

**SPECIAL FEATURE:
HISTORICAL****‘Time-of-Flight Mass Spectrometer with Improved Resolution,’ W. C. Wiley and I. H. McLaren, *Rev. Sci. Instrum.*, 26, 1150 (1955)****Commentary by
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Time-of-flight (TOF) mass spectrometry is a method of mass analysis which continues to undergo rapid development. This is particularly true of the combination of TOF mass analysis with the matrix-assisted laser desorption/ionization (MALDI) method of ionization. The power of this combination is evident from Table 1, which is a summary of current capabilities. Remarkable as some of these characteristics are, current work is likely to produce further improvements, chiefly arising from the use of the recently introduced method of delayed-ion extraction (DE).¹

In the DE experiment, ions are allowed to disperse in the ion source due to their initial velocity while the congeneric neutrals are pumped away. The reduction in ion–molecule collisions minimizes the associated spread in translational energies. In addition, the flight time spread at the detector resulting from the initial velocity spread can be reduced by an appropriate choice of source geometry and delay time. These attempts at improving performance have been so successful that the time resolution of the detector has now become the limitation. It is even not unthinkable today that this will lead to unit mass resolution in the range of 40 000 Da per charge, a significant further improvement in performance.

Given these and other advances in performance of TOF instruments, it is worthwhile to reflect on early efforts to improve performance by time focusing. To this end, the 1955 paper by Wiley and McLaren is reproduced here. It has much to teach us, even today, about TOF mass spectrometry. In considering the work

of Wiley and McLaren, the reader is referred to the recent excellent Tutorial on TOF mass spectrometry by Guilhaus² which appeared in this journal, and which laid out with great clarity, the importance of spatial and velocity focusing in achieving high performance.

The Wiley and McLaren paper deals with several methods of improving resolution in TOF mass spectrometry and it has certainly proved to be a seminal contribution. Not only are the sources of poor resolution identified but also the idea of two-stage acceleration in order to minimize the effects of both spatial and velocity dispersions on time resolution is introduced as is the separate idea of improving resolution by time lag focusing. Wiley and McLaren claim, rather modestly, that ‘In some cases the use of time lag focusing gives greatly improved resolution.’ Today, this is well known and widely accepted, and the effects of Wiley and McLaren’s thinking continues to be felt, as evidenced by the related concept of delayed extraction MALDI/TOF analysis. For their EI source, Wiley and McLaren point out that ‘space resolution and energy resolution place opposite requirements on several system parameters’ and ‘therefore the best overall resolution is a compromise.’ The MALDI ion source is ideally suited for ‘time-lag energy focusing,’ because ions originate from a surface and all have forwarded velocities, thus avoiding limitations due to turnaround times. Although the importance of the work of Wiley and McLaren has long been appreciated it has clearly taken a long time for the implications of this 1955 paper to be fully realized. There are many reasons for the long

Table 1. Current capabilities of the TOF/MALDI combination^a

Mass range (for singly charged ions):	> 1 000 000
Mass resolution (at 3000 dalton/charge):	< 5000 [> 10 000]
Mass measurement accuracy (in favorable cases):	up to 100 ppm [up to 10 ppm]
Detection limits (most favorable cases):	< 10 amol

^a Advances due to DE are given as in square brackets.

development time taken to achieve high-mass range/high-resolution TOF, some technical and some not. The driving factors appear to have been the following.

A suitable ion source was needed

Laser desorption had been introduced as one of the new desorption ionization techniques in the mid-1960s³ and 1970s,⁴ but only gradually did it begin to play a major role in mass spectrometry. Some of the early problems were related to the development of lasers themselves: in the early stages their physical parameters, reliability and performance varied greatly. In addition, the choices available in many parameters, including wavelength (from far-IR to far-UV) and pulse duration (from ns to cw) meant that results were scattered over a wide range of conditions as well as covering a wide range of analytes. The introduction of the laser microprobe (LAMMA) instrument⁵ which used ns UV lasers and TOF mass analysis, and was originally designed for spatially resolved elemental analysis within a biological specimen, provided commercially available instrumentation to investigate laser desorption ionization of organics.⁶ The advantages of using matrices in desorption ionization experiments were reasonably well established at this time, and solid matrices had been shown to increase ion yields in secondary ion mass spectrometry⁷ and laser desorption.⁸ Nevertheless, fundamental investigations into the UV-LD process were required and were undertaken by the author. In the course of these experiments, it appeared reasonable to test small polar and highly absorbing compounds for their ability to co-desorb with and ionize larger bio-organics. Although this work was done in the period from 1984–86, it took until the end of 1987 to establish the general validity of the absorbing matrix concept, including the applicability to high molecular mass biopolymers.

Acceptance of TOF technology

Mass spectrometry has the advantage that there are a variety of ways of measuring mass/charge ratios of gas-phase ions, each with particular advantages. There was, however, some understandable delay on the part of the mass spectrometric research community and instrument manufacturers in adopting TOF technology, given the variety of good choices already available. This delay came despite some obvious advantages of the TOF mass analysis and the progress in mass resolution achieved by introduction of the ion mirror or reflection.⁹ Even though plasma desorption mass spectrometry, introduced in 1974, gave excellent results with biopolymers, at least those with molecular masses below 10 kDa, it was not used in many laboratories until a commercial instrument became available in 1985. Fast atom bombardment (FAB) mass spectrometry, after its introduction in 1981,^{10,11} soon became widely accepted, most importantly because it could be adapted readily to existing magnetic sector and quadrupole instruments.

Availability of high-speed electronic instrumentation

The availability of high-performance time measurement devices, namely time-to-digital converters (TDC) for single-ion counting (PD, SIMS), transient recorders (ADC) for laser ion sources and fast, reliable and affordable semiconductor-based high-voltage switches was important to the development of TOF instrumentation. In 1983, laser microprobe instruments (LAMMAs) were equipped with a Biomation/Gould transient recorder with 100 MHz and 2048 (!) channels, but in practice they provided only 4 bit resolution at the highest sampling rate. The first MALDI spectra were recorded with time windows up to 500 ns in order to reach the necessary time and mass range. In the late-1980s the first high-performance digitizers became available (LeCroy and Tektronics) and subsequently the sampling rate and channel numbers have constantly increased while at the same time the price and mass has dropped. Today 4 GHz transient recorders are available and are required in some cases to allow the increased time resolution achieved by delayed ion extraction. Thus, ion-detector technology now defines the limits in achievable time and mass resolution.

Need for improved instrumentation

The final factor contributing to the development and enhanced performance of TOF instruments was the strong demand from the user community for suitably simple and low-cost methods for biomolecular analysis, particularly molecular mass determination. The growing importance of mass spectrometry in biochemical and biomedical investigations, especially as a result of the success of the FAB-tandem mass spectrometry combination in the peptide sequencing, led to the need for newer methods in mass spectrometry. The constant pressure particularly from the biological research community to improve the mass spectrometric performance in terms of mass resolution and mass determination accuracy has, fortunately, been satisfied to some extent by continuing improvements in mass spectrometry.

CONCLUSION

Finally, it is of interest to note briefly some aspects of the careers of Wiley and McLaren. William C. Wiley received his BS degree from the University of Illinois and was Director of the Applied Physics Laboratory at the Bendix Corporation from 1949 to 1968. Subsequently, he was Vice President and Chief Technical Officer for Leeds Northrup (1971–85). He held several patents, one of which was for the manufacture of hyperboloid electrodes for a quadrupole mass filter using glass extrusion followed by sputtering or vapor deposition of a conductive film. Ian H. McLaren also worked at the Bendix Corporation and was an associate of Wiley. McLaren held several patents, one of which, with Wiley, described the use of ion guides in TOF mass spectrometers to achieve increased sensitivity.

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