

Perfect Timing: Time-of-flight Mass Spectrometry†

M. Guilhaus*, V. Mlynski and D. Selby

School of Chemistry, The University of New South Wales, Sydney, 2052 Australia

In the 1990s time-of-flight mass spectrometry (TOFMS) has reestablished itself as a mainstream technique in mass spectrometry. There have been several developments which have contributed to this. The development of the technique of matrix-assisted laser desorption/ionization (MALDI), a pulsed ionization method, has provided a user-friendly, low-cost window on the high mass regime for the molecular biologist. The availability of high-speed computers has allowed efficient processing of TOF data on the microsecond time-scale. The emergence of practical ion optical approaches for space, time and velocity focusing have improved the resolving power and sensitivity of TOFMS far beyond its limited performance in previous decades. Improved technologies for digitizing fast signals have facilitated the resolution of signals separated by only a few nanoseconds. The coupling of continuous ionization sources such as electrospray ionization (ESI), plasma and electron ionization with orthogonal acceleration TOF mass analysers has been an area of considerable progress in which the high speed and 'full-scan' sensitivity advantages of TOF are being exploited in applications involving high-speed chromatographic separations or transient sample introduction methods. The stability of the mass scale in TOFMS combined with the ability to provide resolving powers ($m/\Delta m$ full width at half maximum) of several thousand provides excellent mass accuracy in important techniques such as ESI. TOF mass analysers are being deployed as the final analyser in hybrid tandem instruments. Commercial instruments now combine quadrupoles and double-focusing mass spectrometers with TOF analysers. Ion-traps have also been coupled with TOF instruments. © 1997 by John Wiley & Sons, Ltd.

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The technique of time-of-flight mass spectrometry (TOFMS) has returned as a prominent mass analysis method. TOFMS can be advantageous compared to scanning technologies because of its 'unlimited' mass range, high speed and the potential for high duty factors (% of ions formed that are detected). Two important causes for the renewed activity in TOFMS can be identified: (i) The development of and need for new ionization methods capable of generating ions of structural significance from high molecular weight materials. In particular, developments in ion sources for molecular biology provide a strong driving force for TOFMS. Matrix-assisted laser desorption/ionization (MALDI)¹ and electrospray ionization (ESI)² have been prominent in this regard. (ii) The facilitating technologies for TOFMS have advanced dramatically during the past decade. These include affordable pulsed lasers, nanosecond digitizers, focal plane detectors and microcomputing power.

The convergence of the need for high mass analysis with the availability of the necessary technology has been perfectly timed. But the recent successes of TOFMS must equally be attributed to research directed at overcoming the physical limitations inherent in the TOFMS experiment. Dispersions in the initial position, time and velocity of the ion population severely limited the resolving power of early TOFMS instruments. Inefficient production, gating and detection of ion

packets have, until recently, placed considerable constraints on the sensitivity of the TOF mass analyser. The need to form discrete packets of ions has provided a challenge in the coupling of continuous ion sources to TOFMS.

The development of the ion mirror (or reflectron)³ and the orthogonal acceleration time-of-flight mass spectrometer (oa-TOFMS)⁴⁻⁶ have been key stages in the revival of TOFMS.

FACTORS CONTRIBUTING TO TOFMS RENAISSANCE

The simplicity of the physical principles of TOFMS underpin its current successes. The mass-velocity relationship for constant energy ions and the electrostatic force on a charge when combined with Newtonian mechanics provide the foundations of all TOFMS equations:

$qV = 1/2 mu^2$	mass-energy relationship
$F = Eq$	force on a charge in an electric field
$F = ma$	Newton's second law
$a = Eq/m$	acceleration in a constant electric field

where q = charge; V = electrical potential through which an ion having charge q 'falls'; m = ion mass; u = ion velocity; F = force experienced by charge; E = electric field strength; a = acceleration.

The availability of numerical algorithms for modelling ion trajectories in lenses and other regions of electrostatic inhomogeneity has also played an important role by allowing instrument developers to refine

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*Correspondence to: M. Guilhaus

their designs quickly with reasonable-to-excellent accuracy in simulation.

High mass

The need to measure the mass of biological molecules and the discovery of matrix-assisted laser desorption/ionization (MALDI) by Karas and Hillenkamp have accelerated interest and progress in TOFMS. Established mass analysers such as quadrupoles and magnetic sectors have fundamental upper mass limits. Transmission in the former vanishes at high mass if resolving power is to be maintained. The $\sqrt{(m/z)}$ dependence of the field strength for the latter is a barrier to very high mass analysis. In contrast, TOFMS simply requires the supply of microsecond quantities of time ($m/z \propto t^2$) to extend the mass range. Thus, in TOFMS, the fundamental limitation at high mass shifts from one of transmission to one of detection.

Digital electronics

Advances in the speed and data handling capacity (both of which are important in TOFMS) of microcomputers needs no elaboration. Progress in high-speed timing electronics has paralleled developments in computing. This can be demonstrated, for example, by comparing the cost per unit of performance for long memory digital oscilloscopes over the last decade. Figure 1 shows that the cost per Msample/s for these devices is falling rapidly. Over the period shown in Fig. 1 the upper limit in maximum digitization rate has risen from 100 Msample/s (1984) to 4 Gsample/s (1996). These are substantial advances which are certainly not mirrored in the field of analogue electronics which support scanning technologies in mass spectrometry.

Speed

The TOFMS experiment involves nearly simultaneous detection of the mass spectrum on the microsecond timescale. Holland *et al.*, was the earliest group to predict the resurgence of TOFMS.⁷ It was argued that

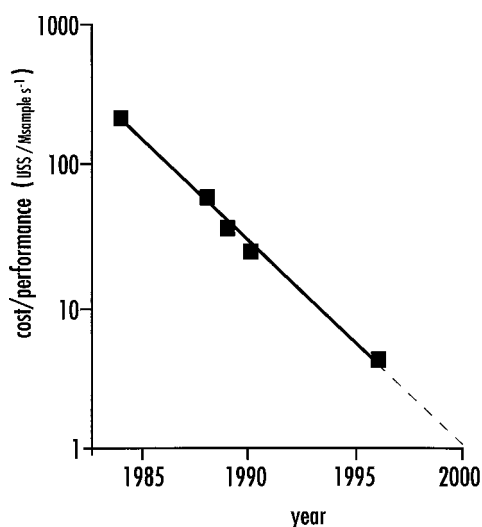


Figure 1. Cost/performance of LeCroy Digital Oscilloscopes expressed as US\$ per Msample/s versus time. Data is inflation indexed and was obtained from prices from LeCroy and their distributors in Australia.

the capability of TOFMS to follow high speed chromatography would bring about a revival. Holland and co-workers highlighted the fundamental limitations of scanning mass analysers for medium to high speed chromatography. Here the observation time at a particular m/z needs to diminish to near or below the transit time of ions through the mass analyser. For example, consider a chromatographic process with a chemical separation band of 500 ms. To record 20 spectra over this band requires a rate of 40 spectra per second. If each m/z observation window is assumed to represent 1/1000 of the scan then the observation time available for that m/z is only 25 μ s. A 4 keV ion of m/z 500 has an inverse velocity of 26 μ s/m and thus, if the analyser has dimensions on the 1 m scale, the transmission time is nearly the same as the observation time. The performance of the mass analyser would be expected to deteriorate rapidly as this condition was reached and exceeded.

Several years after the predictions of the Michigan group, continuous ion source TOFMS instruments could be realized with resolving powers and sensitivities to compete with scanning instruments. It is likely that TOF will be applied increasingly for fast chromatographic processes but it has been high mass and sensitivity, not speed, that have proven to be the main reasons why there is renewed vigorous activity in TOFMS.

SOLUTIONS TO PHYSICAL AND TECHNICAL PROBLEMS

There are significant physical and technical limitations which must be overcome in TOFMS. Reasonable solutions have been found for most of these though more progress is needed and expected in some areas. Important limiting factors in TOFMS include:⁸

(i) the spatial, temporal and velocity dispersions that characterize ion populations as they begin the journey to the detector can significantly broaden the ion arrival-time distribution at the detector. While numerous solutions have emerged to address individual dispersions, few correct for all simultaneously. Ionization from a flat surface, correct implementation of an ion mirror and orthogonal acceleration are perhaps the best solutions currently available.

(ii) The need to 'gate' ions (i.e. form them into temporally discrete packets) may not exist when a pulsed source is used (the pulsed ionization process must have a duration much less than the desired ion arrival-time spread). For continuous ionization sources an ion storage device or gating with orthogonal acceleration is effective.

(iii) The time-scale for measuring and processing signals is demanding. Events are typically digitized on the picosecond or nanosecond timescale. In most real analytical applications a single shot spectrum is recorded in about 50 μ s in which more than 10^4 signal amplitudes should be measured with a dynamic range of 12–16 bits. Moreover, repetition rates for continuous ionization TOFMS can be as high as 20–30 kHz. Currently, affordable (> 100 Msample/s) analogue-to-digital flash converters are limited to 8 bits. Though these can be coupled to multiplexed banks of 16 bit accumulating memory (for sum averaging of data) the

noise in these devices tends to limit the dynamic range to 10–12 bits. Pulse counting techniques, notably time-to-digital conversion (TDC) allow excellent recording of low count rates but suffer from saturation at high count-rates due to statistical coincidence errors. The simultaneous demands of high speed digitization, high spectral acquisition rate and the need for a large linear dynamic range represent a significant technological problem in TOFMS at present. There is a strong need for a wide dynamic range detection system for TOFMS and it is likely that the renewed activity in TOFMS will lead to such systems being developed.

(iv) The ion arrival event of an energetic ion at a focal plane detector is in principle instantaneous. The event must be transduced to an electrical signal wherein the detector and associated electronics display their own characteristic temporal response. These can be shown for a distribution of ion arrival times to add to that distribution in quadrature as shown in Fig. 2.⁹ Fortunately detectors are now available to give pulse widths of 1–2 ns. In these cases resolving power is significantly impaired only at low mass.

(v) The ability of grids and meshes to deflect the trajectories of ions as they pass through the field inhomogeneities in their vicinity (Fig. 3(a)) can easily be overlooked. A deflection of trajectory can shift velocity out of or into the time-of-flight direction and typically a range of these effects exist as the ion packets fill the space between the conductors in a mesh or grid. This creates an additional source of peak broadening which increases as the spacing of wires increases, the difference in electric field strength on either side of the mesh increases and in particular, as the angle of approach of ion to grid deviates from 90°. The last factor is of particular importance in orthogonal acceleration TOFMS. The ion mirror can compensate partially for this effect in the accelerator of the TOFMS. Simulations of ion trajectories through meshes in an oa-TOFMS system are shown in Fig. 3(b). Though the deflection is not significant on a spatial diagram, the magnitude of the change in ion arrival times can be

significant. Figure 3(b) shows the partitioning of velocity (expressed as equivalent kinetic energy) into the two spatial axes of an oa-TOF instrument and Fig. 3(c) shows how this information can be used to select mesh characteristics that will provide performance within acceptable limits.

The ion mirror (reflectron)

This elegant device corrects for initial position and velocity dispersions in the accelerator of a TOFMS instrument. As shown in Fig. 4 an initial spread in position and forward velocity is focused at a short distance into the drift region. Isobaric ions exist simultaneously in a small volume of time-position phase space at this focal point. The initial spatial spread is converted into a substantial velocity spread which the mirror corrects. The first focal point acts as a pseudo-source for the ion mirror and the more energetic ions from this point traverse longer distances in the mirror (they penetrate it further). The high and low energy ions are made to focus at the detector plane. It should be noted that this system does not correct for the turn-around time in the accelerator. For this reason the mirror is well suited to devices that generate ions from surfaces and gaseous sources where a very strong accelerating field is used to minimize the turn-around effect.

Orthogonal acceleration TOFMS

Off-axis TOFMS analysis of ions from continuous ion-beams was known in the 1960s.¹⁰ It was then used as a convenient way to couple TOFMS with an atmospheric pressure ion source. It was not until the late 1980s that a more specific method named *orthogonal acceleration* TOFMS was fully described and its advantages clearly delineated.⁴ Notable amongst the advantages are:

- (i) high efficiency (duty factor) in gating ions from any external continuous ion source;
- (ii) simultaneous correction for velocity and spatial dispersions;

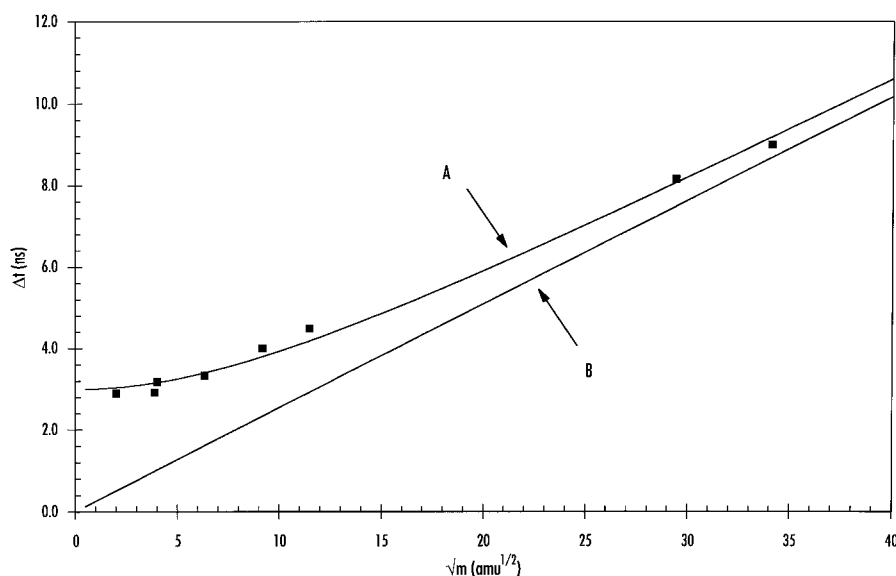


Figure 2. Variation of observed peak width (■) with (m/z) compared with a model (A) that considers the contribution of the intrinsic resolving power of the ion optics (B) and the contribution from fixed sources of temporal spread (t_i) typically in the detector and detection/timing devices. Reproduced from Ref. 9 with permission from the publisher.

(iii) capability, without an ion mirror, of mass resolving powers ten-times higher than with conventional TOF instruments fitted with gaseous ion sources;
 (iv) maximum duty factor at the high mass end of the mass spectrum;

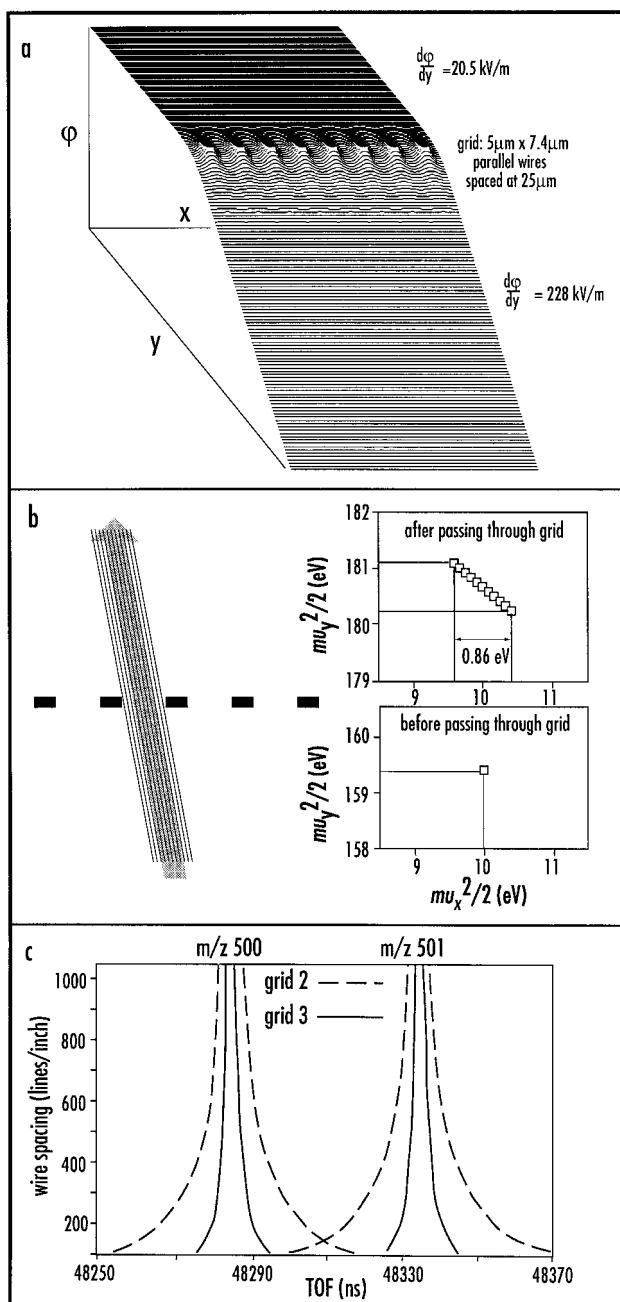


Figure 3. (a) Calculated potential surface $\phi(x,y)$ in the vicinity of an array of parallel finite-thickness conductors dividing planar-symmetric regions of differing electric field strength. (b) Deflection of a set of ions passing through and 'filling' the gap between two conductors. The 'kinetic energy' parameters $\mu_x^2/2$ and $\mu_y^2/2$ are related to each other to conserve total momentum. For ions of equal mass, velocity lost in the x -direction appears in the y -direction. The analysis estimates an effective 'energy-spread' in the TOF dimension and this predicts the contribution of the grid to broadening of the ion arrival time distribution. (c) Predicted contributions to peak widths for different conductor spacing (lines per inch) for approximately $5 \mu\text{m}$ (thick) \times $8 \mu\text{m}$ (wide) conductors for Grid 2 and Grid 3 in the instrument described in Refs 4 and 5. All the data in this figure (a-c) were derived from calculations facilitated by the I-Opt computer program (Ref 20).

(v) minimal temporal dispersion from the gating method.

In its correct configuration, ions are sampled from a nearly parallel ion beam from a continuous ion source. As shown in Fig. 5, a low energy ion beam is allowed to fill an ion accelerator region while it is held in a field-free state. An electric field is propagated by a fast pulse on one or more electrodes/meshes that define the region. The field is designed to apply a force that is strictly and exclusively at right angles to the axis of the ion beam. As the beam is nearly parallel, the ions in it have zero average velocity and minimal velocity spread in the direction of this force prior to its application. The finite width of the beam (a spatial dispersion) can readily be refocused¹¹ without the complication of a simultaneous and substantial velocity dispersion.

In the early off-axis instruments (and some recent ones)^{10,12-14} steering plates have been used to apply axial deceleration to the sampled length of ion beam. Presumably this has been done to direct the ions, for convenience, into a drift trajectory that is at right angles to the ion source. Thus the net acceleration is *not* orthogonal. Guilhaus¹⁵ has shown that the deflection of a 'long' ion packet after orthogonal acceleration causes it to undergo significant distortion with a resulting loss of resolving power as shown in Fig. 6. Recent observations by other groups are in agreement.^{12,16,17} When the deflection step is omitted a *spontaneous drift trajectory* follows. Here the ion velocity in the beam direction is conserved leading to a drift trajectory that is inclined away from 90° . It should be realized that the distance axis for time-of-flight analysis remains orthogonal to the axis of the ion beam. The detector is simply displaced to take into account the component beam-velocity of ions. It is the decoupling of the ion beam velocity spread from the TOF axis that leads to the resolving power advantage of orthogonal acceleration.

Resolving powers of 4000 (fwhm) have been reported for a linear orthogonal acceleration time-of-flight mass spectrometer (oa-TOFMS) with an electron ionization source.⁵ Similar and higher resolving powers have been reported for electrospray TOFMS systems which employ an ion mirror in the drift region of a true orthogonal acceleration TOFMS. It is noteworthy that oa-TOFMS is highly compatible with the ion mirror geometry.

An oa-TOFMS instrument can be arranged for efficient gating of ions from a continuous ion source and the gating introduces minimal temporal spread:

(i) The orthogonal acceleration field can be switched on very quickly and the entire population of ions sampled experiences an effectively instantaneous or reproducible acceleration. Typical pulse rise times of < 100 ns for pulses up to 1000 V are feasible.

(ii) The drift velocity for ions of a specific m/z in the TOF direction after orthogonal acceleration is typically ten times higher than the beam velocity for those ions. Once the ions have been sampled the beam is allowed to refill the accelerator region. The time taken to refill the accelerator matches the time for mass analysis if the drift region is about ten times longer than the length of ion beam sampled. This leads to a high duty factor and the duty factor is highest for the heaviest ion in the mass spectrum.^{4,5}

This method of gating is superior to in-line gating

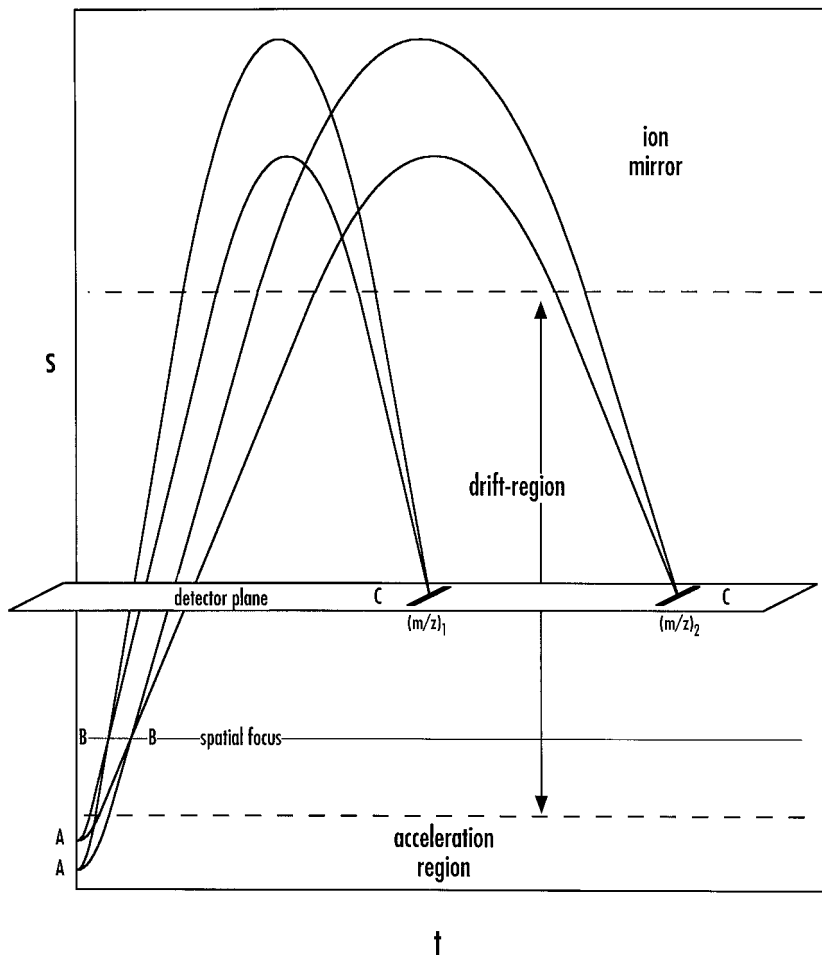


Figure 4. Space-time trajectory diagram showing the principle of the ion mirror in conjunction with a Wiley/McLaren ion source and a planar detector. Reproduced from Ref. 8 with permission.

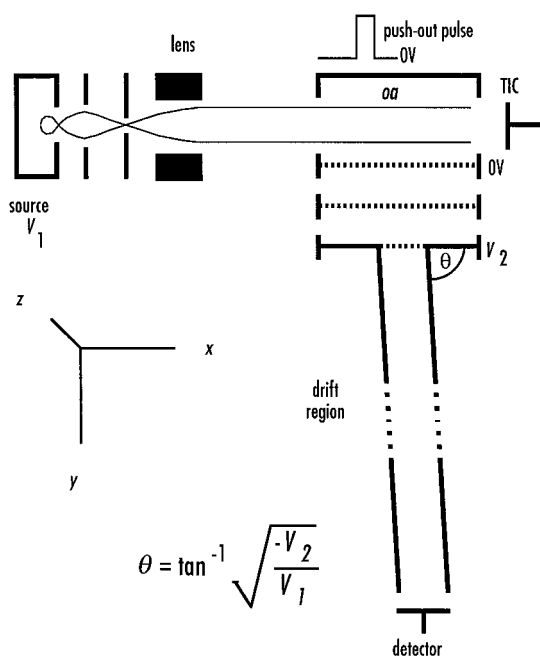


Figure 5. Arrangement of a linear oa-TOF mass spectrometer (reproduced from Ref. 4 with permission).

where the ion beam is ‘chopped’ and analysed along the same axis. Such an approach involves a compromise between sensitivity and resolving power as the packet’s temporal size is reduced.

Other gating approaches for continuous ion sources involve ion trapping. Wollnik¹⁸ has employed a simple electrostatic trap within an electron ionization source while Lubman¹⁹ has used a more complex arrangement with a Paul ion trap to accumulate ions from an external ion source prior to their injection into a reflecting TOFMS.

Predicting instrument performance and peak shapes

The simplicity of the principles of TOFMS allow it to be modelled with reasonable accuracy. For example, the original paper on oa-TOFMS⁴ predicted almost the exact resolving power that was obtained after the instrument was constructed. This was due to the development, in that work, of:

(i) I-Opt,²⁰ an ion trajectory modeling program which, via a finite difference method, calculates the potential function in planes of symmetrical electrode arrangements. Knowledge of the potential function allows prediction of the forces on, and hence motion of, ions located in the plane. At the time this program was developed, similar programs like SIMION²¹ were not

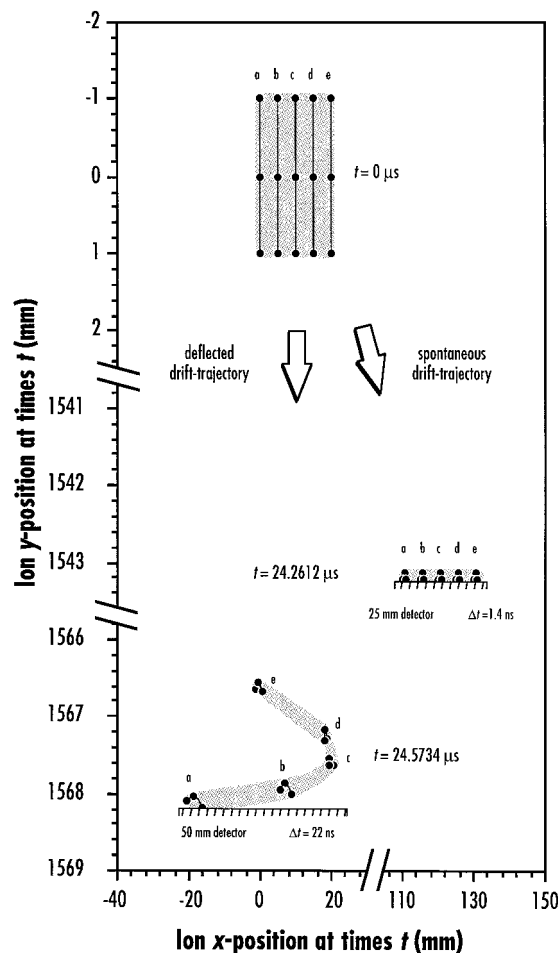


Figure 6. Distortion of ion packet calculated for a TOFMS instrument which employs steering plates to direct ions into an orthogonal drift-trajectory. Reproduced from Ref. 15 with permission.

capable of handling very large data arrays and did not have TOFMS specific features focusing on the time of trajectory (see Figs 3(a), 6 and 7).

(ii) SimTOF, a peak shape modeling program has been developed in this group and is based on the concept of convoluting time dispersions from several sources. Ion arrival time probabilities for one or two ions of specified mass and abundance are calculated based on user defined initial position and velocity functions, grid effects, detector response characteristics and power supply instability. Central to the calculation are convolution integrals and a TOFMS transform operator (Fig. 8(a)). This type of TOF calculation was first described by Owens *et al.*²² but has been substantially developed more recently.²³ Figure 8(b) shows a typical match between simulation and experimental results.

There is little doubt that the availability of programs and computational power for modelling ion motion and peak shapes have been a catalyst for the development of TOFMS instrumentation.

APPLICATIONS OF TOFMS

Conventional matrix-assisted laser desorption/ionization

The recently developed application of matrix-assisted laser desorption/ionization TOFMS¹ is so widely accepted that it needs little introduction. MALDI is a

method for generating small to very heavy gas phase ions via delivery of pulsed laser radiation to a highly absorbing matrix (large molar excess) that contains the sample. Though initially giving only very modest performance in mass accuracy and resolving power, the technique is relatively simple and easy to implement. For the analysis of biomolecules by MALDI, the early instruments gave mass data significantly better than available from gel chromatography techniques. The poor performance of earlier instruments is now widely attributed to the collisional processes thought to take place during desorption. The rapidly moving matrix molecules 'sweep' along the slower high mass ions. This greatly increases their kinetic energy (affecting final ion arrival time) and kinetic energy spread (affecting the distribution of arrival times). These translational effects depend on laser power and the sample preparation technique. It is often required that internal standards be used for a reasonable mass measurement to be made. Use of an ion mirror does not greatly improve instrument performance at very high mass (e.g. > 20 kDa).

Delayed extraction MALDI

A dramatic improvement in MALDI data has been reported recently.^{24–26} The technique used is now called delayed extraction and is related to (but not identical to) time-lag focusing.^{27,28} In delayed extraction the correlation between ion position and velocity (both along the TOF axis) at an optimal delay after (assumed) instantaneous desorption from a flat surface is exploited. Ions are accelerated after delay by a pulsed electric field and it can readily be shown that, for a limited mass range, the acceleration conditions can be chosen to bring about a very narrow arrival time spread. Resolving powers of a few thousand to 10000

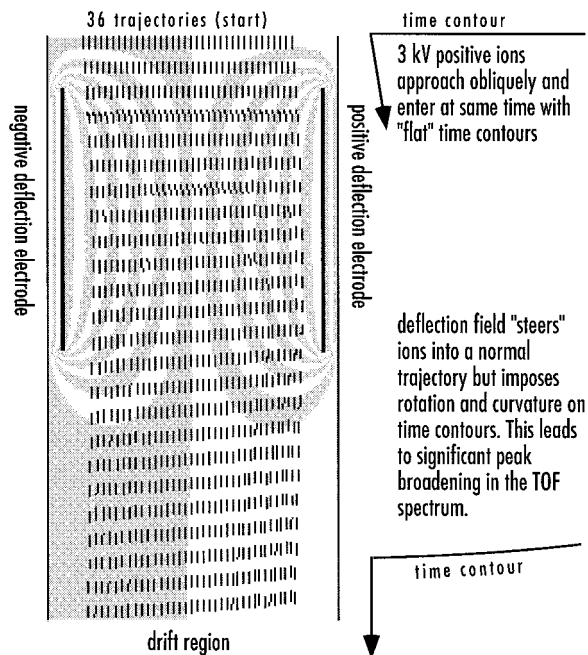


Figure 7. A time-resolved ion trajectory calculation in I-Opt²⁰ for a deflected trajectory arrangement similar to that of Fig. 6. Trajectory display is turned on and off at uniform intervals of time. For a set of ions simulated to begin their trajectories simultaneously, the time-contours of the instrument are apparent.

(fwhm) are reported for linear to reflected geometry instruments as shown in Fig. 9. Mass accuracy and resolving power are greatly improved up to masses of about 20 kDa. The narrower peaks also account for a significant improvement in signal-to-noise ratio (S/N) and hence sensitivity. DE MALDI loses its effectiveness at very high masses (e.g. > 20 kDa).

Orthogonal acceleration MALDI-TOFMS

Through highly suited to continuous ionization processes, oa-TOFMS can be coupled to a pulsed source such as that used in MALDI. This requires a double-pulsed experiment in which the first pulse is that of the laser and the second, after a delay, is to sample (off-axis) the desorbed ions. A sequence of shots with a program of delays may be used to select or discriminate

against specific mass ranges. A number of possible advantages may exist in the MALDI oa-TOFMS configuration:

(i) Selection of ions within a solid angle of the desorption axis together with a fixed delay between pulses sets an upper limit on the velocities of the sampled ion as measured in the direction orthogonal to the desorption axis. Thus there may be a correlation between orthogonal initial-velocity and initial position with a smaller range of velocity than in the desorption axis.

(ii) The desorption process should yield a symmetric zero-centred distribution of ion initial velocity orthogonal to the desorption axis. This condition should not be affected by laser power and matrix composition.

(iii) In order to create the conditions for (i) the distance between the desorption surface and the orthogonal

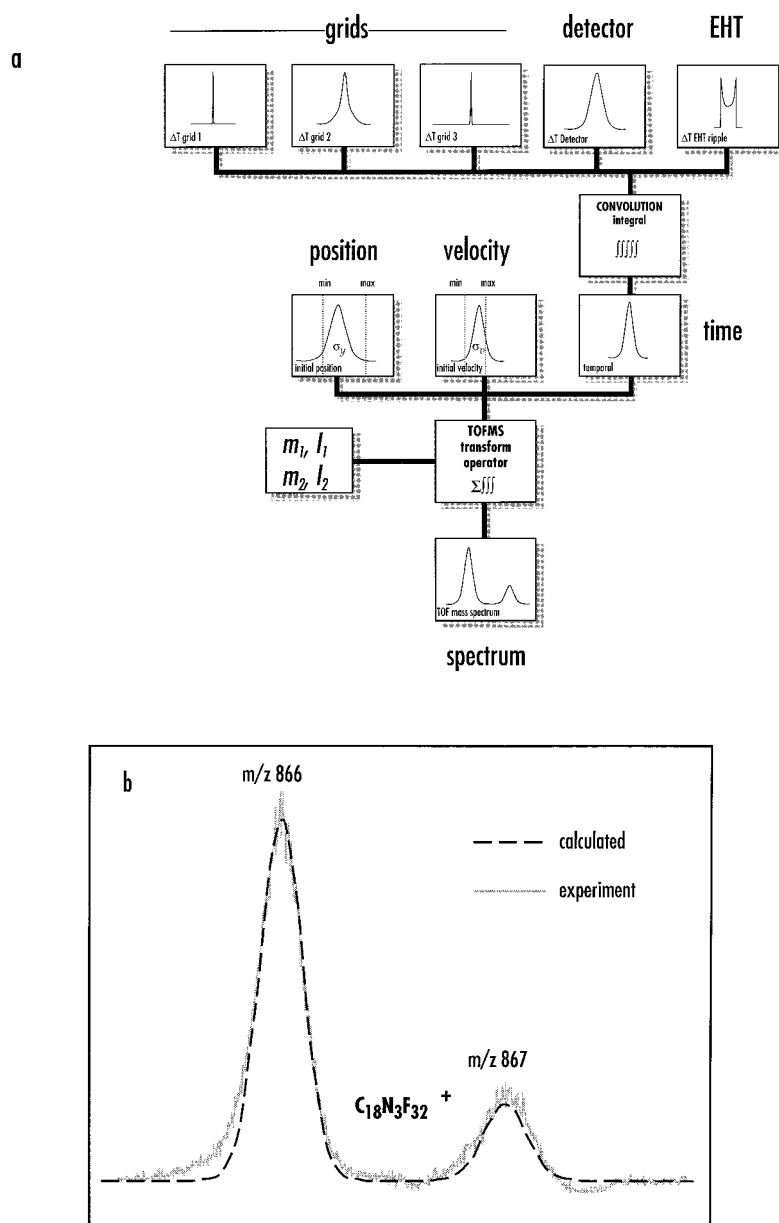


Figure 8. Schematic representation of the SimTOF program (a) and a comparison of peak shapes predicted by the program and measured with an instrument (b).

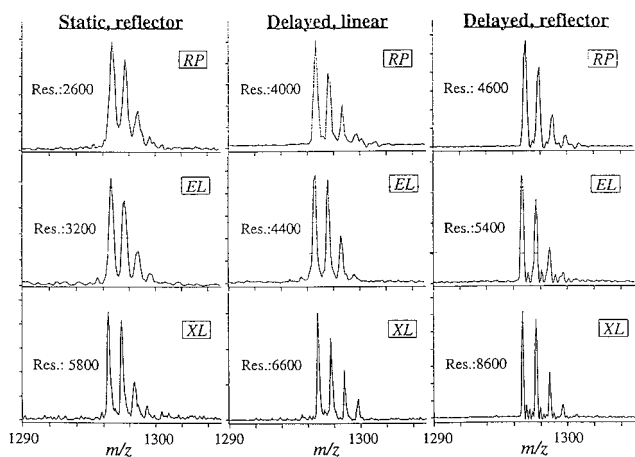


Figure 9. Mass resolving power from linear and reflecting MALDI-TOF instruments of various sizes with and without delayed extraction. The data demonstrate that delayed extraction significantly improves resolving power over the observed mass range. Reproduced from Ref. 25 with permission.

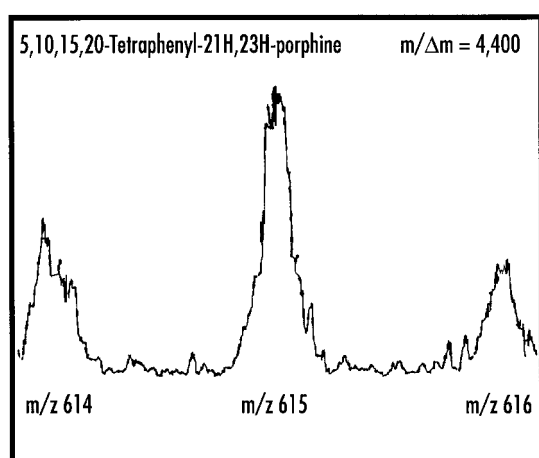


Figure 10. Mass resolving power from a preliminary linear oa-TOFMS instrument³¹ with a MALDI ion source in the authors' laboratory.

accelerator necessitates delays (typically) in the 10^{-5} s regime. Fragmentation during this period would not be expected to contribute to broadening of the arrival time spread or contribute to background chemical noise as would be expected in conventional and delayed extraction MALDI.

Two groups have recently attempted the MALDI oa-TOFMS experiment. Reported results gave resolving powers from about 200 (fwhm)¹⁴ to about 1000 (fwhm).^{29,30} We have adapted a continuous ion source oa-TOF instrument to test the feasibility of MALDI oa-TOF. The preliminary configuration immediately gave resolving powers in excess of 3000 (fwhm) for ions in the range m/z 600 to m/z 2000.³¹ Mass accuracy in the range 0.1 to 60 ppm was obtained (depending on the method of calibration) while mass precision was shown to be fundamentally limited by the digitizer frequency/bandwidth (400 Msample/s, 350 MHz) to about 90 ppm. In a more recent experiment a 4000 Msample/s, 1000 MHz digitizer was used and a resolving power well in excess of 4000 (fwhm) was obtained without an ion mirror (see Fig. 10). Two important conclusions may be drawn from these observations:

- The undersampling and bandwidth of the 400 Msample/s device significantly broaden the observed peak width as discussed earlier in this paper.
- The resolving power of the linear mode oa-TOF configuration is about the same as those reported for a linear delayed-extraction instrument of the same approximate size²⁵ as seen in Fig. 9.

Continuous ion sources

Most mainstream analytical mass spectrometers employ continuous ion sources. In some cases TOFMS offers advantages in speed and duty factor. The main challenge in coupling continuous ion sources with TOFMS is in gating the ions into temporally discrete packets. Ion storage devices and orthogonal acceleration have so far proven to be effective for this.

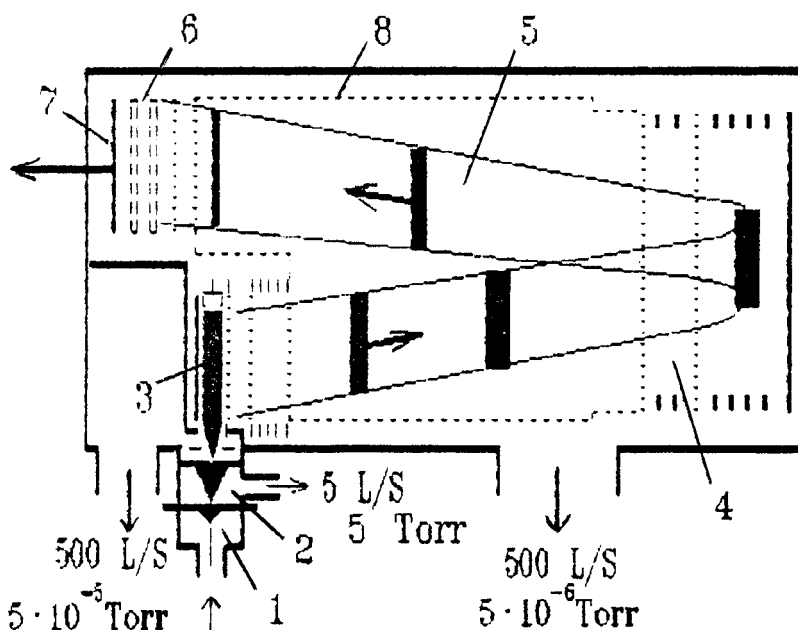


Figure 11. The first reported oa-TOF electro spray mass spectrometer. Reproduced from Ref. 2 with permission.

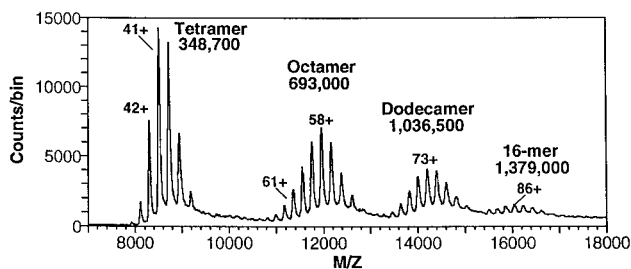


Figure 12. Electrospray oa-TOFMS results showing ions at significantly higher m/z than can be transmitted by instruments based on quadrupole mass filters. The high mass capability of this oa-TOF system allows important characterisation of biopolymers. Reproduced from Ref. 16 with permission.

Electrospray Ionization. Electrospray ionization² is an important new method for generating ions from polar molecules of low to very high molecular weights. The multiple charging which is characteristic of this ionization method more often than not brings ions into the $m/z < 2000$ observation window.

Until recently ESI has been well served by quadrupole mass analysers which cater to the wide energy spread of ions emerging from the high pressure ESI source. However, the relatively low transmission of quadrupoles for ions above m/z 1000 and difficulty in obtaining resolving powers in excess of 2000 are significant limitations in ESI. Moreover the duty factor for a mass spectrometer scanning over 2000 Da is quite low. In 1991 and 1994 Dodonov^{6,32} described the orthogonal acceleration TOFMS system shown in Fig. 11. This device incorporated an ion mirror to give a modest resolving power of about 2000 (fwhm). More recently, Standing and some workers from Dodonov's group published data from a newer longer drift region

version of this device with a resolving power of about 5000.¹⁶ The most recent reports from this group describe the use of a novel collisional cooling RF quadrupole ion guide and resolving powers up to 10 000 (fwhm).¹⁶ Perhaps of even greater significance is the observation, with this instrument, of ions well in excess of m/z 3000 confirming the existence of very high mass biopolymers in the samples (see Fig. 12). Such ions would be very difficult or impossible to observe in a quadrupole system and the high mass accuracy and sensitivity of the oa-TOFMS system combine in this work to provide unique high molecular weight data.

A similar instrumental approach has been used in a commercial mass spectrometer based on a sequence of RF hexapole, quadrupole, hexapole lenses prior to a reflecting oa-TOFMS instrument³³ as shown in Fig. 13. The quadrupole can be used to preselect ions for collisional activation in the following hexapole region. Thus this hybrid oa-TOF analyser can operate in the MS or MS/MS mode. The instrumental arrangement is reported to be extremely sensitive and provides excellent MS and MS/MS data.

Inductively coupled plasma (ICP) mass spectrometry. Most ICP/MS instruments employ a quadrupole mass analyser. The quadrupole has good transmission in the low mass range required for elemental mass spectrometry and also has extremely good rejection of adjacent nominal mass signals (mass abundance typically 10^6). Quadrupoles are also very tolerant of the large energy spread in ion populations from the 5000 K to 10 000 K plasmas used in the ICP source. The large energy spreads from ICP sources necessitate double focusing if sector mass analysers are to be used.

Hieftje^{34,35} has developed an orthogonal acceleration

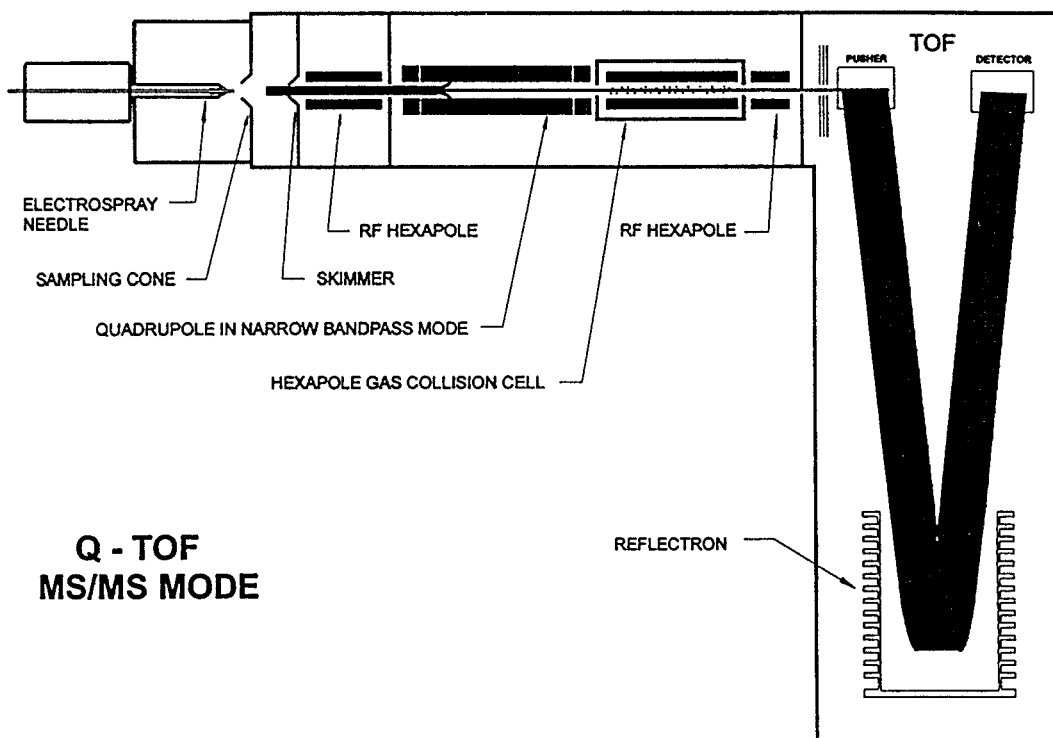


Figure 13. A commercial electrospray oa-TOF mass spectrometer with a low resolution quadrupole stage to preselect ions for MS/MS studies. RF hexapoles are used as ion guides and for collisional cooling of the ion beam. The quadrupole stage can be operated in RF-only mode so that the full ESI spectrum can be obtained in the oa-TOF stage. Reproduced from Ref. 33 with permission.

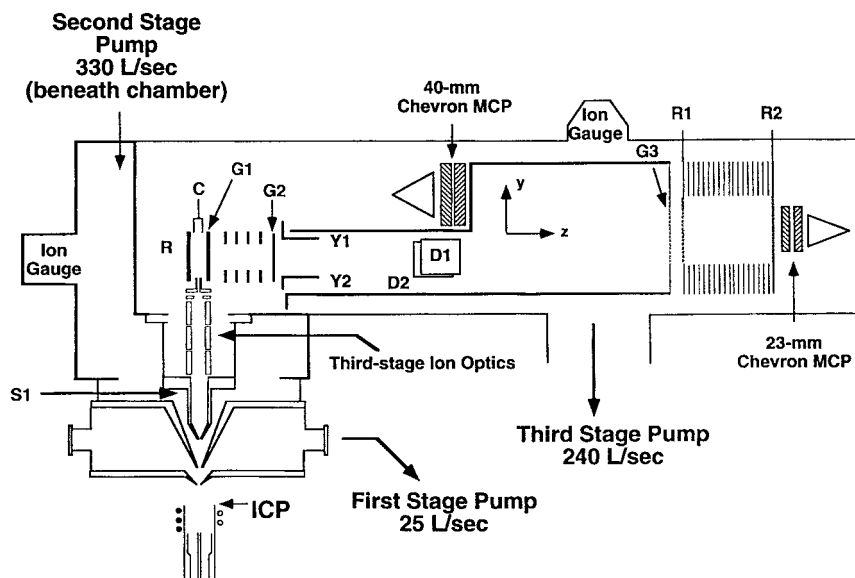


Figure 14. ICP/MS instrument with an oa-TOF mass analyser. Reproduced from Ref. 34 with permission.

reflecting ICP/TOFMS system shown in Fig. 14. This gives a resolving power (typically) of 1600 (fwhm). The instrument is sensitive in principle but suffers in practice from the inability to detect many elements simultaneously.

A commercial ICP/TOFMS instrument is soon to be released with extremely good sensitivity and dynamic range for full multi-element analysis.³⁶ Typical detection limits of 3 pg/mL are attainable along with a linear dynamic range of at least 10^6 . The mass abundance is reported at 10^5 or better. The resolving power of this instrument is typically 1600 (fwhm) and, as in Hieftje's

work, an ion mirror is required to correct for the energy spread from the ion source. Typical signals at low concentrations of heavy and light isotopes obtained on a prototype version of this are shown in Fig. 15.

Fast GC/MS. GC/MS was first carried out using a TOF mass analyser.³⁷ In early GC/MS work packed columns gave bands with widths that were more-or-less well matched to the scanning speed of quadrupole and sector mass spectrometers. The introduction of capillary columns in the 1970s brought a sharp increase in the speed of separation and placed demands on the scanning MS technologies. Narrow-bore capillary GC is now available to facilitate extraordinarily fast separations on the time-scale of seconds rather than minutes. However there exists no scanning mass spectrometer that can adequately follow such processes. TOFMS can in principle follow such processes as has been shown by Wollnik *et al.*³⁸

Van Ysacker *et al.* recently used orthogonal TOFMS to perform similar experiments³⁹ in which 14 compounds were separated in about 40 seconds (see Fig. 16). Spectral *real* acquisition rates were limited to 20 s^{-1} by data transfer from the digitizer (Precision Instruments 9825, Knoxville TN, USA) to the host computer.

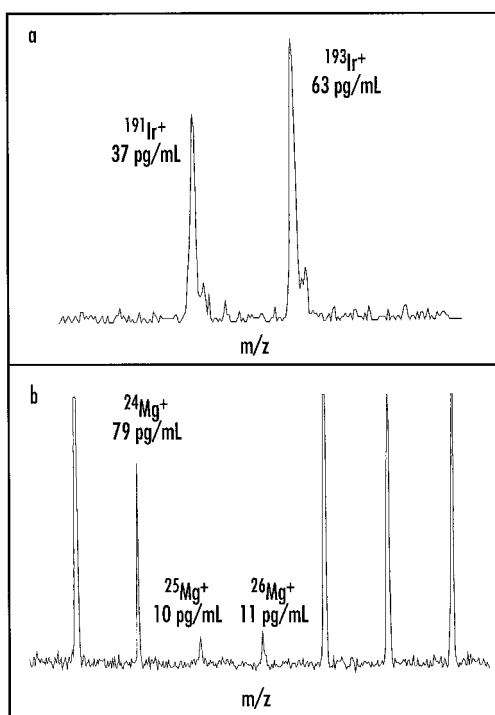


Figure 15. Preliminary results from a prototype commercial ICP/MS instrument with a reflecting oa-TOF mass analyser. The detection limit are a few ppt (1 ppt = 1 part in 10^{12} by mass). The results were obtained in a 10 second integration with similar detection limits apparent for heavy (a) and light (b) isotopes.

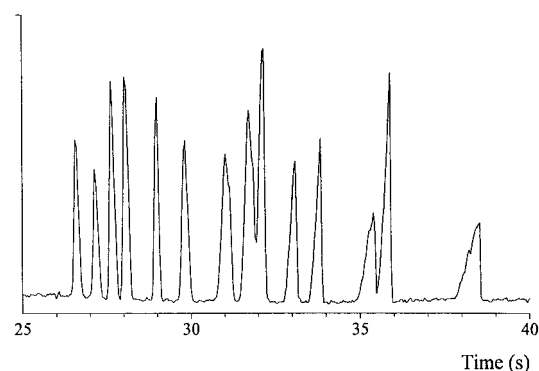


Figure 16. Fast GC/MS data from an oa-TOFMS. Fourteen volatile organics are separated in 40 seconds and the data are presented as a TIC trace. The mass spectra matched library spectra very well. Reproduced from Ref. 39 with permission.

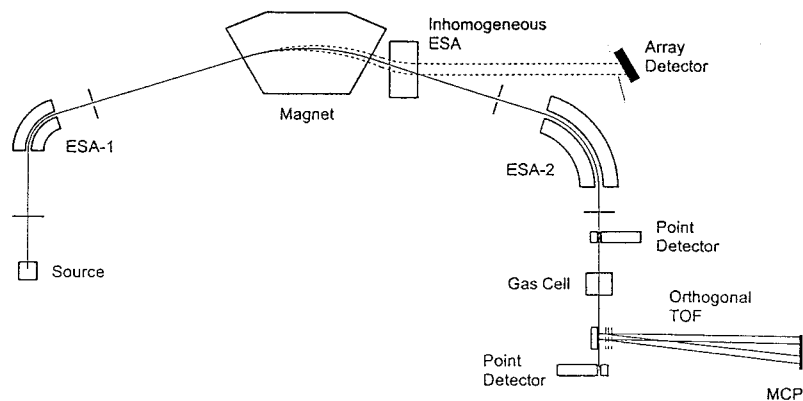


Figure 17. A commercially available hybrid mass spectrometer with double-focusing MS1 and a linear oa-TOFMS. Reproduced from Ref. 41 with permission.

Data transfer to disk would limit rates to about 50 s^{-1} in the absence of the former limit. Coherent noise in the digitizer (based on a 200 MHz, 8-bit flash ADC) limited dynamic range at low sample levels. At high sample levels the limited capacity of the narrow-bore columns (typically measured in nanograms) lead to loss of chromatographic efficiency. The combination of single narrow-bore GC technology with TOFMS thus requires extended low-level sensitivity and very high split ratios in the injector.

Emerging large dynamic-range TOFMS detection systems are under development for ICP/MS³⁶ and these will be useful in high speed GC/TOFMS. The problem of capacity of the columns may well be solved by new multicapillary technology.⁴⁰ Here as many as 900 narrow-bore (40 μm diameter) capillaries are bundled together to provide high sample capacity and high speed simultaneously.

Hybrid instruments and MS/TOFMS

As discussed in an earlier section of this paper, ion traps have been used to accumulate ions from continuous ion sources prior to their injection into a reflecting TOFMS.¹⁹ Also described in an earlier section is the use of a hybrid quadrupole/oa-TOF configuration for MS/MS. The duty factor advantage of the TOFMS stage of this instrument (compared to a scanning quadrupole) should prove to be an advantage in the technology. The high resolving power and mass accuracy of the TOF stage should also be highly beneficial and superior to the second MS stage of a triple-quadrupole instrument.

A now well established MS/MS instrumental arrangement combines a double-focusing mass spectrometer (MS1) with a linear oa-TOF analyser (MS2) as shown in Fig. 17.⁴¹ Once again the high duty factor of the TOFMS provides excellent sensitivity and 'simultaneous' detection of fragment ions. The resolution of MS2 is extremely good and relatively unencumbered by kinetic energy released in the fragmentation processes induced between MS1 and MS2. The tuning and calibration of MS2 is extraordinarily simple (compared to when MS2 is a quadrupole or sector mass analyser). Overall this arrangement challenges the viability of much larger and more costly four (or more) sector mass spectrometers.

CONCLUSION

With continuing improvements in TOF's facilitating technologies and the increasing interest in high mass analysis there is little doubt that TOFMS will continue to play an increasing role in mass spectrometry. This is likely to be the case for both pulsed and continuous ionization methods. The development of new technologies for spatial array detection may challenge TOF in the low mass regime at some time in the future. It is difficult to see a challenger for the very high mass regime especially if it is acknowledged that TOF is superior to quadrupole mass analysis in ESI applications.

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