noise in figure 5 is about 0.2 division peak-to-peak and the pick-up from switched-mode power supplies accounts for the remainder of the noise signal. The 66.4 kDa peak contains about 95,000 electron charges, implying the production of just under 10,000 singly-charged ions per laser pulse, on average.

With SCR1, again summing ten laser pulses, signals are observed at 82 kDa, 122 kDa and 240 kDa, corresponding to MH_3^{3+}, MH_2^{2+} and MH^+ ions, see figure 6. The signal to noise ratio is significantly worse for this sample than

for BSA; the signal at 240 kDa has $\Delta t/t \sim 0.03$, corresponding to a mass resolution of approimately 6 kDa. There are at least 2000 singly-charged ions produced per laser pulse. The peak is noticeably skew, indicating substantial time of flight spreading.

With ten superimposed laser pulses on a fibrinogen L sample, figure 7, peaks were observed at 293 and 149 kDa, with some higher-mass peaks barely resolvable above the noise. Both clear peaks are broad and the low mass peak may be a partially-resolved double peak. The width of the 293 kDa peak implies a mass resolution of about 20 kDa. The average number of singly-charged ions per laser pulse was at least 500.

The FWHM, Δt, of prominent peaks in the time spectra have been measured and the fractional spread in the time measurement $\Delta t/t$, plotted as a function of t, see figure 8. The Fibrinogen data have been excluded from this analysis because both peaks appear anomalously wide.

If an ion pulse arrives instantaneously at the Faraday cup the time spectrum should have the same shape as the amplifier output pulse with a delta function input charge, and its FWHM should therefore be 0.6 µs. In the real case, the pulse is broadened due to the flight time of ions across the grid-collector gap. For massive ions the appreciable velocity spread introduced by MALDI [6] should also be taken into account. As a result $\Delta t/t$ may be written:

$$\Delta t/t = a + b/t + ct^2$$

where $a = 0.0042$, $b = 0.6$, $c = 6.25 \times 10^{-7}$ and t is in µs. In order to derive this result MALDI-produced heavy ions are assumed to have a Gaussian-shaped longitudinal velocity profile [6], with a mean of 750 ms^{-1} and a FWHM of 300 ms^{-1}. Figure 8 compares the expected and observed behaviour of $\Delta t/t$. The data and model show a similar trend, but $\Delta t/t$ is larger than expected. The

source of this discrepancy, which could be accounted for by a fixed contribution to $\Delta t/t$ of about 1% across the mass range, is still to be understood.

DISCUSSION

A Faraday cup detector has been developed, which extends the mass limit for the detection of heavy ions in laser-assisted time-of-flight mass spectrometry, and which has potential for further significant improvement. A similar detector has been evaluated by Lautz, Bahr, Rohling and Hillenkamp [7] with masses up to 66 kDa (BSA). Their detector is less sensitive - the rms noise is about 9000 electrons - but has a faster response (tr ≈ 25 ns) and therefore, potentially, a better mass resolution, although for massive ions time-of-flight spreading is likely to be the dominant contributor to the mass resolution. The output pulse produced by a Faraday cup detector lengthens in proportion to $\sqrt{m}$ at constant accelerating potential, and is also reduced by time-of-flight spreading, so that detecting and timing the charge signal becomes more difficult for high mass ions, but in principle the technique will work with ions of any mass. The Faraday cup detector should therefore be developed further in order fully to explore its limits.

Recently, other authors have reported work on inductive detectors as replacements for microchannel plates [8]. The inductive detector is reported to be not as sensitive to saturation by light ions as the Faraday cup, to be less velocity dependent and, in principle, not to destroy the detected ions. In practice, about 30 % of the ions are destroyed by detector grids, and operation has only been demonstrated with relatively light ions.

References

1. See, for example, F. Hillenkamp, *Adv. Mass Spectrom.* **11A** 354 (1989).

2. R. W. Nelson, D. Dogruel and P. Williams, *Rapid Commun. Mass Spectrom.* 9 625 (1995).

3. eV Products, 375 Saxonberg Blvd., Saxonberg, Pennsylvania 16056, USA.

4. SPICE: Simulation Program with Integrated Circuit Emphasis. PSPICE is commercial software for the PC or Macintosh developed by MicroSim Corporation, 20 Fairbanks, Irvine, CA 92718, USA.

5. EG&G Ortec, Sorbus House, Mulberry Business Park, Wokingham, Berkshire, RG11 2GY, UK.

6. R. C. Beavis and B. T. Chait, *Chemical Physics Letters* **181** 479 (1991).

7. C. Lautz, U. Bahr, U. Rohling and F. Hillenkamp, Poster presented at the International Mass Spectrometry Conference, Budapest (1994).

8. M. A. Park and J. H. Callahan, *Rapid Commun. Mass Spectrom.* 8 317 (1994).

Figure Captions

1. Output pulse from the Faraday cup detector (lower trace) when a short pulse of just under 10^5 electrons was injected into the cup, by applying a 7mV step voltage to one terminal of a 2.2 pF capacitor whose other terminal was connected to the cup (upper trace).

2. Output pulse from the Faraday cup detector when an input signal of 8000 electrons was injected. The system noise was approximately 800 electrons rms.

3. Linearity of the Faraday cup detector. Abscissa: injected charge signal in electrons. Ordinate: ADC channels. The system noise broadens the narrow peak produced by injecting a known constant charge. The mean full width at half maximum of the calibration peaks was 1.05 ± 0.10 channels, corresponding to a system noise of 750 ± 110 electrons rms.

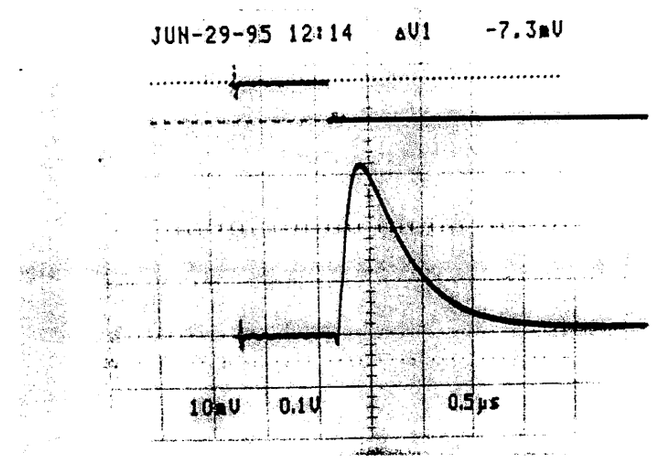
4. Mass spectrum observed from a sample of BSA (66.4 kDa), using the Faraday cup detector in a LaserMAT MALDI time-of-flight mass spectrometer. Note the low-mass peak due to matrix ions.

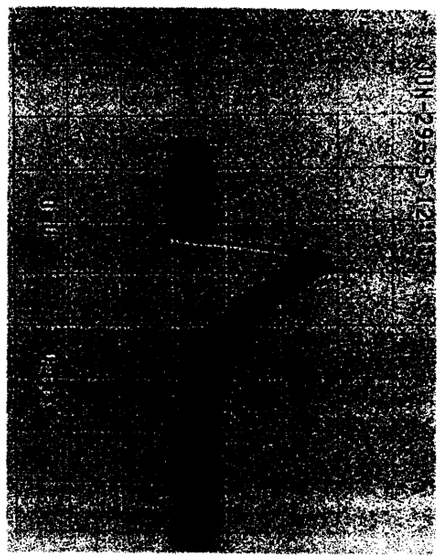
5. The same data as figure 4, with the low mass region excluded and the vertical scale expanded to show the high mass peaks in detail.

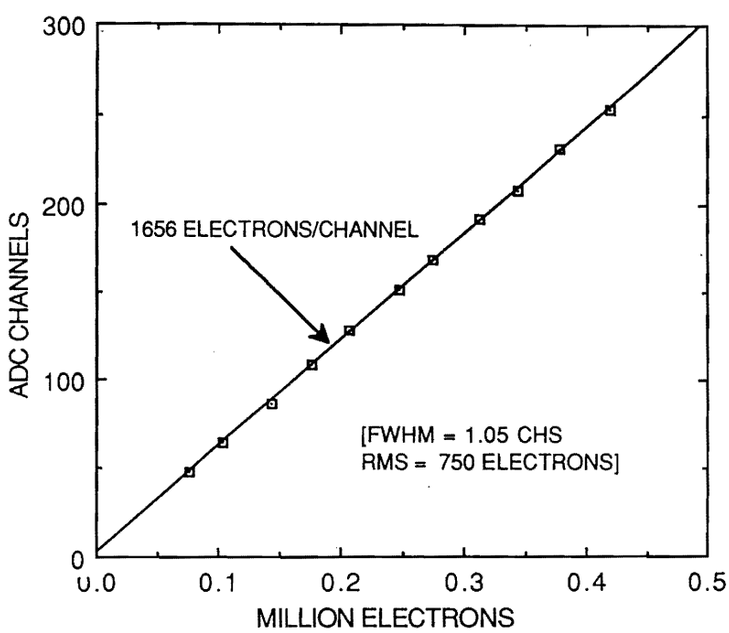
6. Mass spectrum observed from a sample of SCR1 (240 kDa), using the Faraday cup detector in a LaserMAT MALDI time-of-flight mass spectrometer.

7. Mass spectrum observed from a sample of Fibrinogen L (330 kDa), using the Faraday cup detector in a LaserMAT MALDI time-of-flight mass spectrometer.

8. The fractional spread, $\Delta t/t$, in the time-of-flight as a function of the time of flight. The lower curve shows the expected behaviour. For discussion see text.



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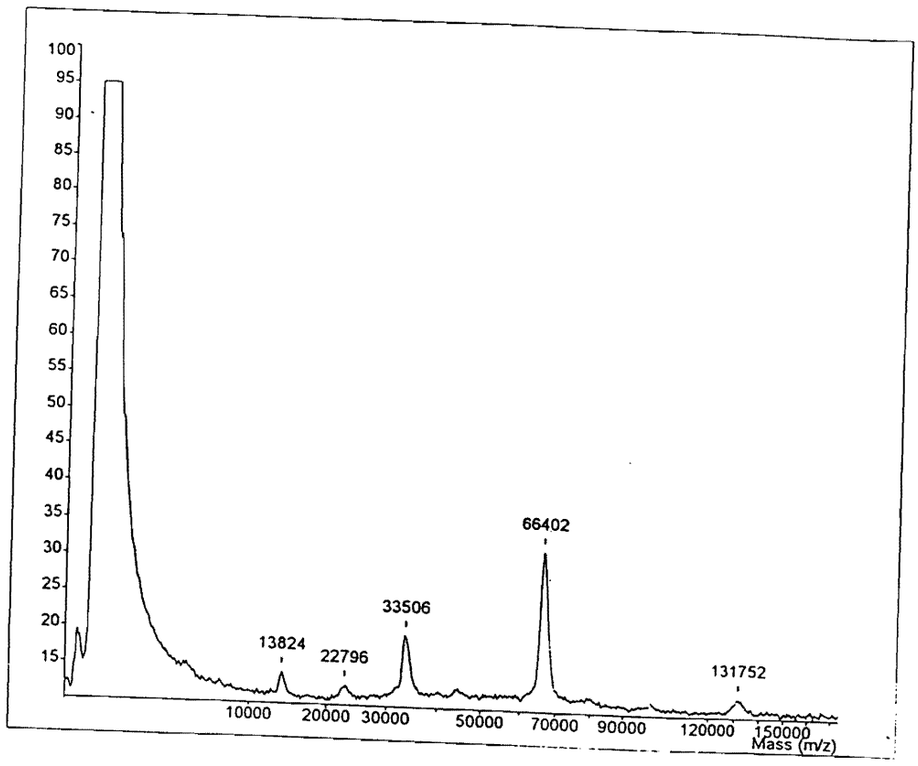
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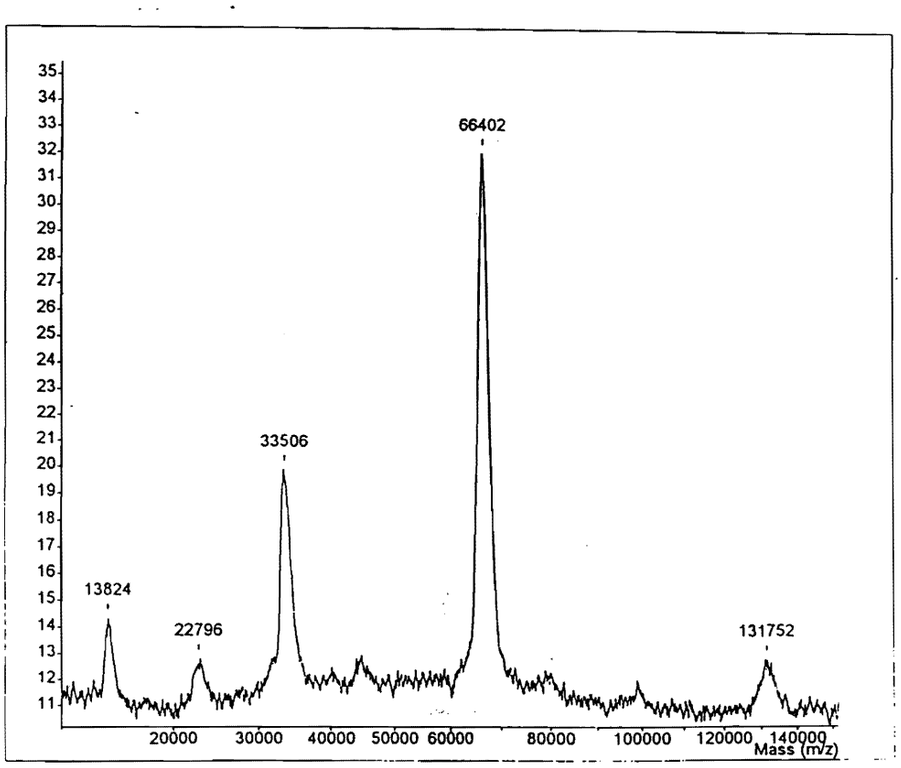
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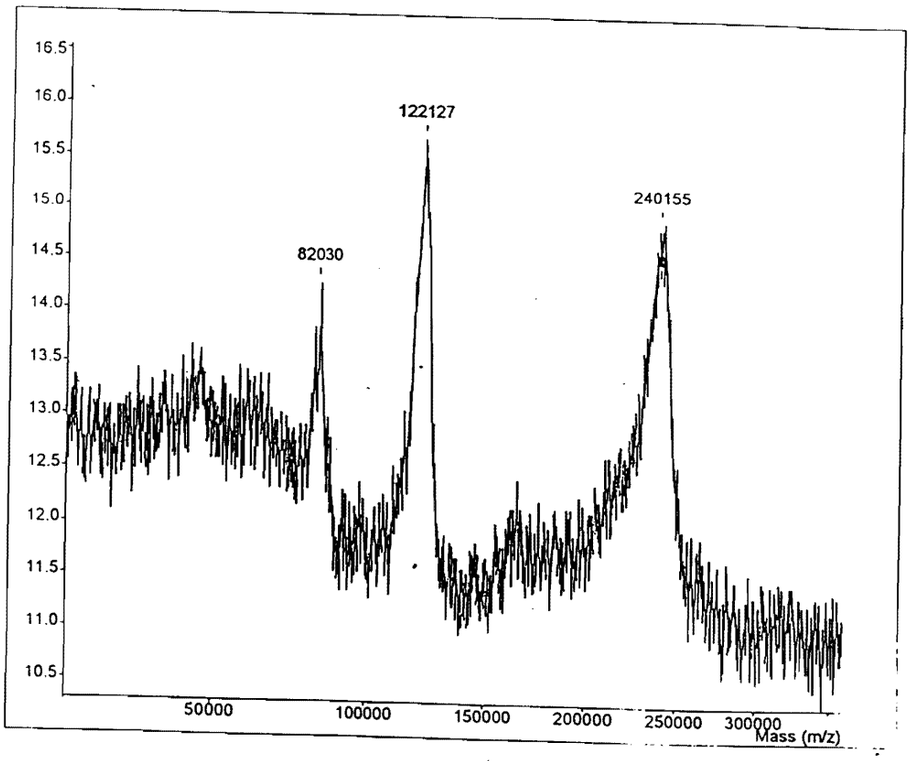
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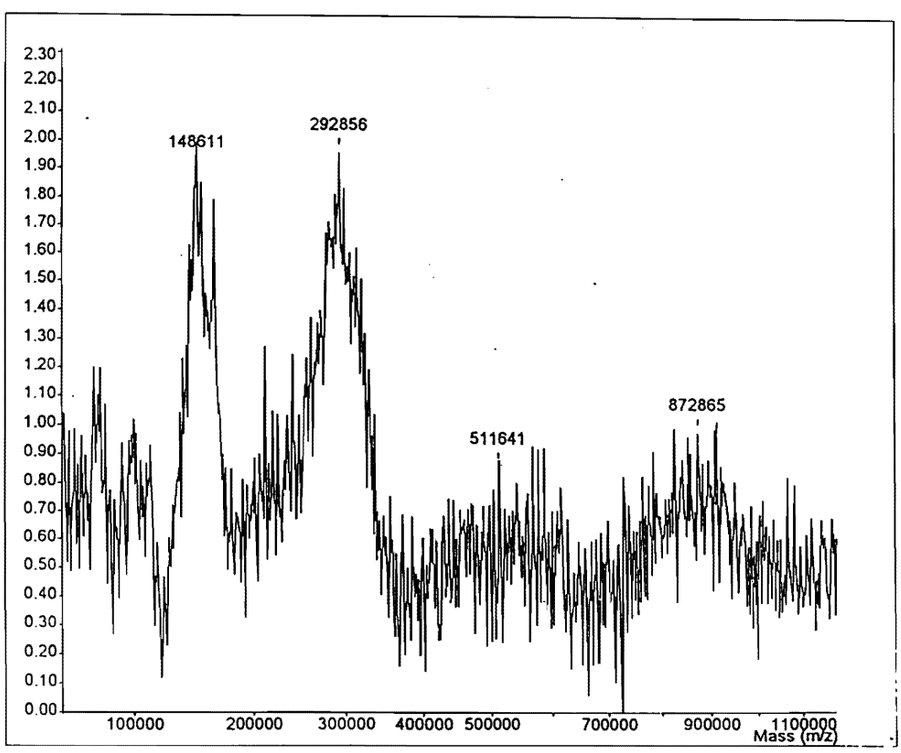
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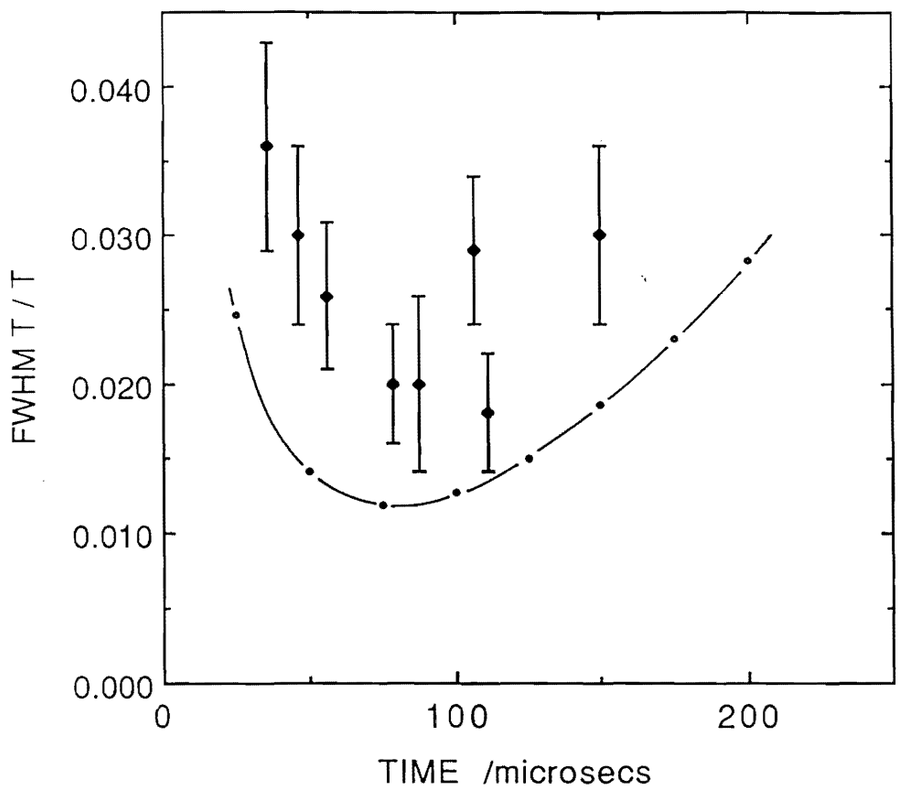
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