CRITICAL INSIGHT

Critical Moments in Time: Reflections on the Development of Orthogonal Acceleration Time-of-Flight Mass Spectrometry

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Abstract

This paper reflects on the historical development of orthogonal acceleration time-of-flight analyzers that have been used routinely for high sensitivity analyses of biological molecules for more than a decade. In particular, the role of the late Michael Guilhaus from the University of New South Wales in Australia is highlighted. This account shows that like most advances in science, successful commercialization of new technology is not straightforward and is often the result of critical contributions of different people and organizations at different points in time.

Key words: Orthogonal-acceleration, Time-of-flight, Tandem mass spectrometry, Quadrupole time-of-flight, Magnetic sector time-of-flight

In July 2010, friends and colleagues gathered at the University of New South Wales in Sydney, Australia to celebrate the life and work of Michael Guilhaus, who had prematurely passed away in October 2009 at the age of 57. His most recent role had been as Director of the Bioanalytical Mass Spectrometry Facility. Like many such facilities around the world, the UNSW facility contains a number of hybrid time-of flight instruments for high sensitivity analyses of biological molecules. During his time as director, Michael and his colleagues used the extraordinary sensitivity and capability of these instruments to probe important biological and analytical questions [1]. They were not unusual. Towards the end of 2011, there had been more than 6000 publications with over 40,000 citations utilizing quadrupole-time-of-flight instruments [2]. These hybrid quadrupole-time-of-flight instruments utilize orthogonal-acceleration (oa)-TOF [3] or orthogonal injection [4] time-of-flight (TOF) as the second mass analyzer. In developing and promoting the benefits of this technology in the early 1990s, Guilhaus ignited a spark that led indirectly to one of the major commercial developments of hybrid technology using time-of-flight as the secondary mass analyzer.

Guilhaus developed his interest in building or modifying instruments as a graduate student at the University of New South Wales (UNSW) [5] and later as a postdoctoral fellow with John Beynon at University College, Swansea, UK. He also combined interesting ion chemistry with a lifelong friendship with Gareth Brenton during his time in Swansea. Guilhaus returned to the UNSW in 1986 to establish his independent research and teaching career. There was an appetite for mass spectrometry development at UNSW with foundations laid in the 1970s by Ian Gregor and Jim Shannon [6], and enhanced by the arrival of Peter Derrick and his grand scale sector instrument in the early 1980s [7]. Jim Dawson (shown in Figure 1) was looking for a new project since he had finished his time with Derrick, who was then in the process of relocating to the University of Warwick, UK. Dawson had considerable skill in optics and electronic control systems developed whilst working on early ion cyclotron resonance systems, first with Keith Jennings as a graduate student at the University of Warwick, UK [8] and later with Nico Nibbering at the University of Amsterdam, The Netherlands [9]. In mid-1986, Dawson and Guilhaus commenced planning a time-of-flight instrument that would offer substantial advantages in terms of resolution and high sensitivity with continuous ion sources. I was working on my thesis in the office next door at that time and while they did not share the details of their “secret project,” I

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Figure 1. Jim Dawson in the late 1980s (photo by Michael Guilhaus)

have no doubt that Guilhaus and Dawson believed they had developed a truly original and exciting concept.

That project was a time-of-flight analyzer with orthogonal acceleration. The concept involved accelerating an ion beam orthogonally away from the axis of their formation to provide both a discrete time event and to minimize the velocity and spatial spread resulting from continuous ionization sources. A key feature of their design was that the flight tube was at an angle. This avoided the need to deflect the orthogonally accelerated ions in order to steer them down an orthogonally orientated flight tube and this, in turn, avoided the degradation in resolution that would otherwise result from such deflection of these ions [10]. The advent of large microchannel plate detectors [11] enabled high sensitivity detection of ions in a plane (rather than focusing into a point), and further advances in electronics and computing were driving a resurgence of interest in time-of-flight mass spectrometry. Dawson and Guilhaus lodged a provisional patent for the design [12] and published the concept shortly thereafter [13].

The patenting due diligence revealed the report of what is now widely understood to be the first instrument with an orthogonal TOF geometry [14]. This instrument was built by the Bendix Corporation in the 1960s and reported only to the US Air Force and so did not appear in the open literature. Guilhaus took full responsibility for the defense of the patent and was over that period engaged in an extensive correspondence with British and US patent attorneys that focused on the differences between their patent and the Bendix

invention [15]. He argued successfully that their design differed from earlier orthogonal instruments in the essential feature of accelerating the ions away from the direction of the initial ionization beam while conserving the axial velocity [16], and the UK and US patents were granted in 1992 [17].

Guilhaus and his associates commenced construction of the first instrument shown in Figure 2. They literally begged and borrowed the parts required since they were yet to obtain any grant funding for the project. By 1994 they were able to achieve a resolution of 4000 at low mass [18]. Dawson meanwhile, focused his attentions on the development of a Macintosh-based software program for ion optical simulations (Ion Opt™), which he had hoped would eventually rival the SIMION program, which also had originated in Australia [6]. Sadly, Dawson's efforts were hampered by an illness that resulted in his untimely death in February 1992.

At about the same time or slightly earlier, Dodonov and colleagues in the USSR developed an orthogonal injection time-of-flight. Their instrument was based on the same orthogonal acceleration principle, and the major advances and motivation were similar. The Russian instrument also incorporated a reflectron, which increased the path length and flight times whilst retaining energy and spatial focusing and, thus, was able to achieve higher resolution [19]. The Australian design focused on very careful modeling of the orthogonal acceleration region to ensure that the beam was well collimated prior to acceleration and to conserve the axial velocity. Dodonov and colleagues filed a USSR patent in February 1987, and reports of their invention became more widely known several years later [19–21]. One of the inventors, Igor Chechnusevich, joined Ken Standing in Manitoba, where an early electrospray TOF instrument was constructed [22], before moving to SCIEX, where he has made a major contribution to the commercial development of electrospray, MALDI, and hybrid TOF technology [23, 24]. Lee and colleagues reported an atmospheric pressure

Figure 2. Michael Guilhaus and his first orthogonal acceleration-time-of-flight. The instrument was designed so that the oa-region was visible and accessible

TOF in 1991 [25], and Boyle and Whitehouse reported an electrospray TOF in September 1992 [26]. Several other groups were also working on hybrid [27] or tandem axial-TOF instruments [28, 29].

That two groups on opposite sides of the world independently developed similar technology unaware of the work of the other seems remarkable today. In the late 1980s, however, the political situation in USSR was turbulent. Travel to Australia was time-consuming and expensive and there was no Internet or e-mail. There is no evidence that the original Russian patent was uncovered during the patenting due diligence. It appears that Guilhaus became aware of Dodonov's work in late 1992 since the copy of the PCT filing of a second USSR patent SU89/00228 in Guilhaus' files has a library date stamp of 3 December 1992 presumably following the Symposium on tandem time-of-flight convened by Bob Cotter in August 1992 [19] or perhaps through the proceedings of the Amsterdam conference [20]. In mid-1992, Guilhaus embarked on an overseas trip to promote their design, starting with a presentation at the American Society for Mass Spectrometry Conference in Washington. Alerted to their project by John Race, who, as Sales Director for VG Analytical, was a regular visitor to Australia, Bob Bateman made a point of attending Guilhaus's presentation and invited him to visit their factory in Manchester, UK the following week. After spending a day with Guilhaus, Bob Bateman had decided the concept was sufficiently interesting to warrant VG building an oa-TOF [30].

Bateman quickly realized that the oa-TOF might provide a second mass analyzer for a magnetic sector as an alternative to the complex and expensive four-sector instruments. Around the same time, Eddie Clayton had suggested to Bob that they consider a magnetic sector-TOF after hearing about David Russell's magnetic sector-axial TOF instrument [27]. Bateman and Clayton published a paper [31] proposing the tandem magnetic sector-orthogonal acceleration TOF in August 1992, in part to try and prevent anyone else successfully patenting this idea. Bateman provided a copy of the paper to Guilhaus prior to publication in case he had some objection or wished to claim co-authorship, neither of which he did. The magnetic sector-oa-TOF provided an elegant solution to the difficulties that had plagued other configurations, including four-sectors and sector-quadrupole instruments [32–34]. VG went on to successfully commercialize this technology, receiving orders for the first magnetic sector oa-time-of-flight instruments late in 1992 [35].

In remarks presented to the July 2010 Guilhaus symposium by John Hoyes on his behalf, Bateman affirmed that the meeting with Guilhaus was critical to VG (now Waters) efforts in this area [30]. He suggested that they would probably not have become aware of the technology until late in 1993 and by then the intellectual property for this and subsequent developments, such as the hugely successful quadrupole-oa-TOFs that followed [36], may have been very different. Bateman's account accords with the information he provided to me in 1996, which formed the basis of the

successful nomination of Guilhaus by the Australian and New Zealand Society for Mass Spectrometry for the International Society for Mass Spectrometry Curt Bruneé prize in 1997.

In seizing the possibility that oa-TOF could serve as a secondary mass analyzer, Bateman no doubt recognized two immediate advantages that relate to the fundamentals of the collision processes underpinning tandem mass spectrometry. The majority of tandem mass spectrometry instrumentation then (and now) used collision-induced dissociation to induce the diagnostic product ions. In this process, the precursor ions collide with a target gas, absorb energy, and decompose to product ions. In the high energy, fixed length collision cells used in magnetic sector instrumentation at the time where the precursor experienced only a small number of collisions, there are two characteristics of the collision dynamics that are relevant. The first is that the product ions have *approximately* the same velocity as the precursors and so are indistinguishable in an axial time-of-flight direction without some post-collision acceleration. The second, more challenging issue is that the large precursor ions lose translational energy as a result of the collision and so that energy focusing of the resulting product ions can depend on both the mass [37] and the nature [38] of the product ions. By accelerating the product ions in an orthogonal direction, any difficulties arising from differences in axial velocities owing to a spread of energies in the product ions become irrelevant. It is not surprising, therefore, that the oa-TOF tandem mass spectrometry took off so quickly. Simultaneously, the problem of collision energy loss was solved with a technology that was simpler to construct than many other hybrid combinations and offered all the time-of-flight advantages of speed and sensitivity.

While the main fuel for the rapid advances in biological mass spectrometry has been the developments of electrospray and matrix-assisted laser desorption, the oa-TOF has played a critical supporting role. This account of one aspect of TOF development shows that it relied on the experience and ideas of many people in both university labs and instrument companies. This demonstrates that it is often difficult to isolate credit for an invention to a single inventive step, especially when a confluence of factors point technology in a particular direction as was happening in the late 1980s. The approach undertaken by Dawson and Guilhaus to hold the ideas in confidence until a patent had been lodged and then attempt to license or sell the technology for a commercial return was typical of the approach of most university technology transfer offices at that time. A similar approach has been followed for much of the ensuing two decades. More often than not, as in this example, a commercial return is not realized because the protected intellectual property is only one piece of a puzzle, or one step along the way. The desire to protect a future return that is rarely realized often stands in the way of the sharing of knowledge and ideas that is necessary to advance technology rapidly when trying to solve challenging problems. Universities may be better placed to realize a more

substantial return from encouraging their staff to engage with those who can rapidly commercialize technology though research contracts, student support, and enhanced reputation. From a purely personal point of view, as I was writing this account, I reflected that Dawson and Guilhaus did not share their ideas with me despite a close friendship and collaboration on other projects. I was at the time about to finish up and move to the US and they were open in their concern in respect to the intellectual property leaking to my new US colleagues. Had they chosen to discuss their ideas, given that my thesis was focused on energy loss of large ions during collision-induced dissociation, I have cause to wonder whether I would have had the insight that Bob Bateman had to see the potential of orthogonal acceleration for tandem mass spectrometry. I suspect not, as I am not sure I had sufficient wisdom at the time.

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