International Journal of Mass Spectrometry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

Time-of-flight mass spectrometry (TOFMS): From niche to mainstream

K.G. Standing [a], Marvin L. Vestal [b,*]

[a] Department of Physics & Astronomy, University of Manitoba, Canada
[b] SimulTOF Systems, Sudbury, MA, United States

ARTICLE INFO

Article history:
Received 21 April 2014
Received in revised form 4 September 2014
Accepted 4 September 2014
Available online xxx

Keywords:
Time-of-flight mass spectrometry
MALDI
PDMS

ABSTRACT

World War II electronic advances suggested the use of time-of-flight for mass measurements, leading to the development of a commercial TOFMS instrument by Bendix. This instrument used electron impact ionization, but the subsequent application of fission fragment bombardment (PDMS), coupled to TOFMS, was responsible for significant advances in the mass spectrometry of large biomolecules. Bombardment by accelerated MeV or keV ions, again coupled to TOFMS, was found to be equally successful. Although these TOF methods were the only ones initially capable of measuring the masses of really large biomolecules, most mass spectrometrists were still wedded to sector/quadrupole instruments for high/low-end mass measurements. The "coup de grace" for TOF (as generally believed) was the discovery of a suitable matrix (glycerol), which enabled the use of sector/quadrupole instruments for measurements of large biomolecules ("fabulous FAB"). Ironically, it was the discovery of suitable matrices for laser excitation that revived TOFMS, aided by the additional accuracy provided by the reflecting geometry, and the subsequent development of orthogonal injection, as well as the coupling to liquid chromatography. Enormous technical advances in TOF were driven by the invention of MALDI and facilitated by the parallel advances in digital electronics. All of mass spectrometry has benefitted from these technical advances, but TOF most of all because of the need for high speed acquisition and large data storage capacity. Thus TOF is now in the mainstream of biological applications of mass spectrometry.

1. Introduction

The classical methods of mass spectrometry stem directly from those pioneered by J.J. Thomson over 100 years ago [1]. They rely on the deflection of accelerated ions by magnetic fields. By contrast, time-of-flight mass spectrometry (TOFMS), as its name suggests, depends only on a time measurement. It could thus be argued that the measurement of the flight time of an ion is the simplest method of determining its mass.

The most straightforward variation of the technique measures the flight time of an accelerated ion as it passes down an evacuated pipe: $m/q = 2V/v^2$, where m and q are the molecular mass and charge, V is the accelerating potential, and v is the ionic velocity, determined by the ion's kinetic energy ($1/2\,mv^2 = qV$), and measured by the flight time [2]. If only singly charged ions are present, the lightest group reaches the detector first, followed by groups of successively heavier mass.

Nevertheless, the technique does require rather precise time measurements, which were not available until after World War II [3]. Apparently W.E. Stephens (Fig. 1) of the University of Pennsylvania was the first to propose a TOFMS instrument; his abstract presented at the April 1946 meeting of the American Physical Society [4] reads: "**A Pulsed Mass Spectrometer with Time Dispersion**: Advances in electronics seem to make practical a type of mass spectrometer in which microsecond pulses of ions are selected every millisecond from an ordinary low-voltage ion source. In traveling down the vacuum tube, ions of different M/e have different velocities and consequently separate into groups spread out in space. If the ions are collected in a fixed Faraday cage and the current amplified, then pulses of current corresponding to different ion M/e will be dispersed in time. If the amplified current pulses are put on the vertical plates of an oscillograph whose sweep is synchronized with the pulses, then an M/e spectrum of the ions will be exhibited. This type of mass spectrometer should offer many advantages over present types. The response time should be limited only by the repetition rate (milliseconds). The indication would be continuous and visual and easily photographed. Magnets and stabilization equipment would be eliminated. Resolution would not be limited

* Corresponding author.
E-mail address: marvin.vestal@simultof.com (M.L. Vestal).

http://dx.doi.org/10.1016/j.ijms.2014.09.002
1387-3806/

Fig. 1. W.E. Stephens. First to propose a time-of-flight mass spectrometer.

by smallness of slits or alignment. Such a mass spectrometer should be well suited for composition control, rapid analysis, and portable use. A mass spectrometer of this type is being constructed."

In fact, Stephen's mass spectrometer was not actually constructed until several years later [5], by which time other TOFMS instruments had been built [6,7]. However, the abstract does indeed describe the type of TOFMS device that was constructed within the next few years.

We may note that the advantages of the TOFMS mass spectrometer claimed by Stephens were rather modest. In particular, its resolution was determined entirely by μsec measurements, neglecting the improvements that could be made by nsec electronics. Also the "unlimited" mass range of the instrument was not mentioned, thus ignoring the possibility of measuring the masses of large biomolecules. Both these capabilities were to appear in succeeding decades.

2. The first practical TOF

The history of time-of-flight mass spectrometry begins for practical purposes with the work of Wiley and McLaren [8–10]. They described a two-field pulsed ion source that could produce either space focusing or velocity focusing, but not both simultaneously. They concluded:

> Both the best compromise and the quality of the resulting resolution depends on the actual initial space and energy distributions. Lag systems give preferred treatment to energy resolutions; and no lag systems to space resolution. Hence the best method of operating depends on the space and energy distributions encountered. In some cases the use of time lag focusing gives greatly improved resolution. In others it seems to make little difference.

These principles were largely ignored by the developers of TOF instrumentation for the next 30 years when they were rediscovered by Brown and Lennon for MALDI [11].

3. The coincidence TOF mass spectrometer

In 1960 Rosenstock [12] proposed a coincidence mass spectrometer in which the time measurement was initiated by detection of a secondary electron produced by a gas phase ionization event, and time measurement terminated by detection of the corresponding positive ion at a second detector. A schematic diagram of the apparatus is shown in Fig. 2. The coincidence principle was previously used in studies of nuclear phenomena and in measuring the time-of-flight of high energy particles, but this was the first application on the molecular scale of single ion counting with time-of-flight measurements using a time-digital-convertor (TDC). The electronics employed state-of-the art transistor circuits (circa 1960) designed by Robert Chase [13] of Brookhaven National Laboratory. The advantages of using coincident detection are that ionization processes with very small cross sections can be observed, and distributions of electron energy/and or angle may be measured

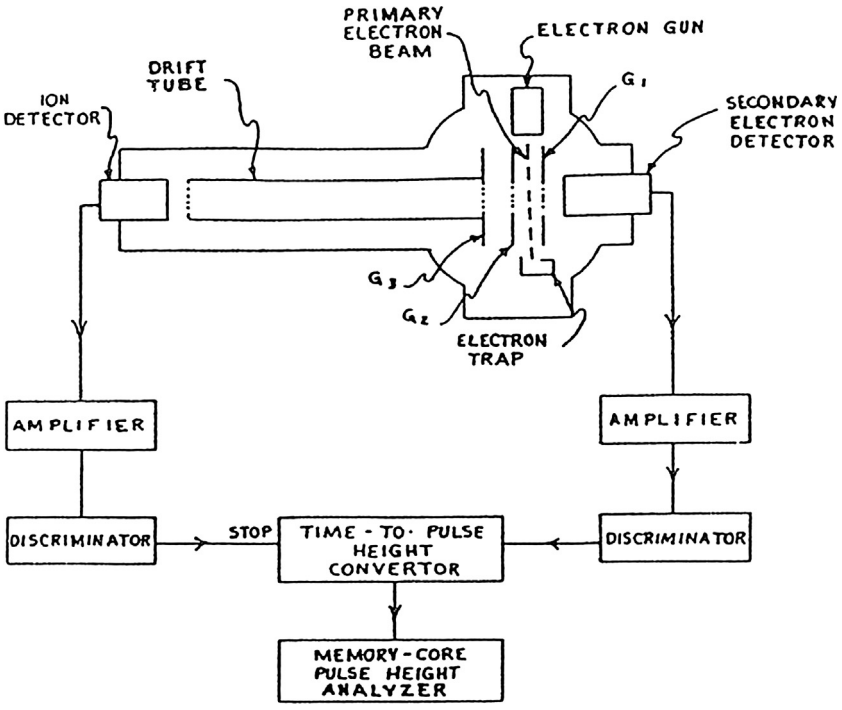

Fig. 2. Schematic diagram of the coincidence mass spectrometer proposed by Rosenstock.