Technical Article

Boost Time of Flight Mass Spectrometry with Low Noise, High Speed ADCs

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Abstract

Time of flight mass spectrometry (TOF MS) has become a critical instrument for applications in many fields, especially for its irreplaceable role in clinical microbiology laboratories for bacterial identification. At the heart of TOF MS is the low noise, high speed analog-to-digital converter (ADC). In this article, we review the fundamentals of TOF MS with a focus on its key parameters. This article discusses the relationship between TOF MS parameters and ADC specifications. Mixed-signal front-end (MxFE®) ADCs demonstrate that low noise, high speed ADCs can greatly improve metrics of TOF MS including mass accuracy, mass resolution, and sensitivity.

Introduction to TOF MS

Mass spectrometry (MS) is an analytical technique for quantifying known/unknown molecules within a sample based on molecular weight. By ionizing elements and/or molecules in the sample into gaseous ions with or without fragmentation and then separating them in a mass analyzer, the elements and/or molecules are characterized by their mass-to-charge ratio (*m/z*), or location of the pulses, and relative abundance, or the amplitudes of the pulses, in the mass spectra.

A mass spectrometer consists of three major components: the ion source for producing gaseous ions from the sample under test, the mass analyzer for separating ions according to their *m/z* ratios, and the ion detector for detecting the ions and the relative abundance of each ion species. The detector output is conditioned and digitized to produce a mass spectrum. Several mass analyzers with fundamentally different strategies for separating ions of different *m/z* values are available.[1] Figure 1 shows major blocks of quadruple and TOF MS.

In TOF MS, ions formed by a short ionization event are accelerated by an electrostatic field so that ions of different *m/z* have the same kinetic energy but different velocities. The ions then travel over a field-free drift path and arrive at the detector with different flight time—the lighter ions arrive before the heavier ones do, as illustrated in Figure 2. In practice, the flight time of a pack of ions of the same *m/z* distributes to form a pulse that can be as narrow as a few hundred picoseconds (ps) due to differences in initial spatial distributions and energy (or velocity) in the acceleration region. Each pulse is the sum of signals corresponding to multiple independent ion arrival events and often is characterized by the full width at half-maximum (FWHM) parameter.

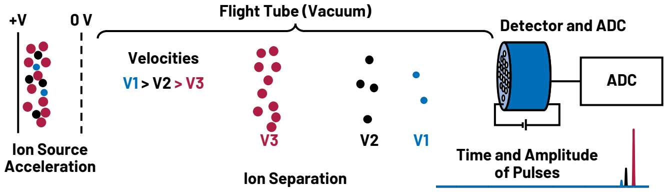

Figure 2. An illustration of time of flight mass analyzer.

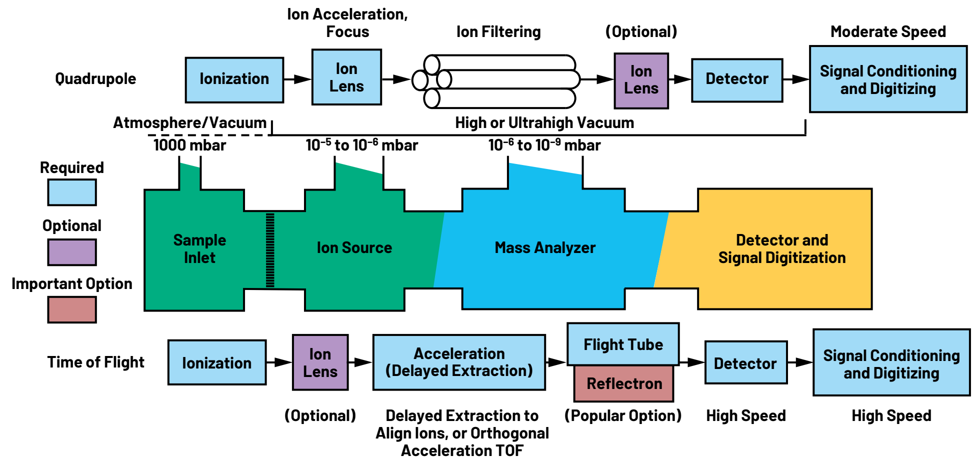

Figure 1. Major blocks of quadruple and TOF MS.

A detector, such as a microchannel plate (MCP) detector, detects incoming ions and produces an electric current of pulses. The electric current is recorded with a time-to-digital converter (TDC) or a high speed ADC. While TDC can be extremely fast down to a few ps, it has a limited dynamic range for registering the amplitude of the pulses. High speed ADCs can achieve 2 or more giga samples per second (GSPS) with 10-bit, 12-bit, or even higher bit resolution, allowing precise registration of both timing and amplitude of the pulses. We will discuss important specifications of high speed ADCs that impact the performance of the TOF MS.

Applications of TOF MS

TOF MS has gained significant interest since the 1990s when the matrix-assisted laser desorption and ionization (MALDI) was invented and commercialized.[2] The MALDI technology ionizes the matrix molecules, typically organic acids, and vaporizes the sample molecules at the same time with ultraviolet (UV) laser pulses from hundreds of ps to a few nanoseconds (ns). In the gas phase, the matrix molecules transfer protons to the sample molecules so that the sample molecules are protonated and become charged ions. Because the matrix absorbs most of the laser energy, molecules in the sample retain their integrity without fragmenting or decomposing, making MALDI the most compelling ionization method for the analysis of biological macromolecules. With easy coupling between MALDI and TOF MS, unlimited mass range, high sensitivity, and high throughput, TOF MS has become an essential tool for biomedical research, drug discovery, and clinical applications where analytes are often macromolecules.

Notably, MALDI TOF MS plays an irreplaceable role in clinical bacterial identification with its fastest turnaround time of 4 hours, compared to 72+ hours by conventional or other novel technologies.[3] Short turnaround time is critical to the care and outcome of patients suffering from bacterial infections. Additional advantages of MALDI TOF MS include easy sample preparation, low operation cost, and the potential to identify some rare bacteria. With antimicrobial resistance posing a major threat to human health around the world, there is a trend for MALDI TOF MS as a point-of-care device.[4]

Key Parameters of TOF MS

The ability of TOF MS to quantify the different analytes in the test samples depends on many factors, including choice of sample ionization method, configuration, and timing characteristics of electric fields for accelerating and guiding the ions towards the ion detector, detector efficiency, and signal digitization. We limit our discussion to key specifications of TOF MS that are related to signal digitization, including mass range, mass accuracy, mass resolution, repetition rate, and sensitivity.

The mass range is the range of molecular weight of molecules in the sample and is related to several factors, including accelerating voltage, flight tube length, sampling rate, and repetition rate. The mass range requirement varies from application. For instance, the bacterial identification by MALDI TOF MS measures ribosomal markers in the mass ranges of 2,000 Da to 20,000 Da.

Since mass is calculated from flight time, the mass accuracy of TOF MS is primarily determined by the accuracy of time measurement of the pulses. In practice, the arrival time of each pulse is calculated by fitting the pulse to a Gaussian function and finding the peak. The ADC sampling rate determines the number of samples for an individual pulse and is critical for fitting the pulse.

The mass resolution is a measure of the closest distinguishable separation between two neighboring pulses in the spectrum. It is often defined as the ratio of the ion mass to the width of the corresponding mass pulse. A typical definition of the width of a pulse is the FWHM. The narrower the pulse is, the higher the mass resolution is, meaning a better differentiation between two ion packs with close molecular weights. While the mass resolution can be significantly improved by orthogonal acceleration and reflectron, the ADC sampling rate and noise performance also affect this key specification.

In TOF MS, the mass spectrum is the summation of signals from many repeats rather than a single transient that includes only a single process of ionization, acceleration and drifting, and ion detection and digitization. More importantly, for test samples with multiple molecules of different molecular weights and concentrations, a single ionization event may neither produce ions of all molecules of interest nor the ratios proportional to their concentration. Summation is an efficient and practical approach to reduce such sampling error and improve the signal-to-noise ratio (SNR). Hence, the repetition rate is an important and practical specification of TOF MS for SNR and throughput. The latest TOF MS can achieve 1 kHz or faster scan, meaning each transient takes 1 millisecond (ms) or less. Increasing the ADC sampling rate shortens the duration of each transient for a faster repletion rate.

The sensitivity of TOF MS is the capability to detect the molecules with the lowest concentration in the samples. It is collectively determined by many factors such as the chemical background noise, the range of concentrations of all molecules of interest, the noise figure and dynamic range of the detector and the ADC, and the number of transients summed for the final mass spectrum. In practice, the system sensitivity can be optimized by identifying the bottleneck factor and/or balancing these factors.

Desired ADC Specifications for TOF MS

Low noise, high speed ADC is critical to the system performance of TOF MS. As previously discussed, the accuracy of time measurement and the system noise level are two important specifications of TOF MS instrument. While there is a workaround for system noise level by summation of repetitive measurement, the accuracy of the time measurement is determined by the sampling rate and the aperture jitter of the high speed ADC. Considering the pulses can be as narrow as a few hundred ps in TOF MS instrument with orthogonal acceleration and reflectron, there are only a few samples for an individual pulse at a 5 GSPS sampling rate. Every sample is crucial to find the peak of the pulse when the samples are fitted to a Gaussian function. Hence, sampling rate and aperture jitter are desirable ADC specifications.

The sensitivity is determined by the system noise level that can be improved by summation of repeated measurements. However, the number of repetitions limits the throughput of the instrument. The noise performance of ADC is important for achieving targeted sensitivity with fewer repetitions. There is often a misperception pertaining to the performance of ADC that its SNR is proportional to its bit resolution. ADCs with a sampling rate of 1 GSPS or above often use the pipelined architecture and have specifications including an effective number of bits (ENOB) and noise density/noise figure/SNR/etc. However, pipelined ADCs cannot achieve the bit resolution since they suffer several disadvantages contributing to the noise, including high gain and large bandwidth op amps required to reduce errors, capacitor mismatch, and the power dissipation of the front-end sample-and-hold (S/H) and op amps.[5] The ENOB is input frequency and sampling rate dependent and calculated with signal-to-noise and distortion ratio (SNDR). For instance, the 12-bit AD9081 has an ENOB of 8 bits at 4 GSPS with an input frequency of 4500 MHz. ENOB is not a good measure of the ADC noise performance. Noise density is a step closer to the practical noise level but bench test with Gaussian pulses holds the ground truth of the noise performance of ADC and therefore the sensitivity of TOF MS instrument.

Bench Test of Low Noise, High Speed ADC

The MxFE offers smart integration of RF ADCs, digital-to-analog converters (DACs), on-chip digital signal processing, and clock/phase-locked loop (PLL) for multichip synchronization. MxFE parts with high speed ADCs only are also available. For simplification, our bench test used the AD9082, which has both ADCs and DACs integrated, as shown in Figure 3. The integrated DAC was used to generate a narrow Gaussian pulse train with an FWHM of 0.5 ns and amplitude controlled by a combination of digital scaling and external attenuators. The Gaussian pulses are much closer to the signal in mass spectra than the typical single-tone signal for ADC characterization. Two ADC channels are set up for digitizing signal: CH1 for various amplitudes saturated or attenuated by varying the external attenuators and CH2 as reference for the signal strength above 90% full-scale (FS) without saturation. The sampling rate was 6 GSPS in our test for sufficient samples for each pulse.

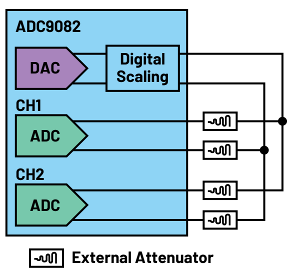

Figure 3. A block diagram for high speed ADC test with the AD9082.

Three types of tests were performed:

- Attenuation and saturation tests: CH2 with fixed 7 dB attenuator pair as a reference; CH1 with 8 dB, 9 dB, and 10 dB attenuator pair for attenuation cases and 3 dB and 1 dB attenuator pair for saturation cases.
- Weak signal measurement with up to 20 dB attenuation: CH2 connected directly to DAC output as a reference with –16 dBFSC scaling; CH1 with 10 dB attenuator pair for <32% FS signal and 20 dB attenuator pair for <10% FS.
- Noise measurement: CH2 with fixed 7 dB attenuator pair as reference; CH1 with 50 Ω termination.

For each test, we acquired >10 µs data and repeated the data acquisition 10 times for reproducibility check. We plotted and analyzed the data in MATLAB®. The 10 repeats were aligned and plotted for each test case. Figure 4 showed a single pulse in the test where CH1 is 3 dB lower than CH2. The 10 repeats were well overlapped for both channels, demonstrating high reproducibility of the data acquisition.

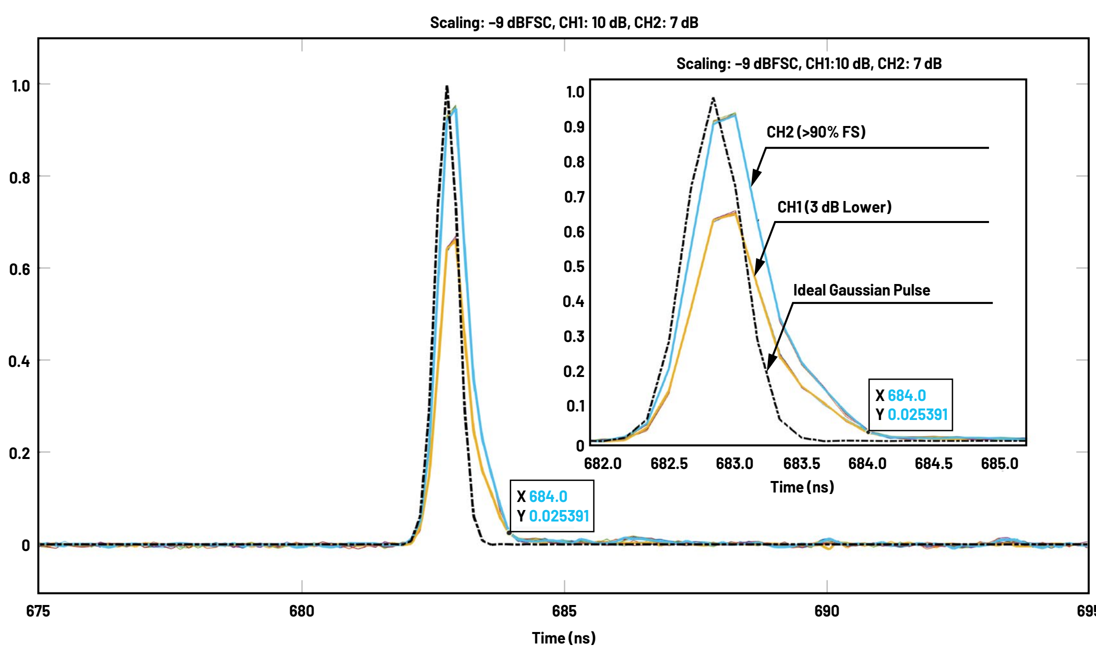

Figure 4. Overlap of the 10 repeats demonstrated high reproducibility of the data acquisition.

The AD9082 ADC has an overload protection circuit, which will be activated if the amplitude of the input is higher than the upper limit. There is often a recovery tail at the falling phase of the pulse if the protection circuit is activated, resulting in a clipped peak at FS and a recovery tail. A shorter recovery tail is important for accurate time and hence mass measurement for TOF MS. Figure 5 showed the plot of five cases with either saturation (up to 6 dB) or attenuation. There was a recovery tail of <0.4 ns for 6 dB saturation, suggesting minimal recovery widening when the protection circuit was activated.

To test ADC performance with weak input, we acquired the signal attenuated by 10 dB and 20 dB, as shown in Figure 6. The clean trace of the signal was at 10% FS, or attenuated by 20 dB, suggesting minimal noise contributed by the ADC.

For the ADC noise floor, CH1 was connected with 50 Ω terminator while CH2 remains at >90% FS, as shown in Figure 7.

We analyzed the noise data by plotting the histogram and calculating its standard deviation, as shown in Figure 8. The standard deviation of this case was at 0.0025, suggesting an SNR of 52 dB at FS.

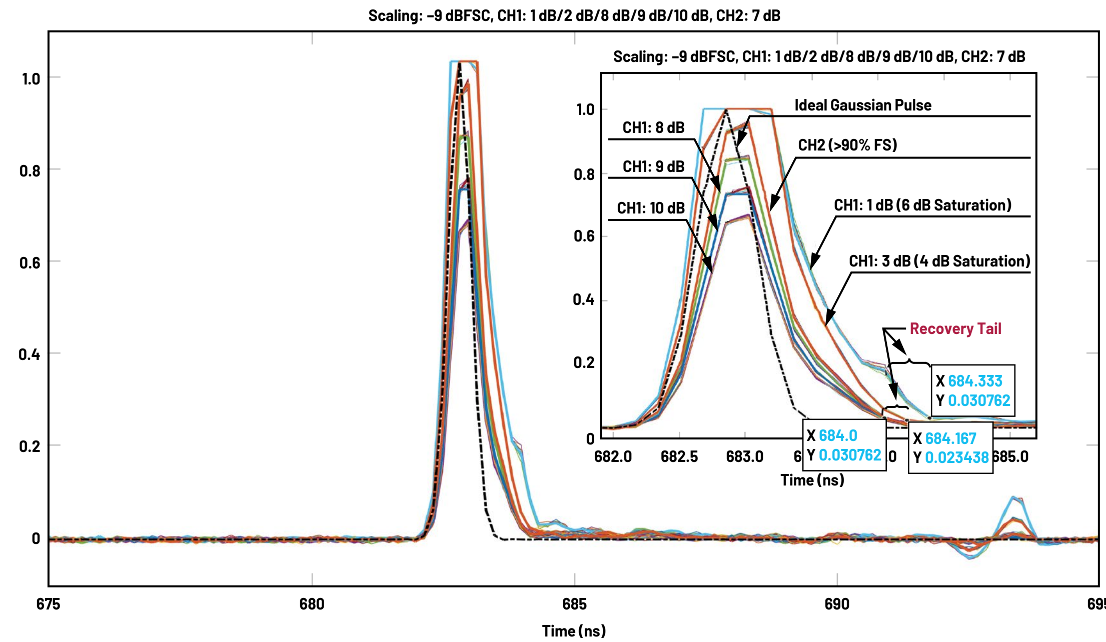

Figure 5. Overlap of five test cases with either saturation or over attenuation.

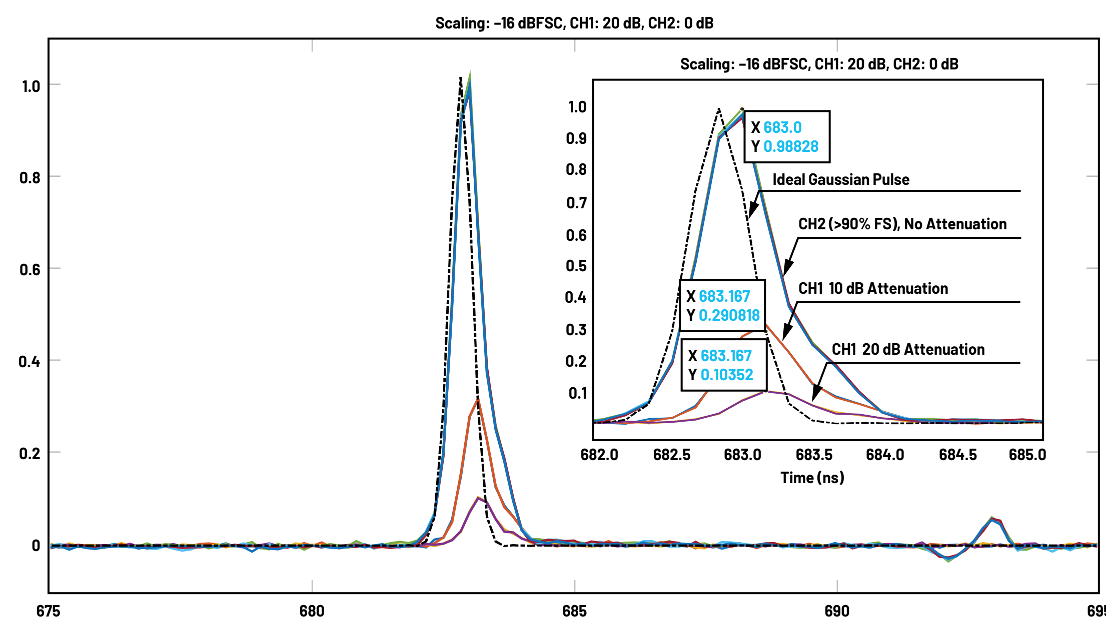

Figure 6. Test cases with input attenuated by 10 dB and 20 dB.

To further quantify the accuracy of time measurement and noise performance, we segmented each pulse with the peak in the center of a 30 ns window. We then fitted each pulse with a Gaussian model to measure its FWHM. We used 12 ns data on each side, or 24 ns total, of the 30 ns window as the baseline for noise calculation.

Figure 9 was the plot of the complete acquisition for the test case of input at 10% FS and zoom-in of a single pulse with Gaussian fit and segmented baseline. Table 1 listed the mean and measured FWHM and calculated SNR.

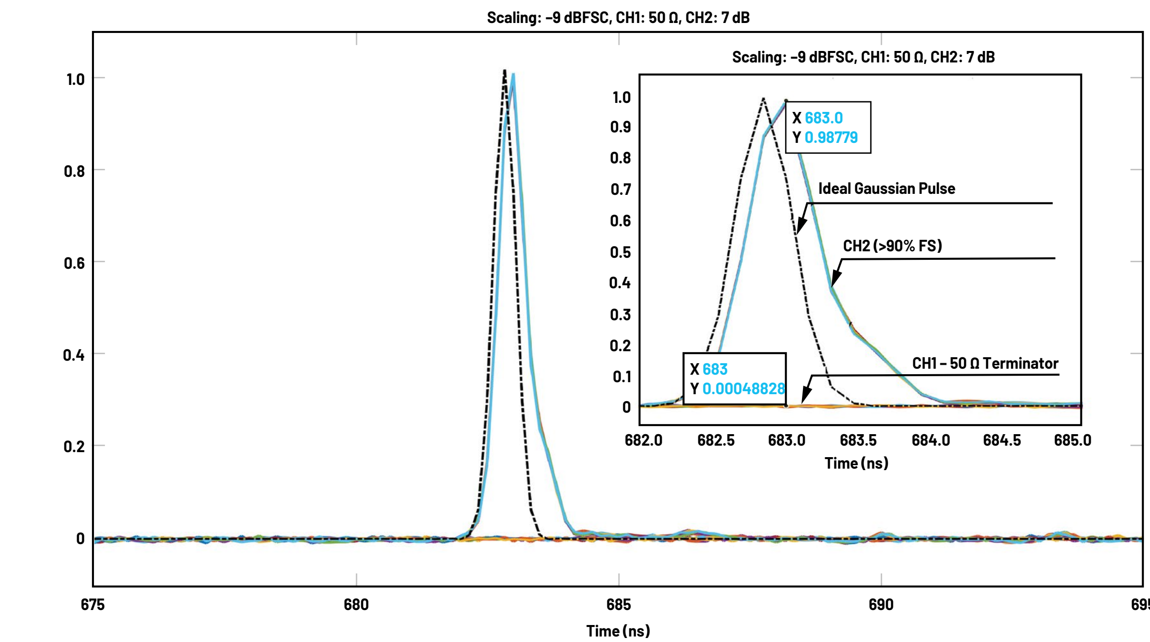

Figure 7. Noise floor measurement with CH1 connected with 50 Ω terminator.

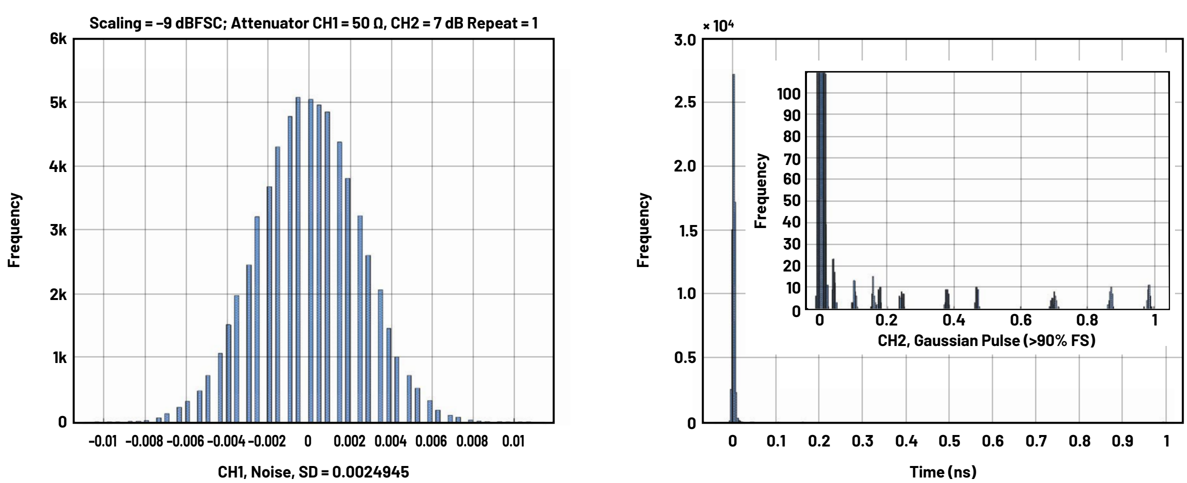

Figure 8. Histograms of noise floor (CH1, left) and FS signal (CH2, right) measurement.

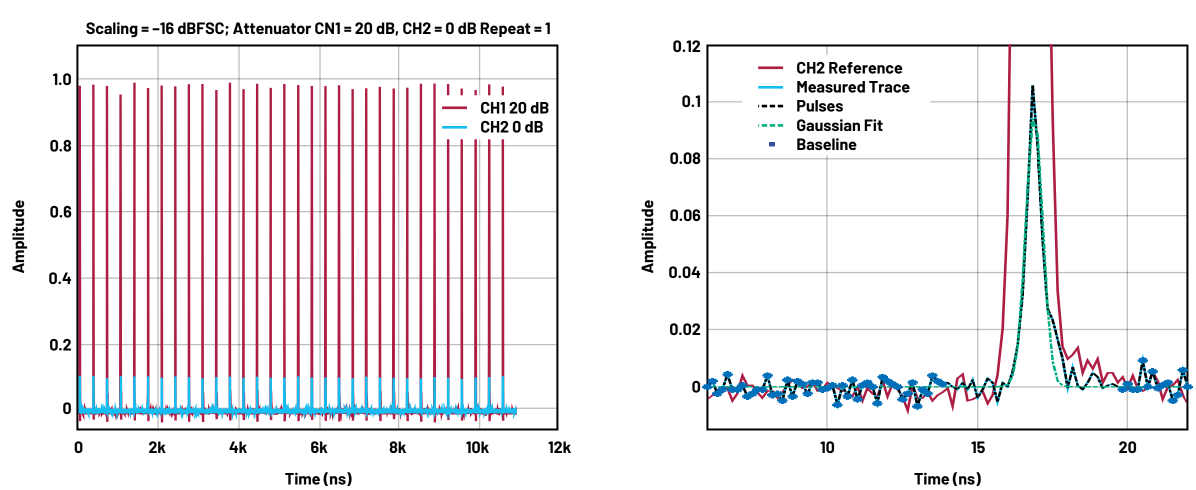

Figure 9. Pulse and baseline segmentation for FWHM and SNR measurement for the test case of input at 10% FS.

Table 1. Measured FWHM and SNR for the Test Case of Input at 10% FS

CH #	FWHM (ns)		SNR (dB)	
	Mean	SD	Mean	SD
CH1 (20 dB)	0.6722	0.0141	32.07	0.468
CH2 (0 dB)	0.6657	0.0056	40.98	0.203

We measured the FWHM and SNR of all test cases with input attenuated from 1 dB to 20 dB. The results were summarized in Table 2. The results suggested accurate time measurement with consistent FWHM readout across various input amplitudes.

Table 2. Measured FWHM and SNR

Cases	FWHM (ns) CH1/CH2		SNR (dB) CH1/CH2	
	Mean	SD	Mean	SD
CH1=8 dB, CH2=7 dB	0.6543/0.6531	0.0050/0.0028	46.21/47.28	0.275/0.363
CH1=9 dB, CH2=7 dB	0.6656/0.6532	0.0037/0.0024	46.24/47.22	0.408/0.439
CH1=10 dB, CH2=7 dB	0.6549/0.6520	0.0028/0.0024	47.44/47.05	0.587/0.273
CH1=10 dB, CH2=0 dB	0.6708/0.6652	0.0075/0.0044	41.72/41.02	0.556/0.248
CH1=20 dB, CH2=0 dB	0.6722/0.6657	0.0141/0.0056	32.07/40.98	0.468/0.203

Discussion and Conclusion

With the establishment of MALDI TOF MS as standard care for bacterial identification in clinical microbiology laboratories and growing interest in proteomics for personalized medicine, the MALDI TOF MS is expected to continue its growth momentum in healthcare in the coming decades. There are also broad applications of TOF MS in biomedical and drug discovery research, food safety, and environmental surveillance because of its advantage for intact molecules with a wide range of molecular weights. With superior noise performance and sampling rate 3× to 6× faster than the ADCs in the current generation of TOF MS instruments, the low noise, high speed ADC is a critical part of next-generation high performance TOF MS instruments. The high sampling rate makes it possible to reduce the footprint of TOF MS instrument without sacrificing performance because it can reduce the length of the flight tube and hence the burden of the vacuum system. A smaller footprint is important for point-of-care applications and various field applications of TOF MS.

There are limitations in our bench test of the AD9082, including limited availability of external attenuators for creating test cases with low amplitude input (such as 1% FS, or 40 dB attenuation), impedance mismatch causing reflection in the data, and open space without shielding of electromagnetic interference. The reported SNR of the test cases was lower than its actual value because reflection in the baseline caused by impedance mismatch was not removed in the noise calculation. MxFE evaluation boards along with graphic user interface (GUI) software are available for more intensive test. Detailed instructions aided by live demonstration can facilitate setting up the customer evaluation system. Prototyping with MxFE samples is easy with guidance from an experienced application team.

The measured FWHM and SNR demonstrate superior time accuracy and noise performance of the MxFE ADCs. The up to 10 GSPS sampling rate of MxFE available on the market gives the flexibility to design next-generation TOF MS with better mass accuracy and mass resolution, higher sensitivity, and an even smaller footprint. In addition, MxFE ADCs are backed by power, clocking, and driver products to help ensure seamless systems integration and optimization.

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