Suppressing Noise in TOF-MS with FASTFLIGHT™-2

D. A. Gedcke

Synopsis: This application note describes the sources of noise that determine mass accuracy and detection limits in Time-of-Flight Mass Spectrometry, when employing a digital signal averager for data acquisition. Techniques are described for reducing both the random and correlated noise contributions to achieve better mass accuracy and lower detection limits. The discussions of random and correlated noise are relevant to several other signal-processing applications.

How Signal Averaging Affects Noise

The main purpose of a digital signal averager is to improve the signal-to-noise ratio, while recording the time signature of a repeatable signal. In general, it can be used to extract signals from a noisy environment in a broad set of signal-processing applications. However, this application note focuses on managing noise with a digital signal averager in the field of time-of-flight mass spectrometry (TOF-MS). The ORTEC FASTFLIGHT-2 will be used as a specific, illustrative example. Many of the principles discussed are transferable to other signal-processing applications.

Briefly, a digital signal averager consists of:

- a synchronization trigger,
- a sampling clock that determines the frequency at which the analog signal is sampled,
- a flash ADC that samples the analog input signal and converts it to a digital record, and
- a memory that sums the records from successive scans.

The trigger is used to align the start of each record with the same point on the repeated analog signal. That enables successive records to be lined up for summing or averaging. A typical sampling period for the ADC is 0.5 ns, and an exemplary record length is 100 µs. Anywhere from 1 to 65,535 records are summed to produce an averaged record. For convenience, the summed or averaged record will be referred to as a "spectrum" in the TOF-MS application.

It is helpful to categorize the noise processed by a digital signal averager as either random (uncorrelated) noise or correlated noise. Noise is "correlated" if it is systematically linked to the time of stimulation of the repeated signal, and/or correlated with the sampling clock employed in the digital signal averager. *Because of the invariant relationship between correlated noise and the signal, summing or averaging many samples of the signal does not improve the signal-to-correlated-noise ratio.* Correlated noise behaves like it is an inseparable feature of the signal.

Random noise is any source of undesired interference whose time of occurrence is not correlated with the signal. *The ratio of signal to **random** noise improves as the square root of the number of records averaged.*

Simply stated, a digital signal averager can improve the signal-to-noise ratio for random noise but not for correlated noise. Thus, the correlated noise becomes the ultimate limit for extracting weak signals, when many samples of the signal are averaged. Fortunately, for most practical cases, the dominant noise is random, and the digital signal averager is productive in improving the signal-to-noise ratio.

The Digital Signal Averager in a TOF-MS

Figure 1 shows the application of the FASTFLIGHT-2 in a typical time-of-flight mass spectrometer. The ionized molecules are injected into the acceleration chamber of the TOF-MS. Periodically, (e.g., at 100 µs intervals) a high voltage acceleration pulse of amplitude V is applied to the acceleration electrode. This causes the ions of mass m and charge z to accelerate through the grounded grid, and drift with constant velocity from the grid to the detector. Lighter molecules are accelerated to a higher velocity, while heavier molecules achieve a lower velocity. Thus, the time of flight, t, over the distance d from grounded grid to detector is

$$t = \frac{d}{\sqrt{2V}}\sqrt{\frac{m}{z}} \qquad (1)$$

Consequently, the flight time is a measure of the mass-to-charge ratio, m/z, of the ionized molecule.

When a group of molecules having the same m/z value strikes the microchannel plate detector, the detector produces an output pulse whose amplitude is approximately proportional to the number of impinging molecules. The Fast Preamplifier amplifies these pulses to make them suitable for the 0 to –500 mV range of the FASTFLIGHT-2. As viewed in the resulting time spectrum, the widths of these pulses are typically in the range of 1 to 6 ns, with the upper limit determined by imperfections in the ion optics of the spectrometer, and the lower limit set by the bandwidth of the electronics.

There are two options for synchronizing the acceleration pulse in the TOF-MS with the triggering of the scan in the FASTFLIGHT-2. To achieve the lowest jitter between the acceleration pulse and the sampling clock, the FASTFLIGHT-2 Trigger Output should be used to initiate the acceleration pulse. This Trigger Output is precisely synchronized with the free-running sampling clock in the FASTFLIGHT-2. Alternatively, the TOF-MS can decide when to activate the acceleration pulse, and an attenuated copy of that pulse is used to trigger the start of a scan in the FASTFLIGHT-2 via the Trigger Input. With the external trigger input, there is an uncertainty of ±1/2 of the sampling period in synchronizing the sampling clock with the acceleration pulse. For a 500 ps sampling interval (2 GS/s sampling rate), that uncertainty is ±250 ps. For peaks wider than 1 ns in the spectrum, this will cause less than a 6% broadening. The choice of triggering mode does have an effect on the correlated noise, and this will be addressed below.

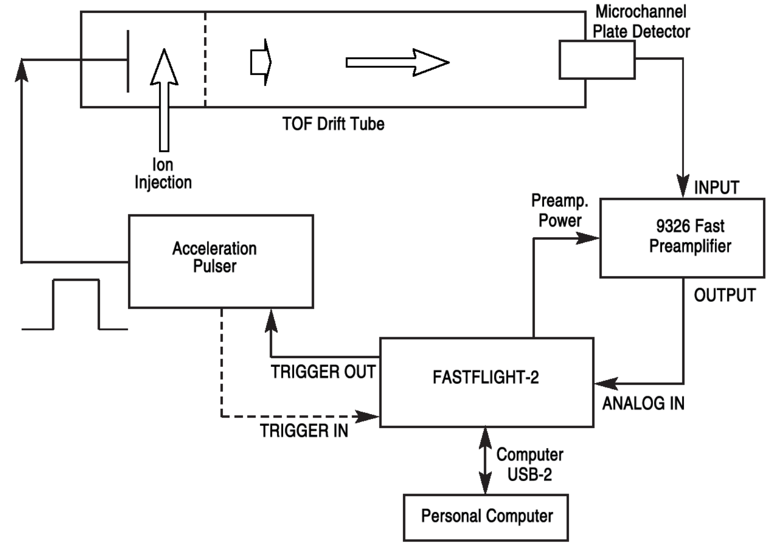

Figure 1. A simplified depiction of the FASTFLIGHT-2 Digital Signal Averager employed in a time-of-flight mass spectrometer.

Sources of Random Noise in the TOF-MS Application

In order of significance, the random noise sources encountered in the TOF-MS application with a digital signal averager fall into the following categories:

1. Statistical fluctuations in the number of ions from the acceleration source in the TOF-MS
2. Statistical fluctuations in the gain of the microchannel plate detector
3. Thermal noise from the preamplifier input stage
4. Thermal noise of the analog input stage in the digital signal averager
5. Unrelated environmental electrical interference
6. Power supply and power line noise.

Statistical Fluctuations in the Number of Ions and the Detector Gain: For the vast majority of TOF-MS spectra, items 1 and 2 are the dominant contributors to the uncertainty in signal amplitude. In ORTEC application note AN61[1] the percent standard deviation, $\sigma_A\%$, in the area under the peak, A, is shown to be

$$\sigma_A\% = \frac{\sigma_A}{A} \times 100\% = \frac{\sqrt{1+\left(\frac{1}{n_e}\right)}}{\sqrt{N}} \times 100\% \qquad (2)$$

Where N is the number of ionized molecules detected in the peak, and n_e is the average number of electrons released at the cathode of the detector by a single molecule. Given that generous limits for the value of n_e are 1 to 100, the square root in the numerator in equation (2) ranges from 1.414 down to 1.005. Table 1 summarizes $\sigma_A\%$ for the two extreme ranges of n_e for interesting values of N.

Table 1. Statistical Fluctuations in the Peak Area due to the Number of Ions Detected

Number of Ions N	$\sigma_A\%$ Lower Limit (%)	$\sigma_A\%$ Upper Limit (%)
1	100.5	142
100	10	14
10,000	1	1.4
1,000,000	0.1	0.14

Even more important for mass spectrometry, the uncertainty in measuring the centroid position of the peak can be shown[1] to have the same form as equation (2), i.e.,

$$\sigma_C\% = \frac{\sigma_{tC}}{\sigma_{ft}} \text{ x } 100\% = \frac{\sqrt{1+\left(\frac{1}{n_e}\right)}}{\sqrt{N}} \text{ x } 100\% \qquad (3)$$

Where $\sigma_C\%$ is the standard deviation in measuring the position of the peak centroid, expressed as a percentage of the inherent jitter in the flight time of a single ion from the acceleration region to the cathode of the detector. More specifically, σ_{tC} is the random error in the peak centroid, and σ_{ft} is the inherent jitter in the flight time of a single ion. Thus, Table 1 can be used to estimate the uncertainty in the measured value of m/z via equations (3) and (1).

Equations (2) and (3) both show the importance of collecting a large number of ions in each peak in the spectrum. The percent errors decline in proportion to the square root of the number of ions in the peak. If the number of ions from each acceleration pulse cannot be increased, N can be increased by summing records from many acceleration pulses. That is the benefit offered by the digital signal averager.

Thermal Noise from Analog Amplifiers: Every amplifier contributes random noise. The amount of noise is normally determined by the resistors and amplifying devices used in the input stage of the amplifier. Because this noise is a function of temperature, it is usually characterized as thermal noise. Manufacturers will usually specify the equivalent input noise over the specified bandwidth of the amplifier. For example, an equivalent input noise of 50 µV rms for the preamplifier implies that the "root-mean-square" (rms) random noise at the output of the preamplifier will be 50 µV x 10 = 500 µV, if the preamplifier has a gain of 10.

If the equivalent random input noise for the digital signal averager is 1 mV rms, then the combined random noise from the preamplifier and digital signal averager will be

$$\sigma_{TN} = \sqrt{\left((0.5 \text{ mV})^2 + (1 \text{ mV})^2\right)} = 1.12 \text{ mV} \qquad (4)$$

Expressed as a percent of full scale (500 mV), this is a relatively small number, i.e.,

$$\sigma_{TN}\% \text{ FS} = \frac{\sigma_{TN}}{500 \text{ mV}} \text{ x } 100\% = 0.22\% \qquad (5)$$

Consequently, its contribution is normally small compared to the contribution from ion statistics in Table 1.

Environmental Electrical Interference, Power Supply and Power Line Noise: These contributions can usually be rendered negligible by careful design and installation. It is important to keep the cable connections short, particularly from the detector to preamplifier, and to avoid ground loops.

Sources of Correlated Noise in the TOF-MS Application

Typical sources of correlated noise are:

a) Electrical interference caused by, or synchronized with the TOF-MS accelerator pulse.
b) Coaxial cable reflections of the analog input signal.
c) Ringing of the detector output signal following each pulse.
d) Residual noise correlated with the sampling clock and trigger within the digital signal averager.

The Acceleration Pulse in the TOF-MS has rapidly rising and falling edges and a large voltage amplitude. These factors generally combine to cause images of the rising and falling edges to be detected by the more sensitive analog electronics in the spectrometer. These leading and falling edge spikes are often visible in the first ten microseconds of the digital signal averager spectrum. Delaying the start of the scan until these edges have passed is a productive scheme for suppressing that interference.

Coaxial Cable Reflections can cause an attenuated copy of the signal to appear at a delayed time in the spectrum. The delay time is related to the transit time for a reflection to return to the receiving end of the cable. It is most important to ensure that the cables have the proper impedance and are accurately terminated with that characteristic impedance. Proper receiving-end termination is crucial. Series termination in the characteristic impedance at the sending end can be helpful, where feasible. Sometimes the cables can be kept short enough to hide any reflections within the originating peaks.

Ringing of the Detector Output Signal inserts damped oscillations after every peak. Keeping the coaxial cable connection between the detector and the preamplifier extremely short can help to limit the duration of the ringing. But, ultimately, careful impedance matching in the detector design is necessary to minimize the ringing.

Residual Correlated Noise within the Digital Signal Averager: Once the analog signal is converted to a digital representation by the ADC a lot of digital routing and processing ensues. In the averager memory bits are being toggled at a rate controlled by the 2 GHz sampling clock. It is inevitable that attenuated images of these extremely fast bit transitions will be picked up by the sensitive analog input circuits. This interference can be conveyed by radiation, or by conduction through the power lines and along the ground plane of the circuit board. Careful design and layout is used to minimize this source of correlated noise. But, it can become the limiting source of noise when averaging more than a few hundred records per spectrum.

Measuring the Equivalent Input Noise of a Digital Signal Averager

Figure 2 shows the dependence of the equivalent input noise of the FASTFLIGHT-2 on the number of records averaged. The measurement is made by collecting a spectrum with no signal connected to the analog input. The rms noise in the spectrum is computed from

$$\mathrm{NOISE}_{rms} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - Y_{av})^2}{n-1}} \qquad (6)$$

Where y_i is the signal amplitude for point i in the spectrum, and Y_{av} is the average amplitude for all n bins in the spectrum.

$$Y_{av} = \frac{\sum_{i-1}^{n} y_i}{n} \qquad (7)$$

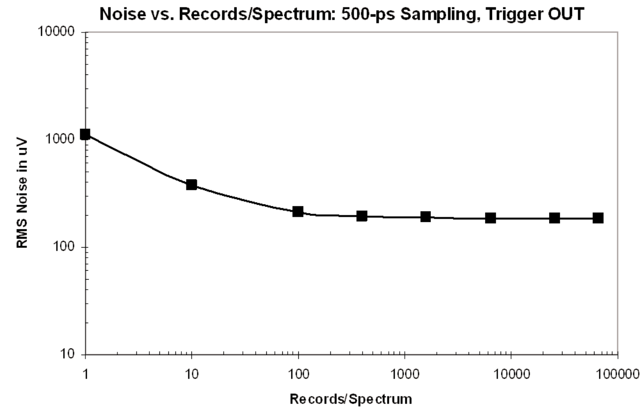

Figure 2. The equivalent input noise (µV rms) for the FASTFLIGHT-2 versus the number of records summed, with 0.5 ns sampling in the Trigger Output mode.

The $\text{NOISE}_{\text{rms}}$ value is transformed into an equivalent input noise by dividing by the number of records summed in the spectrum, R, and multiplying by the full scale range in mV divided by the full scale range in LSB (least significant bits), i.e.,

$$\text{Equivalent Input Noise (rms)} = \left(\frac{500\ \text{mV}}{255}\right)\left(\frac{\text{NOISE}_{\text{rms}}}{R}\right) \qquad (8)$$

If the noise spans less than 1 LSB at the ADC, it is necessary to add a dithering that increments between records, but remains at a constant voltage during each record. Without this dithering, the noise cannot be measured accurately. For the FASTFLIGHT-2, this requires turning on the Precision Enhancer for the noise measurement.

From 1 to almost 100 records/spectrum in Figure 2, the equivalent input noise decreases in proportion to the square root of the number of records/spectrum. But, beyond 100 records/spectrum the noise floor is reached. This noise floor is caused by the correlated noise, which does not decrease as additional records are added to the average.

Dithering the Trigger Suppresses Correlated Noise

Figure 3 shows the results of the same measurement as in Figure 2, except the Trigger Input Mode was selected instead of the Trigger Output mode. In Figure 3, the equivalent input noise continues decreasing in proportion to the square root of the number of records averaged until circa 10,000 records/spectrum. Beyond 10,000 records/spectrum, a hint of the correlated noise floor is beginning to appear. Moreover, the correlated noise floor in Figure 3 is more than a factor of 20 below the noise floor in Figure 2.

Why does the Trigger Input Mode lower the correlated noise by a factor of 20? In managing the memory, the 2 GHz sampling clock is divided down to 31.25 MHz, i.e., a 32 ns period. As a result, the rather ragged correlated noise pattern tends to repeat every 32 ns. The time at which the Trigger Output is generated is synchronized to the 31.25 MHz clock. Consequently, the Trigger Output is synchronized to the repeating 32 ns correlated noise pattern. The Trigger Input, on the other hand, defaults to the nearest 2 GHz clock pulse. Thus the Trigger Input randomly samples all phases of the 32 ns correlated noise pattern. That tends to average the correlated noise towards zero.

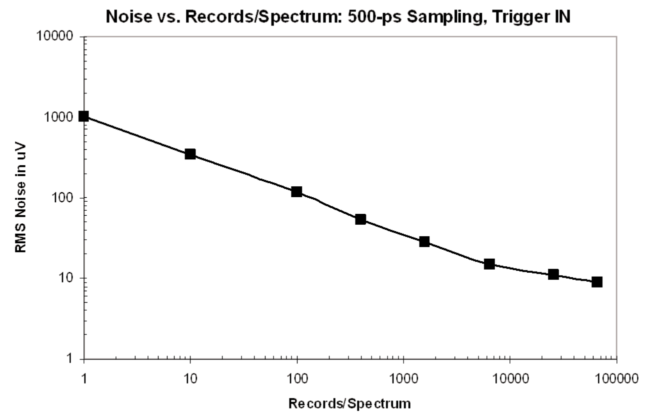

Figure 3. The same measurement as in Figure 2, but in the Trigger Input Mode.

Subtracting the Correlated Noise Pattern

To the extent the correlated noise pattern is repeatable, it can be saved and subtracted from each acquired spectrum to reduce the noise floor. The conditions for acquiring spectra are chosen, and a correlated noise reference spectrum is acquired under the same conditions, with the signal source turned off. This reference spectrum is subsequently subtracted from each acquired spectrum to squelch the correlated noise. Pragmatically, about a factor of 5 to 10 suppression of the correlated noise can be achieved by this scheme. To achieve the higher suppression ratio, the dc offset of the correlated noise reference spectrum must match the dc offset of the spectrum that contains the signal. Any mismatch of the dc offsets results in the toggling of slightly different bit patterns, and that alters the correlated noise pattern. The correlated noise pattern reference must also be collected with enough records averaged to render the random noise insignificant. If the pattern is precisely repeatable with a 32 ns period, only a 32 ns image needs to be stored for subtraction. Enough 32 ns intervals can be averaged in a single reference spectrum to easily suppress the random noise error.

Adaptive Correlated Noise Subtraction

A more efficient algorithm for subtracting correlated noise has been implemented in the FASTFLIGHT-2. It derives the estimate of the correlated noise pattern from the background regions between peaks in each spectrum[2] as the spectrum passes through the Data Formatter and Compressor on it way to the computer. Typically, there are enough 32 ns intervals in the background to allow a sliding average to continuously update the correlated noise pattern to the local conditions in the spectrum. This adaptive scheme results in higher ratios for correlated noise suppression and eliminates the issue of dc offset mismatches. Correlated noise suppression ratios as high as 20 are achievable.

Figure 4 shows the suppression of correlated noise achieved by turning on the adaptive correlated noise subtraction for the Trigger Output Mode. The correlated noise floor is now as low as was obtained with the Trigger Input Mode.

Figure 5 shows the effects of turning on the adaptive correlated noise subtraction algorithm in the Trigger Input Mode. Only a slight lowering of the correlated noise floor is achieved in this case.

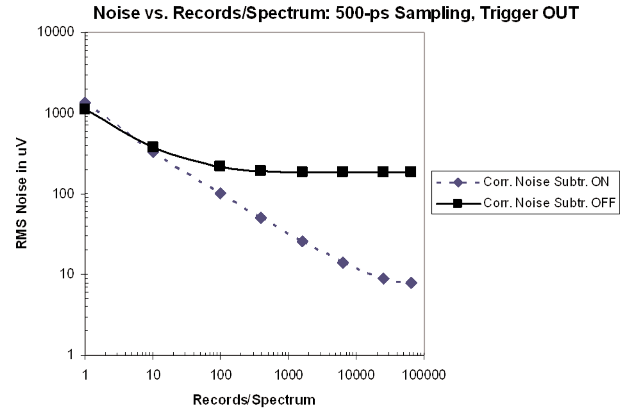

Figure 4. The same measurement as Figure 2, but the curve for adaptive correlated noise subtraction has been added (dashed line).

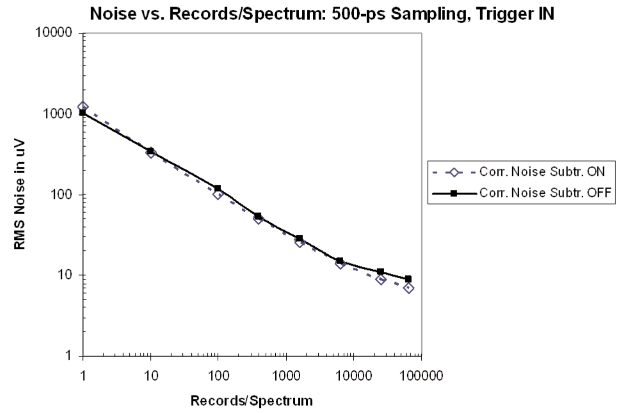

Figure 5. The same as Figure 3, but the curve for adaptive correlated noise subtraction has been added (dashed line).

Duet Operation for Lower Correlated Noise

Figure 6 shows a scheme[3] for lowering the significance of correlated noise by an additional factor of 10. It employs two units of the FASTFLIGHT-2 operating in parallel. Preamplifier A and digital signal averager A provide the normal acquisition of the full range of signals from the microchannel plate detector. Preamplifier B amplifies the signals by an additional factor of 10 before they are presented to digital signal averager B. This makes the signals a factor of 10 larger compared to the correlated noise in digital signal averager B, thus lowering detection limits by that same factor on the smaller signals. Of course, the larger signals will exceed the full-scale range of the ADC in digital signal averager B. Hence, the spectra from digital signal averager A are used for processing the larger signals, and the spectra from unit B are referenced for the smaller signals.

A few details are worth mentioning briefly. The 50-Ω splitter, that presents the preamplifier A output to digital signal averager A and preamplifier B, must have adequate high-frequency bandwidth to avoid signal distortion. The quality of the 50-Ω splitter in the trigger path is less critical, because it is processing the trigger logic pulses.

If the TOF-MS requires an external trigger input, FASTFLIGHT-2 A can provide its Trigger Output to the TOF-MS and the Trigger Input of FASTFLIGHT-2 B.

The "Busy Out" to "Trigger Enable" connections between the two digital signal averagers are used to ensure neither unit tries to acquire a new scan until both units are ready. The "10 MHz Clock Out" from unit A is synchronized to the 2 GHz sampling clock of unit A via a phase-locked loop. Providing that signal to the "10 MHz Clock In" for unit B forces the 2 GHz sampling clock in unit B to lock its phase and frequency to the 2 GHz sampling clock in unit A. This ensures that the two time scales are precisely synchronized. Naturally, small differences in the signal transit time through the coaxial cables and preamplifiers will induce a slight difference for zero time in the two spectra. But, this time shift can be eliminated by a simple calibration of the zero offset.

The duet arrangement can lower detection limits by circa another factor of ten beyond the previously discussed methods, when correlated noise controls detection limits.

Noise Thresholding

This method has been used since the earliest days of MALDI TOF-MS. The concept is simple[4]. The baseline between pulses is shifted far enough below the zero of the sampling ADC so that the noise in the absence of pulses is just off-scale. Consequently, the noise on the baseline will not be summed or averaged when multiple records are added to form the spectrum. Bona fide pulses, caused by the ionized molecules hitting the detector, will have sufficient amplitude to rise into the digitizing range of the ADC. Consequently, the pulses will be summed, whereas the noise on the baseline will not. This method can completely eliminate the correlated noise contribution to the baseline. However, it does introduce a non-linearity in the amplitude response that is most severe on the smallest pulses. Also, it does not eliminate the correlated noise pattern that is superimposed on the recorded pulses.

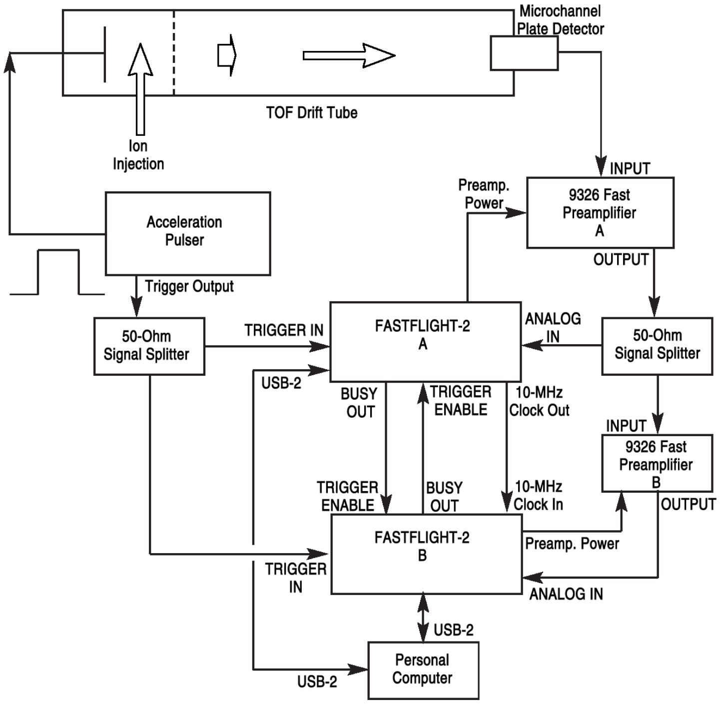

Figure 6. Duet arrangement for increased dynamic range, with the TOF-MS triggering the FASTFLIGHT-2 units.

Conclusions

Detection limits and the precision with which the mass can be measured in TOF-MS depend on both the random and the correlated noise in the spectrum. The number of ionized molecules recorded in a peak and the detector gain statistics are the dominant sources of random noise. The percent error from these two sources can be reduced by counting more molecules. Increasing the number of ionized molecules can be accomplished by raising the concentration of ions injected at the accelerating source and/or by summing a large number of records from successive acceleration pulses. The later function is facilitated by a digital signal averager.

When summing more than a few hundred records, correlated noise can become the limiting factor setting detection limits for weak signals. The correlated noise floor can be reduced by a factor of circa 20 by a) subtracting the known correlated noise pattern from each spectrum, or b) by dithering the triggering of the record with respect to the sampling clock. Operating two digital signal averagers in parallel, one with a factor of 10 higher gain than the other, can result in a further factor of 10 reduction of the correlated noise. In some cases "noise thresholding" can be effective in improving detection limits.

Employing the above strategies for noise reduction can lead to a dynamic range for pulse amplitudes in the neighborhood of 50,000:1 to 500,000:1, as measured from full scale to the root mean square limits of the residual correlated noise. Under the usual circumstances where acquisition time is limited, detection limits and mass precision will be controlled primarily by the number of ionized molecules recorded in the peak[5].

References

[1] D.A. Gedcke, *How Counting Statistics and the ADC Sampling Interval Control Mass Accuracy in Time-of-Flight Mass Spectrometry,* ORTEC Application Note AN61, July 2001.

[2] U.S. Patent No. 5,995,989.

[3] Beavis, Ronald C., *Increasing the Dynamic Range of a Transient Recorder by Using Two Analog-to-Digital Converters,* J. Am. Soc. Mass Spectrom. (1996), 7(1), 107–113.

[4] ORTEC Application Note AN53, *Diving Deep into Single-Ion Counting with FASTFLIGHT*, www.ortec-online.com, Sept. 2000.

[5] ORTEC Application Note AN59, *How Counting Statistics Controls Detection Limits and Peak Precision,* www.ortec-online.com, May 2001.