



Origins of Tandem Mass Spectrometry

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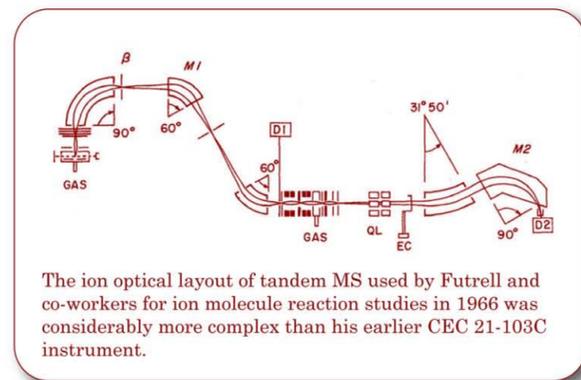
The development of tandem mass spectrometry, or MS/MS, evolved along several lines, in several labs and in several countries. As Cooks and Beynon¹ pointed out in an earlier paper:

“Too often this process (of creating a new field of science) is seen as the culmination of measured progress and rational planning; which it can be but seldom is. The role of serendipity, random choice, and even error in advancing research has been noted before, but, even among scientists, it tends to be underestimated.”

This poster traces some of those random events leading to tandem mass spectrometry.

SECTOR BEGINNINGS

Research into ion molecule collision processes stretches back to the beginning of the previous century. Interaction of electrons with molecules was investigated by Thomson² in 1900 and positive ions with molecules by Wien³ in 1916. In the early '60s, Lindholm and co-workers began a series of reports on charge-exchange collisions between positive ions and a variety of small molecules using a 'double mass spectrometer'⁴. Futrell and co-workers began their research in charge-exchange reactions a few years later at Wright-Patterson Air Force Base using a modified



The ion optical layout of tandem MS used by Futrell and co-workers for ion molecule reaction studies in 1966 was considerably more complex than his earlier CEC 21-103C instrument.

Consolidated Engineering Corporation 21-103C mass spectrometer.

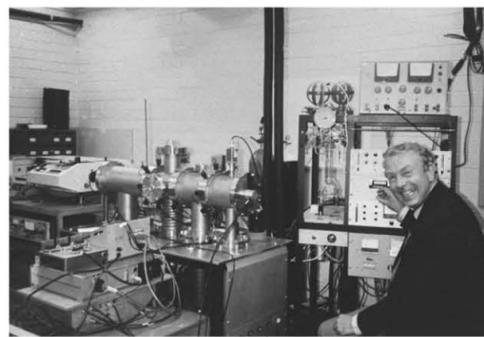
During this same period, McLafferty's group, first at Purdue⁵ and later at Cornell⁶ mounted a series of studies investigating the source of metastable ions in mass spectra from

magnetic sector instruments. These studies led naturally to the use of gas cells in the ion flight path to create metastable ions by collisional activation. A very special case of MS/MS analysis was reported by these researchers in 1967⁷ in which it was shown that a mixture of isomeric hydrocarbons could be differentiated on the basis of the metastable transitions of the molecular ion.

Beynon, shortly after arriving at Purdue in 1969, continued studies of metastable ions begun earlier by McLafferty and shortly thereafter developed the technique of ion kinetic energy spectroscopy (IKES)⁸; a tool to permit 'the route of formation of ions in the mass spectrum to be deduced'. Several years later, Cooks began a collaboration with Beynon that led to the development of MIKES in the early '70s. (See Poster "MIKES (Mass-Analyzed Ion Kinetic Energy Spectrometry): History & Significance") Up until this period, the various studies of ions undergoing unimolecular or collision induced decomposition fell under the broad umbrella of 'fundamentals' at mass spectrometry conferences. In 1976, Cooks and co-workers⁹ used MIKES for the analysis of a mixture of dialkyl ketones. Soon, instruments that had been used for 'fundamentals' became more widely recognized as analytical tools in their own right.

OTHER MASS ANALYZERS

One of the first departures from magnetic sector mass analyzer technology for tandem mass spectrometry was the quadrupole mass filter. Just as in the sector world, initial instrumentation focused on the fundamentals of ionization and fragmentation. Vestal, Futrell and co-workers utilized a tandem quadrupole mass filter¹⁰ for research on the photodissociation cross sections for a variety of small positive and negative ions. This instrumental approach was extended by McGilvery and Morrison in the mid '70s for their photo dissociation studies¹¹ with a triple quadrupole instrument. In their 1978 paper, the authors stated "The technique is not limited to molecular parent ions, but can be extended to the study of any ion which can be produced in the source."



James Morrison with the triple quadrupole mass analyzer at La Trobe University

This was taken to heart by Yost who in the late '70s after working in Morrison's lab in Australia, introduced the triple quadrupole instrument with Enke¹² as a general purpose analytical MS/MS instrument. The use of the RF-only center quadrupole as a collision cell resulted in very high collision efficiency as well as high ion transmission, important parameters in tandem MS instruments. The RF-only quad is a common element in many modern MS/MS instruments where other elements may not be based on quadrupole mass filters.

POLITICAL CORRECTNESS COMES TO MASS SPECTROMETRY

A convenient shorthand method of referring to ions, their origins and their endpoints, came into use very early in the development of the field. Ions selected for further study were called parent ions and ions formed from them as a result of collision induced dissociation were referred to as daughter, grand-daughter ions, etc. In 1992¹³, an objection to this anthropomorphic and sexist language in a field as august as mass spectrometry was raised and this terminology¹⁴ has since been abandoned. Precursor and product ions replaced parent and daughter ions in the '90s.

Another area of instrumentation research with its roots in the '40s gave rise to yet another variety of tandem mass analyzers; ion cyclotron resonance (ICR). By 1970, groups both in the United States¹⁵ and in the United Kingdom¹⁶ began development of more sophisticated versions of this simple mass analyzer. The addition of Fourier transform analysis, sophisticated mathematical processing, high-speed computers and multiple staged ion ejection followed by subsequent collisional activation has trans-

formed an afterthought mass analyzer, the omegatron¹⁷, into one of the most powerful tandem instruments today. The ability to perform 'MS to the nth' experiments is unique to MS/MS instruments based on this type of mass analyzer and provides a powerful tool in fundamental studies.

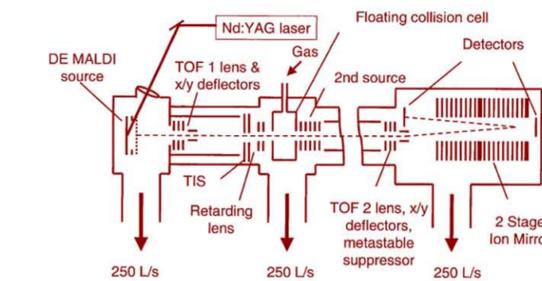
ALPHABET SOUP INSTRUMENTS

The rapid adoption of tandem mass spectrometry by the instrument manufacturers and the mass spectrometry community has led to a sometimes confusing alphabet soup of equipment.

- B = magnetic sector
- E = electrostatic sector
- Q = quadrupole mass filter
- q = RF-only quadrupole
- ToF = Time-of-Flight mass analyzer
- FT = Fourier transform
- ICR = ion cyclotron resonance

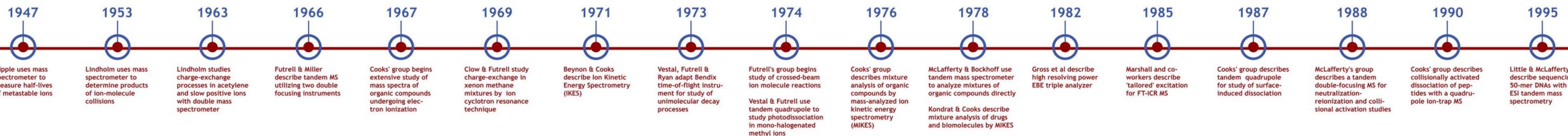
Given only the few mass analyzer elements listed here, the number of combinations that are actually realized in tandem instruments is amazing. Besides the letters spelling out the combined instrument, the specifics of the combination; e.g., BE, B/E, B²E and EB spell out different instruments and/or experiments.

Mamyrin's pioneering reflectron¹⁸ time-of-flight (ToF) mass analyzer breathed new life into a mass analysis tool that had long been regarded as dead. Developments in laser and particle desorption ionization prompted renewed interest in the ToF as well. (See Poster "40th Annual Conference 1992 Washington DC") Now, high resolving power ToF mass analyzers serve as the second MS in a variety of different 'alphabetic' combinations to form particularly useful instruments for the biological community. In some cases, both mass spectrometers are ToF analyzers.



The ion optical layout of a tandem ToF-ToF used by Yergey and co-workers for de novo sequencing of peptides

It is hard to imagine that researchers who first began to assemble tandem mass spectrometers for fundamentals research 50 years ago could envision the instruments of today and the type of problems to which they are being applied. Coupled with advances in ionization methods, the tandem mass spectrometer is a major player in the 'omics' revolution in biology today.



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