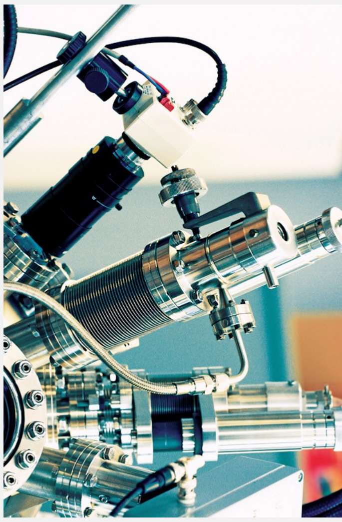
Application Note

Mass Spectrometry and the Modern Digitizer



The scientific field of Mass Spectrometry (MS) has been under constant research and development for over a hundred years, ever since scientists discovered that charged particles could be separated via electromagnetic fields based on their charge-to-mass ratio (Q/m). While spectrometry systems now come in numerous configurations their performance largely depends on a few fundamental elements. In the modern Mass Spectrometer this is normally the ion source (for exciting ions from the material under analysis), the mass analyzer, the particle detector and its associated electronics. Figure 1 shows a simplified block diagram of these principle parts.

Ion Sources

In MS the number of ion sources is extensive and each comes with its own advantages and disadvantages for analyzing different solids, liquids and gasses. The method of ionization plays a key role in what type of samples can be analyzed. For example, for solid or liquid biological samples it is common to use techniques such as electrospray (ES) or matrix-assisted laser desorption/ionization (MALDI) while for analyzing compounds with high molecular weight a chemical ionization process may be more appropriate.

Mass Analyzers

Once ions are excited from a sample they are then passed to a mass analyzer via electric or magnetic fields. In essence the field applies a force to the ions. And as ions with different mass and charge are accelerated at different rates they can be separated. Again there are a number of different mass analyzers used in MS and each offers benefits and drawbacks. Some of the more common mass analyzers are based on a technique known as Time-of-flight (TOF). This method accelerates ions through the same electric field. The analyzer then measures the flight time for each ion to travel to the detector. For ions carrying the same charge their acceleration and velocity will be dependent only on their mass. Light particles will arrive at the detector first and the heavier ones will follow.

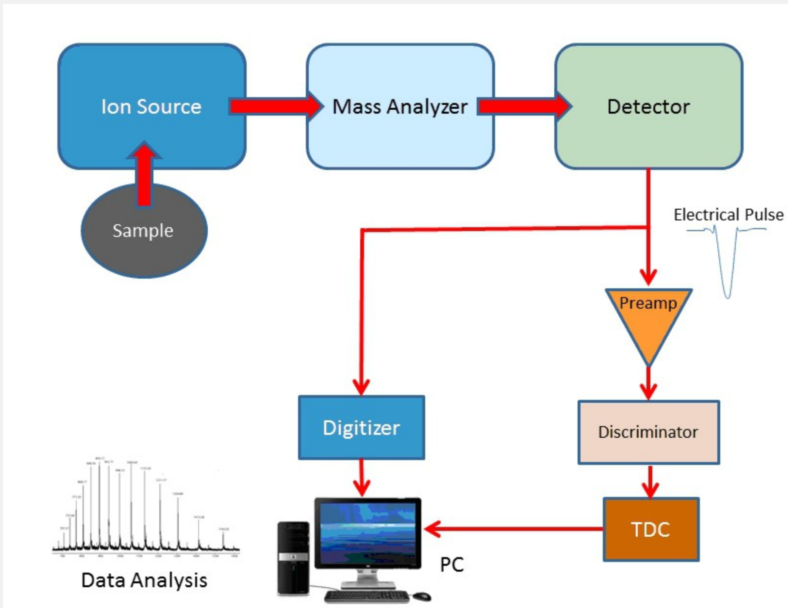


Figure 1: The three main elements of a mass spectrometer are the ion source, mass analyzer and detector. Following that is electronics that is used for acquiring and analyzing the generated electrical pulses.

Other mass analyzers allow selective mass filtering by using oscillating electrical fields (such as a radio frequency quadrupole field generated by four rods) and magnetic fields. While these techniques add to the complexity of an instrument they also offer the possibility of increased measurement resolution and sensitivity.

Detectors

The final piece of the Mass Spectrometer is the detector. This usually consists of an electron multiplier which is used to detect the arrival of a charged particle and convert it to an electrical pulse. The process generally uses a number of electrically charged plates to create an electron avalanche after a charged particle has impacted on the starting electrode. Electron multipliers are available in a variety of designs and materials. Common multipliers include "discrete dynode" multipliers that cascade electrons using sequential multiplying electrodes, each at a different potential voltage, and "continuous dynode" multipliers that use semiconductor materials and curved designs to produce a funneling effect. The result is the creation of electrical pulses that are transferred to electronics for subsequent measurement and analysis.

Analyzing the Pulses

The simplest Mass Spectrometers use current or charge to voltage converters to allow analog measurement. More sophisticated systems use pulse or ion counting methods involving pre-amplifiers, discriminators, counters, time to digital converters (TDC's), digital oscilloscopes and digitizers (as shown in Figure 1). Most modern TOF MS systems are using either TDC or digitizer technology.

Using a TDC

A TDC provides a very cost effective way of measuring the arrival time of each TOF event and allows the creation of a histogram for the mass spectrum (showing the number of times a pulse with a specific arrival time occurs). They are well suited to ion counting systems, such as those found in ESI or LCMS, where ideally single ions hit the detector at any moment.

Available with a wide range of time resolutions (from tens of nanoseconds to a few picoseconds) TDC's can be used to make very accurate TOF measurements. However, TDC's only provide timing information and other characteristics, such as pulse widths and heights, are generally lost. In addition, TDC's have difficulty resolving multiple pulses that are produced by ions arriving at the detector at the same or similar times. The TDC will count these sorts of multiple pulses as a single event. This can make using TDC's in systems where multiple ions hit the detector at each peak (such as with MALDI-TOF) very problematic.

Another issue in dealing with multiple pulses is that it can cause a time skew effect (shifting the mass peak). The TDC only detects one edge of the pulse which may occur at slightly different times for pulses that are created by single and multiple events. This can become a significant problem, particularly in high ion count rate situations.

Finally, in order to create a spectrum with good dynamic range it's necessary to make a lot of acquisitions. In practice this can be tens of thousands. This becomes extremely challenging if the system has a low repetition rate, which will be the case if it relies on a laser shot being fired several times per second.

First Generation Digitizers and Averagers

To overcome the shortfalls of using a TDC it's possible to use a digitizer and acquire the entire pulse waveform. A digitizer that is well matched to the detector will not only be able to measure the pulse arrival time but also its shape and amplitude. Furthermore, a digitizer with sufficient acquisition memory can capture, with a single trigger, a number of pulses arriving at different times in the same acquisition. As such, it can operate as a multi-hit device acquiring pulses over time periods that may be from microseconds to tens of milliseconds.

Historically, the use of digitizers was restricted to MS with ion source event rates that were relatively low. For example, in MALDI-TOF systems, where the repetition rate of the laser is usually less than a few hundred Hertz. The reason for this is that once a digitizer makes an acquisition it normally needs to offload the digitized data to a host computer before it can make another acquisition. Most early PC based digitizers where built on PCI technology and as such where only able to transfer data at rates of around 100 MB/s. This led digitizer manufacturers to create products with additional memory as well as on-board summation hardware, usually with a field programmable gate array (FPGA), so that multiple acquisitions could be processed and stored on-board the digitizer. The additional hardware effectively reduces the amount of data that needs to be sent to the computer. Products with this capability are sometimes referred to as signal “averagers” or integrating transient recorders.

With their faster trigger and acquisition rates averagers are suited to working with the higher repetition rates found in spectrometers such those using a continuous ion source, like in most orthogonal acceleration (aoTOF) machines, or ions that are produced by Inductively Coupled Plasma (ICP). In these systems the repetition rates can be tens of KHz.

The main disadvantages of averager products is their cost (which is usually higher than a conventional digitizer) and the fact that the summation hardware often has limited acquisition memory, thereby restricting the maximum single shot capture time.

Current Generation Digitizers and Analyzers

The latest generation of digitizers has gone a long way towards eliminating these short falls. By using a PCIe bus, rather than the older PCI, data transfer speeds can now easily surpass 3 GB/s. Furthermore, most fast digitizers now also come with FPGA technology as standard. The ultra-fast transfer rates and FPGA technology effectively allow users to choose their own signal processing path. Acquired waveforms can be pushed to the PC as fast as they are acquired so that both hardware and software based averaging processes can be utilized as appropriate. For example, Spectrums M4i.2230-x8 digitizer card shown in Figure 2 can sample at rates up to 5 GS/s, has bandwidth over 1.5 GHz and 4 GSamples of on-board memory. As such, it is can comfortably make long acquisitions and capture fast sub-nanosecond pulses. The unit has an FPGA which when utilized can enable the summation of 32 kSamples acquisitions at trigger rates up to 150 kHz, or 128 kSamples acquisitions at rates up to 38 KHz. For even longer acquisitions the card has been tested making software summations of 512 kSamples acquisitions at rates over 6 KHz. The ability to sum multiple long acquisitions in software is due largely the cards 8 lane, generation 2, PCI bus that supports data transfer rates up to 3.4 GB/s.

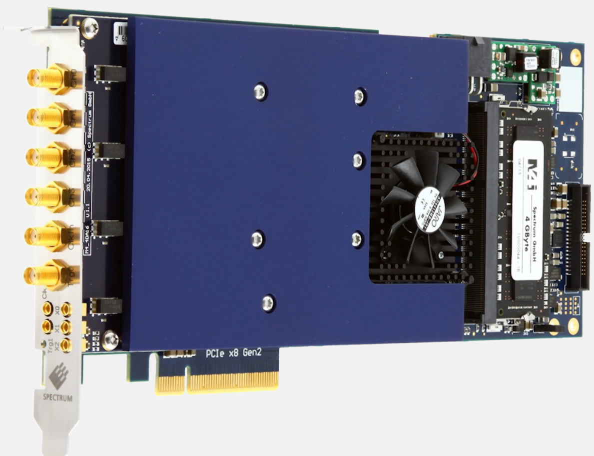


Figure 2: The Spectrum M4i.2230-x8 digitizer card is ideal for capturing pulses as narrow as 500 ps and offers on-board FPGA based averaging along with ultra-fast 3.4 GByte/s data transfer

For further details on how the M4i series digitizers perform hardware and software averaging, including the setup and test results, please see the Product Note "Using Software Based Fast Block Averaging" available here

http://spectrum-instrumentation.com/en/using-software-based-fast-block-averaging

Another feature of the modern digitizer is that it can also operate in a fashion similar to a TDC. With the appropriate firmware (such as Spectrums "Block Statistics" option) the cards can be setup to perform a peak detection function. This effectively locates the position of a peak (with respect to a trigger point) together with its maximum or minimum vale. This mode can operate at very high trigger rates and the results can be used to create histograms of the peak positions

Selecting a Digitizer

With the wide variety of MS instruments on the market no single digitizer product can cover all possible systems. Consideration needs to be given to key specifications such as sampling rate and bandwidth, which define the narrowest pulses that can be digitized, as well as vertical resolution and sensitivity, which affect dynamic range and the ability to acquire both large and small pulses. Spectrum has a wide range of digitizers offering a variety of performance capabilities. The following table summarizes the models that are most suited to use in Mass Spectroscopy.

Model	Channels	Sampling Rate	Resolution	Bandwidth	Memory Per Channel	Hardware Block Averaging	Hardware Block Statistics	Data Transfer Speed
M4i.2230-x8	1	5 GS/s	8 Bit	1.5 GHz	4 GSample	Optional	Optional	3.4 GB/s
M4i.2220-x8	1	2.5 GS/s	8 Bit	1.5 GHz	4 GSample	Optional	Optional	3.4 GB/s
M4i.2221-x8	2	2.5 GS/s	8 Bit	1.5 GHz	2 GSample	Optional	Optional	3.4 GB/s
M4i.2210-x8	1	1.25 GS/s	8 Bit	500 MHz	4 GSample	Optional	Optional	3.4 GB/s
M4i.2211-x8	2	1.25 GS/s	8 Bit	500 MHz	2 GSample	Optional	Optional	3.4 GB/s
M4i.2212-x8	4	1.25 GS/s	8 Bit	500 MHz	1 GSample	Optional	Optional	3.4 GB/s
M4i.4450-x8	2	500 MS/s	14 Bit	250 MHz	1 GSample	Optional	Optional	3.4 GB/s
M4i.4451-x8	4	500 MS/s	14 Bit	250 MHz	512 MSample	Optional	Optional	3.4 GB/s
M4i.4420-x8	2	250 MS/s	16 Bit	125 MHz	1 GSample	Optional	Optional	3.4 GB/s
M4i.4421-x8	4	250 MS/s	16 Bit	125 MHz	512 MSample	Optional	Optional	3.4 GB/s
M4i.4410-x8	2	130 MS/s	16 Bit	65 MHz	1 GSample	Optional	Optional	3.4 GB/s
M4i.4411-x8	4	130 MS/s	16 Bit	65 MHz	512 MSample	Optional	Optional	3.4 GB/s

Table 1. Spectrum offers an extensive range of digitizer products with ADC resolutions of 8, 12, 14 and 16 bits and sampling rates up to 5 GS/s.

Application Note

Low amplitude pre-amplification

Figure 3. The SPA series amplifiers are ideal for use where low level detector signals need to be amplified prior to being input into a digitizer.

For low amplitude pulses, that may require amplification before being input to the digitizer, Spectrum also offers a range of small and compact pre-amplifiers (as shown in Figure 3) that can be used with most of the above digitizer products. These low noise amplifiers are available with AC and DC coupling, 50Ω and 1 MΩ impedance, gains of x10, x100 and bandwidths up to 2 GHz.

For further information on the full range of pre-amplifiers please visit our web site at:

http://spectrum-instrumentation.com/en/external-pre-amplifier

Case Study

Figure 4. The laser system (foreground) used by a REMPI based Mass Spectrometer (back left corner) developed at Latrobe University

As mentioned above the ion source plays a key role in determining the type of sample that can be analyzed by a particular spectrometer. One technique that offers great potential for the pharmaceutical industry is resonance-enhanced multi-photon ionization (REMPI). REMPI is a laser-based gas phase spectroscopy combined with ab initio calculations generating precise structural information on molecules such as neurotransmitters. The result is a rigorous platform for understanding the molecule behavior and ultimately, rationalizing drug design. The resonant two photon ionization technique allows electronic (and IR) spectra to be measured for molecules cooled to a few degrees Kelvin. This results in beautiful, simplified spectra that can be interpreted in terms of the possible conformers of the molecule.

The technique relies on a time-of-flight mass spectrometer, where particular ions are selected based on their arrival time. Figure 4 shows a REMPI MS system developed at Latrobe University, Melbourne, Australia.

This instrument uses a Spectrum 250 MS/s, 14 bit PCIe digitizer (model M3i.4121-exp) for data collection, display and analysis. Figure 5 shows screen shots of the instruments set-up window and results while running spectra. Digitizer control and data analysis is performed using a customized program that was developed using LabVIEW.

Figure 5. LabVIEW based instrument setup with screen shots of running spectra

Conclusion

The field of MS continues to develop as instruments with ever improving resolutions and sensitivities are designed and manufactured. As modern digitizers offer the ability to acquire electronic signals with better time resolution (higher sampling rate) and improved vertical dynamic range (more bits of resolution) they are playing a key part in this change. In addition, the ability of modern digitizers to transfer data at speeds some 30 times faster than their predecessors has allowed more processing to be performed in a PC. This new capability enables digitizers to be used in more MS applications as it reduces acquisition time limitations, helps to simplify the products, as well as lowering their cost and complexity.