

# High-Performance Data Acquisition for Fourier Transform Mass Spectrometry

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**Abstract:** High-performance data acquisition and processing (DAQ) systems are characterized by their ability to capture, process, and transmit data with high speed, precision, and efficiency. Among commercial solutions for Fourier transform mass spectrometry (FTMS), the FTMS Boosters developed by Spectroswiss stand out. These systems enhance the capabilities of FTMS platforms, such as Orbitrap and ion cyclotron resonance (ICR) instruments, by improving mass resolution, sensitivity, and data handling. This review highlights the impact of FTMS Boosters across six key applications: mass spectrometry imaging, charge detection mass spectrometry (CDMS) and charge determination analysis (CHARDA), biopharmaceutical analysis, isotope ratio and trace analyses, super-resolution mass spectrometry, and complex mixture analysis. By advancing FTMS capabilities, FTMS Boosters not only elevate performance but also extend the operational lifespan of legacy FTMS systems, offering a sustainable and cost-effective path to improved MS functionality. As FTMS technologies advance with an increasing focus on acquiring and processing big data, FTMS Boosters, and other high-performance DAQ systems are set to become indispensable in addressing the growing demands of data-intensive scientific research and applications.

**Keywords:** Charge detection mass spectrometry · Complex mixture analysis · Isotope ratio analysis · Mass spectrometry imaging · Super-resolution mass spectrometry

## 1. Introduction

Fourier transform mass spectrometry (FTMS) platforms, including ion cyclotron resonance (ICR) and Orbitrap instruments, have fundamentally transformed molecular and macromolecular analysis, supporting fields from biopharmaceutical research to environmental science.<sup>[1–7]</sup> Known for their high resolution, accuracy, and sensitivity, FTMS instruments are beneficial in applications requiring detailed molecular characterization, such as mass spectrometry imaging (MSI),<sup>[8]</sup> complex mixture analysis, isotopic ratio determination, biotherapeutics structural analysis, and quantitative proteomics. However, the inherent limitations of built-in data acquisition (DAQ) systems, compounded by constraints introduced by associated data reduction procedures,<sup>[9–11]</sup> may restrict these platforms in applications demanding ultra-high or ultra-low spectral resolution, enhanced sensitivity, and higher throughput. The recent advent of high-performance DAQ systems has created an opportunity to mitigate these constraints and to enhance the capabilities of FTMS instruments and expand their application landscape.

A general high-performance DAQ system integrates fast and precise data capture with advanced processing and efficient data handling.<sup>[12]</sup> It is ideal for applications that require real-time data analysis, operations with large data sets, or very high measurement accuracy. Furthermore, high-performance DAQ systems often offer configurable channels, triggering options, and support for multiple signal types (analog, digital, and mixed-signal), enabling them to adapt to various application needs. All the above directly apply to modern FTMS technology, where a wide range of applications demand exceptional performance and flexibility in data acquisition and processing methods.

FTMS Boosters (Spectroswiss, Lausanne, Switzerland) are high-performance DAQ systems specifically engineered to address and overcome the intrinsic limitations of standard FTMS

instrumentation and meet modern FTMS demands.<sup>[13]</sup> These DAQ systems have been externally interfaced with almost every type of FTMS instruments employed in academic and industrial analytical laboratories, Fig. 1.

By improving resolution, sensitivity, throughput, and data processing efficiency, FTMS Boosters address limitations of conventional FTMS systems, enabling more precise, robust, and efficient analyses in diverse applications. These include spatial lipidomics and metabolomics, biopharmaceutical research for analyzing monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs), isotope ratio (IR) analysis and trace pollutant detection in environmental sciences, multiplexed quantitative proteomics, and complex mixture analysis. This brief review introduces fundamentals of high-performance DAQ system architecture and highlights selected examples of applications. It examines how FTMS Boosters enhance analytical workflows in laboratories utilizing legacy FTMS equipment and those striving to extend the boundaries of FTMS capabilities with state-of-the-art setups.

## 2. High-Performance Data Acquisition and Processing Systems

*Key Factors of a High-Performance DAQ System.* The following factors, taken together, differentiate a high-performance DAQ system from a regular one: (i) high (horizontal) sampling rate; (ii) high (vertical) resolution; (iii) low noise and high signal-to-noise ratio (SNR); (iv) large bandwidth; (v) advanced data processing capabilities; (vi) extended transients or long record lengths; and (vii) high throughput and data transfer rates. In the following, we will briefly review these factors and discuss their relevance to FTMS Boosters.

(i) *High (Horizontal) Sampling Rate.* High-performance DAQ systems can sample signals at rates of several million samples per second (MS/s) or even giga-samples per second (GS/s) and apply advanced digital signal processing (DSP) algorithms to the sampled data in real-time. A sufficiently high sampling rate enables the system to accurately capture all (e.g. sinusoidal) signals within a broad frequency range of interest (e.g. generated by trapped os-

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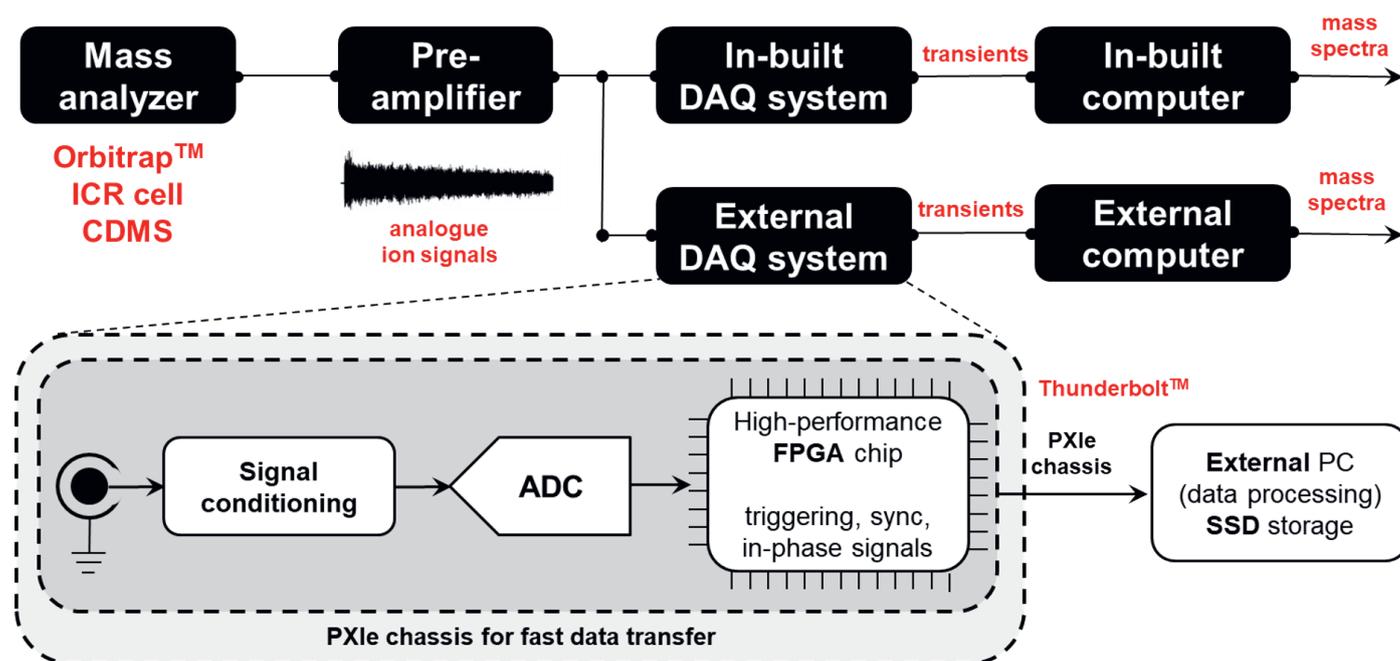


Fig. 1. FTMS Booster systems architecture and their external interfacing to FTMS and charge detection mass spectrometry (CDMS) instruments. ADC: analog-to-digital converter; FPGA: field programmable gate array; PC: personal computer; SSD: solid state drive.

cillating ions). This accuracy is achieved by avoiding phase and amplitude distortions in the final digital data through advanced DSP applied to the intermediate digital signal sampled at a high rate. The intermediate signal is then reduced without loss of information to a smaller-sized final digital signal, adhering to the Nyquist criterion. Additionally, advanced DSP techniques can be applied to the acquisition of a start-stop trigger signal, which is also sampled at a high rate, further ensuring precise and reliable data acquisition. The FTMS Boosters sample the input signals at rates of up to 250 MS/s and save the corresponding output digital signals at a suitable sample rate (several possible values down to 0.279 MS/s), which is chosen automatically as a function of the FTMS instrument and the lowest  $m/z$  value of interest. In FTMS, the latter corresponds to the highest oscillation frequency of the ions.<sup>[14]</sup>

(ii) *High (Vertical) Resolution.* The analog-to-digital converter (ADC) resolution determines the amplitude quantization of sampled data. High-performance DAQs often use 14-bit or even 16-bit ADCs, providing accurate data and allowing finer differentiation between the signal levels. The FTMS Boosters employ 14-bit ADCs, offering a sufficiently low quantization error below the noise errors defined by the FTMS ion detection circuitry.

(iii) *Low Noise and High Signal-to-Noise Ratio (SNR).* High-performance DAQ systems feature low-noise analog electronic front ends and are designed with advanced shielding considerations to minimize electronic noise in mass spectra. This design helps prevent the inclusion of spurious electronic noise peaks, which is particularly critical when digitizing low-level signals or signals with amplitudes spanning a wide dynamic range.

(iv) *Large Bandwidth.* With a sufficiently large bandwidth, a high-performance DAQ system can accurately digitize a given frequency range of interest. The FTMS Boosters offer a frequency bandwidth of 100 MHz, matching data sampling requirements and allied real-time DSP algorithms that correspond to the most advanced and demanding FTMS instruments, such as 21 T FT-ICR MS platforms.<sup>[14,15,16]</sup>

(v) *Data Processing Capabilities.* Advanced processing capabilities, such as real-time digital filtering, Fourier transform (FT), super-resolution (SR) algorithms, and signal direct current (DC) level adjustment, enable high-performance DAQ systems to per-

form data manipulation and analysis during acquisition. These capabilities reduce the reliance on extensive post-processing and streamline the overall workflow. Crucially, FTMS Boosters can digitally decode input trigger signals from the FTMS instrument, allowing precise synchronization of the acquisition start time with an external 'start' trigger signal. Additionally, they enable the acquisition of the complete transient signal from the 'start' trigger to the 'stop' trigger, ensuring comprehensive and accurate data capture. In contrast to FTMS Boosters, conventional built-in DAQ systems are typically configured to acquire only a fixed number of data points from the 'start' trigger.<sup>[17]</sup> Furthermore, they may exhibit significant jitter in the acquisition start time relative to the precise timing of the 'start' trigger.

(vi) *Extended Transients or Long Record Lengths.* High-performance DAQ systems often can record extended data streams (longer transients), which is valuable for applications that require continuous or long-duration monitoring, such as ultra-long transients, to achieve ultra-high resolution.<sup>[14]</sup> Strikingly, FTMS Boosters allow users to record transients of arbitrary length, including continuous (e.g. >10 min) acquisition of time-domain data in CDMS applications.<sup>[6,18,19]</sup>

(vii) *High Throughput and Data Transfer Rates.* High-performance DAQ systems employ fast data transfer buses and interfaces (e.g. PCI Express®, PXI Express™, USB 3, Gigabit Ethernet®, Thunderbolt™) that allow them to transfer large volumes of data quickly and efficiently within the system and to external file servers or post-processing systems, making them suitable for high-throughput applications. All FTMS Booster models are built on the PXI/PCI Express buses, whereas the latest generation systems add a Thunderbolt™ interface for high-speed connection with a computer or a workstation.

*Key features of the FTMS Boosters.* In line with the above considerations, the architecture of the FTMS Boosters includes the ultra-low-noise PXI amplifier (designed and manufactured by Spectroswiss) with matching frequency bandwidth and several signal conditioning options (signal amplifiers, input impedances, differential and single-ended input modes), multi-channel low-noise high-resolution ADC, a high-performance field programmable gate array (FPGA) chip with digital triggering options and advanced DSP algorithms, and fast buses for rapid transfer

of large data sets. The FTMS Boosters acquire time-domain ion signals (transients) in parallel with the built-in DAQ electronics of the FTMS instruments. As such, the original mass spectra (*e.g.* RAW files from Orbitraps) and transients can be acquired in parallel without noticeable influence on each other, Fig. 1.

The key abilities of the FTMS Boosters include: (i) taking care of the heavy data, removing the technical challenge to acquire large and extremely large datasets and ultra-long transients away from the built-in DAQ systems; (ii) maximizing sensitivity through simultaneous acquisition of low and high gain transients *via* a proprietary PXI amplifier; (iii) uniquely providing in-hardware phased transients for direct and phase artifact-free absorption mode FT (aFT) mass spectra generation; (iv) supporting advanced triggering options, recognizing both the ‘start’ and ‘stop’ triggers, and thus increasing experimental design flexibility and performance, including maximizing the ion detection duty cycle and allowing extended transient recording during all the time ions ring in the mass analyzer; (v) offering transients for post-processing capabilities, including the use of advanced signal processing approaches (advanced FT and non-FT methods, such as SR signal processing).<sup>[20]</sup>

Up to now, there have been two main FTMS Booster models developed: for the acquisition of a single waveform or a transient (Orbitraps and CDMS applications) and for the acquisition of two waveforms, *e.g.* a detect signal and an excite signal in FT-ICR MS, or two detect signals in CDMS. Furthermore, the FTMS Booster models differ by their computer arrangement: an embedded computer that is integrated with the PXI chassis (models X2 and X3), and a standalone data processing workstation connected to the PXI chassis *via* Thunderbolt™ (models X2T and X3T). The latter models are state-of-the-art and offer more flexible and powerful data processing capabilities.

### 3. Selected FTMS Booster Applications in FTMS and CDMS

#### 3.1 Mass Spectrometry Imaging

Mass spectrometry imaging (MSI), employed for mapping spatial distributions of molecules within biological samples,<sup>[21]</sup> benefits from FTMS platforms capable of high-resolution and high-accuracy measurements.<sup>[8]</sup> Nevertheless, conventional FTMS systems may struggle with the resolution and sensitivity demands of actively developing MSI approaches. High resolution is essential in MSI for distinguishing molecules from isobaric masses, particularly in lipid and metabolite profiling. Moreover, minor lipid or metabolite species can be biologically significant yet challenging to detect with conventional systems.

*Ultra-high Mass Resolution on FT-ICR MS Platforms.* In the original study by Kooijman *et al.* from 2019,<sup>[22]</sup> an FTMS Booster interfaced with a 7 T LTQ FT-ICR MS increased the mass resolution by six times for desorption electrospray ionization (DESI) MSI. One of the key advancements was achieved by acquiring transients and converting them into absorption mode Fourier transform (aFT) mass spectra. This approach typically doubles the resolution compared to the magnitude mode Fourier transform (mFT) mass spectra commonly used in FT-ICR MS.<sup>[9,23]</sup> Another improvement stemmed from the FTMS Booster’s ability to record transients during overhead time, thereby maximizing the ion detection duty cycle. With the enhanced resolution, Kooijman and coworkers could distinguish isobaric lipid species with mass differences in the mDa range, exemplified for brain tissue imaging applications. This capability is important in lipidomics research, where slight molecular differences can signal distinct biological pathways or disease states. The obtained improvement in mass resolution also facilitated better spatial resolution in MSI, revealing more detailed molecular distributions within biological samples.

More recently, Vandergrift *et al.* (2022) demonstrated the FTMS Booster’s capacity to handle these challenges when paired with a flagship 21 T FT-ICR MS and nanospray DESI (nano-DESI) MSI.<sup>[24]</sup> The external DAQ system allowed them to achieve a mass resolution greater than 830,000 at  $m/z$  825 while maintaining low parts-per-billion (ppb) mass accuracy. This high mass resolution enabled Vandergrift and coworkers to perform isotopic fine structure (IFS) analysis, which is beneficial for accurate molecular annotation.

In another work by Vandergrift *et al.* (2023),<sup>[25]</sup> the authors highlighted how the FTMS Booster allowed them to detect mass splits as small as 2.4 mDa in lipid species within MSI experiments using the same 21 T FT-ICR MS with FTMS Booster-enabled nano-DESI and MALDI imaging modes. Such high-resolution capabilities, exceeding 1.3 million at  $m/z$  943, permitted a high level of molecular detail. Resolving isobaric lipid species within complex tissue samples improved molecular annotation accuracy, ultimately resulting in a 1.5-fold increase in molecular identifications.

*Ultra-high Mass Resolution on Orbitrap Platforms.* In the study by Grgic *et al.* (2023),<sup>[26]</sup> an Orbitrap Q Exactive HF mass spectrometer equipped with an FTMS Booster achieved mass resolutions around 1 million in the 600–950 Da lipid mass range, Fig. 2.

In the case of Orbitrap FTMS, the conventional mass spectral representation (in the enhanced FT, or eFT, mode) inherently operates at the absorption mode FT (aFT) resolution performance level.<sup>[10]</sup> Consequently, achieving higher resolution requires the acquisition of longer transients.<sup>[14]</sup> Fig. 2 illustrates this with the acquisition of 7-second transients and highlights the corresponding increase in resolution. The improvement in resolution, coupled with the ability to perform absorption FT (aFT) processing, provided more accurate lipid identifications, and increased the number of identified compounds.

Another notable strength of FTMS Boosters is their ability to upgrade legacy ICR and Orbitrap FTMS instruments, making high-resolution MSI more accessible. Above, we described such development for an LTQ FT-ICR MS instrument upgrade.<sup>[22]</sup> More recently, in the study by Leach *et al.* (2024),<sup>[27]</sup> an FTMS Booster was integrated into an older hybrid linear ion trap (LTQ) Orbitrap platform, initially limited by its lack of modern data acquisition technologies such as eFT and aFT. With the FTMS Booster, the LTQ Orbitrap platform achieved an eight-fold increase in mass resolution, equivalent to the performance of newer high-end FTMS systems, but without any hardware modifications. This cost-effective improvement demonstrates the practical value of FTMS Boosters, allowing laboratories to access cutting-edge performance. Therefore, by revitalizing older FTMS instruments, such as LTQ FT-ICR MS and LTQ Orbitraps, FTMS Boosters facilitate access to high-resolution MSI.

#### 3.2 Charge State Determination Mass Spectrometry

Recently, FTMS has found increasing utility for characterizing large and heterogeneous biomacromolecules, such as monoclonal antibodies (mAbs), antibody-drug conjugates (AbDCs), and viral vectors. Orbitrap-based native MS and charge detection mass spectrometry (CDMS) rely on the built-in DAQ systems for precise charge and mass determination of high-mass ions.<sup>[6,18,28]</sup> Still, traditional FTMS systems may lack the resolution and sensitivity required for these high-mass applications.

*Ultra-long Transients in Orbitrap-Based CDMS.* Deslignière *et al.* conducted pioneering work by modifying a Q Exactive ultra-high mass range (UHMR) Orbitrap mass spectrometer to extend transient acquisition times from the typical 1–2 seconds to an impressive 25 second period.<sup>[29]</sup> Such ultra-long transients, made possible by the FTMS Booster, significantly enhanced sensitivity, resolution, and charge state determination accuracy. Overall, the

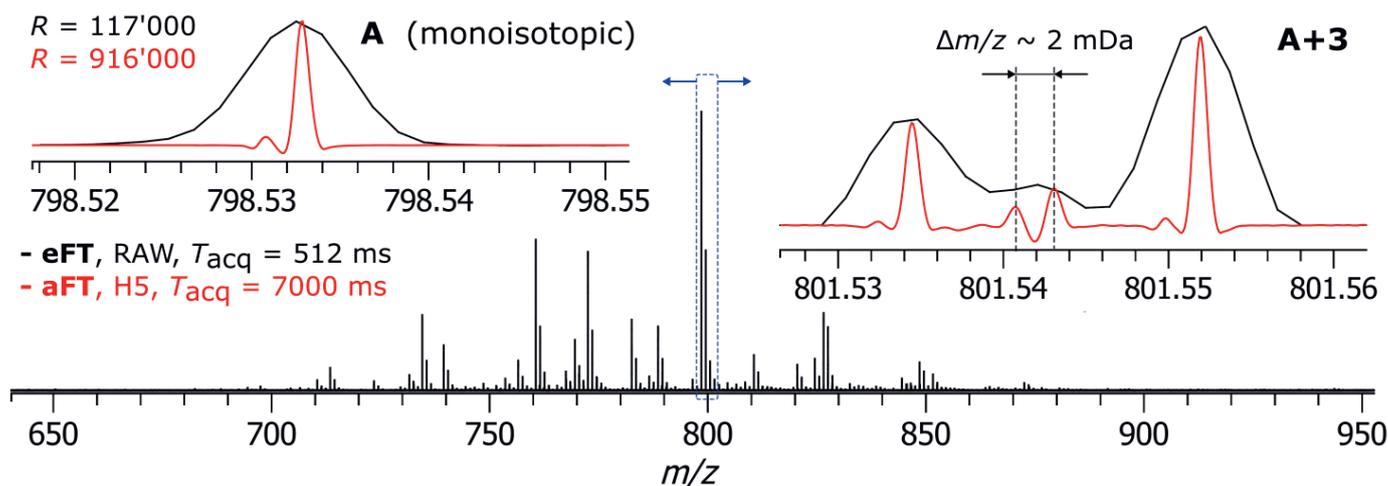


Fig. 2. MALDI imaging MS analysis of a mouse brain tissue section performed using a Q Exactive HF (50 scans, RAW, eFT, resolution setting 240,000 at  $m/z$  200, black trace) equipped with FTMS Booster X2 (50 scans, aFT, 7 seconds transients, red trace).<sup>[26]</sup> Transients with the extended length were acquired in parallel with the RAW mass spectra, utilizing the FTMS Booster's capability to acquire data during the user-controlled overhead duration.

FTMS Booster allowed for longer ion detection without compromising system stability, achieving a five-fold increase in SNR, a 25-fold improvement in mass resolution, and it narrowed charge state standard deviations from 2-3 elementary charges to more precise levels.

The FTMS Booster DAQ system thus overcame the limitations of the built-in DAQ system in the Orbitrap, which is not designed to handle the extensive datasets generated by ultra-long transients. The FTMS Booster efficiently managed data transfer, storage, and processing, further facilitated by selectively recording lower-frequency ion signals (above a certain  $m/z$  value). The CDMS improvements provided by the FTMS Booster appear particularly impactful for characterizing large, heterogeneous biomolecules, such as adeno-associated viruses (AAVs), which are commonly used in gene therapy.

**Charge Determination Analysis.** In 2021, Lyutvinskiy *et al.* introduced charge determination analysis (CHARDA),<sup>[30]</sup> a technique that adds a third dimension to traditional mass spectrometry by estimating charge states for ensembles of ions – distinct from the individual (single) ion analysis used in CDMS applications – and visualizing these charge states in color-coded mass spectra. CHARDA's innovative ability to estimate charge state is based on ion signal decay rates in transients, allowing it to overcome the limitations of conventional methods. By integrating CHARDA with the transient acquisition by FTMS Booster on Orbitrap platforms, Lyutvinskiy and coworkers demonstrated a practical approach to deduce charge states even when isotopic distributions are overlapping or skewed (*e.g.* in the analysis of the isotopically depleted samples). Additionally, the extended transient lengths made possible by the FTMS Booster enabled more accurate and stable charge estimation across a broad range of ions. The visual aid provided by CHARDA's color-coded spectra simplifies the analysis of complex datasets by highlighting overlapping signals.

### 3.3 Protein Analysis Mass Spectrometry: Intact Mass and Top-Down

For applications in biopharmaceutical research, particularly those involving mAbs and AbDCs, FTMS instruments have proven valuable due to their ability to provide both low-resolution and high-resolution data.<sup>[7,31,32]</sup> However, standard FTMS instruments may face limitations, especially when complex fragmentation patterns are generated in tandem MS for top-down analysis or ultra-low/ultra-high-resolution data is required for intact mass analysis. The addition of FTMS Boosters has improved these applications

by providing an optimum resolution that matches the needs of a particular sample complexity and supporting advanced data processing.

**Understanding Protein Analysis with FTMS.** Nagornov *et al.* revisited the isotopic beat patterns in transients in FTMS analysis of large proteins, including mAbs.<sup>[33]</sup> Isotopic beats, caused by constructive and destructive interference of signals from isotopic ions,<sup>[34,35]</sup> need to be considered due to their impact on resolution and SNR, particularly in large biomolecules with complex charge state distributions. The FTMS Booster's ability to access and store transients enables optimized data processing for maximum SNR and optimum resolution.

The study utilized the FTMS Isotopic Simulator software tool (Spectroswiss) to model isotopic beat patterns of proteins, revealing how different parameters, such as FT processing settings, influence spectral profiles. This simulation capability, combined with the transient access and methods enhancement provided by FTMS Boosters, aids in the optimization of analytical protocols.<sup>[36]</sup>

**Practical Applications in Biopharma.** By enabling regular and extended transient acquisition, FTMS Boosters improve the ability to generate mass spectra for individual proteoforms across multiple charge states.<sup>[32,37]</sup> In their 2021 study, Nagornov *et al.* focused on the analysis of AbDCs and antibody-oligonucleotide conjugates (AbOCs), particularly in determining drug-to-antibody ratios (DARs), an essential metric for assessing the quality and efficacy of AbDCs.<sup>[38]</sup> DAR values indicate the number of drug molecules conjugated to each antibody, directly impacting the pharmacokinetics and therapeutic activity of AbDCs. However, traditional methods for DAR analysis can be challenging due to the complexity of AbDC/AbOC samples, which consist of multiple proteoforms and charge states. Using FTMS Booster, Nagornov and coworkers were able to acquire and process transients to deliver ultra-low-resolution performance and allied proteoform integration, thus facilitating direct DAR estimation and minimizing the need for additional sample processing steps such as deglycosylation. The ability to analyze complex AbDC/AbOC samples rapidly and accurately represents an advancement for drug development workflows, as it reduces time and costs while increasing throughput in research.

**Multiplexed Middle-Down Mass Spectrometry for Antibody Analysis.** Szrentić *et al.* investigated the use of multiplexed middle-down (MD) MS in studying the connectivity of light and heavy chains in mAbs, a critical factor in therapeutic drug devel-

opment.<sup>[39]</sup> MD MS involves analyzing large subunits (25–100 kDa) derived from intact proteins (mAbs), but achieving sufficient sensitivity can be difficult in complex samples.<sup>[7]</sup> Srzentić and coworkers demonstrated that using aFT spectral and transient averaging across multiple liquid chromatography-tandem mass spectrometry (LC-MS/MS) runs significantly improved the sensitivity of MD MS analysis. The ability to perform unreduced data averaging provided a viable solution for capturing low-abundance product ions, including the internal product ions,<sup>[40,41]</sup> essential for characterizing mAb subunits and detecting critical quality attributes, including primary structure details.

### 3.4 Isotope Ratio and Trace-Level Analyses

In environmental sciences, isotope ratio (IR) analysis and low ion counting are crucial for understanding trace levels of pollutants and isotope distributions, such as in uranium isotope analysis and persistent organic pollutant detection.<sup>[42,43]</sup> Traditional approaches to IR analysis rely on techniques such as thermal ionization and inductively coupled plasma mass spectrometry. Still, FTMS instruments have become increasingly attractive alternatives due to their ability to handle complex isotopic distributions.<sup>[44,45]</sup> However, they face challenges in achieving high sensitivity and precise low-abundance isotope detection due to spectral dynamic range limitations and automatic data reduction procedures.

*Isotope Ratio Analysis of Uranium.* Bills *et al.* demonstrated the impact of FTMS Boosters in enhancing isotope ratio measurements on a Q Exactive Focus Orbitrap FTMS system.<sup>[42]</sup> When coupled with a liquid sampling-atmospheric pressure glow discharge (LS-APGD) ion source,<sup>[46]</sup> the FTMS Booster extended the capability of the benchtop Orbitrap to detect, resolve, and accurately quantify low-abundance uranium isotopes, some of which were below the detection limit of the initial Orbitrap setup. As a result, Bills and coworkers enabled the successful simultaneous detection of low-abundance uranium isotopes, *e.g.* <sup>234</sup>U and <sup>235</sup>U, and then the precise measurement of their isotope ratios (relative to <sup>238</sup>U), which are essential for nuclear forensics and environmental safety applications.

Therefore, the FTMS Booster's ability to capture (extended) transient data, along with absorption mode FT (aFT) processing, and unreduced data representation enhanced mass resolution and significantly improved the dynamic range compared to traditional Orbitrap setups. Indeed, aFT data representation yields positive and negative spectral data points, proportionally increasing the SNR upon full profile aFT spectral averaging. FTMS Boosters thus offer a powerful alternative for IR analysis of rare elements in environmental samples and nuclear materials.<sup>[43]</sup>

*Trace-Level Analysis of Persistent Organic Pollutants.* Persistent organic pollutants or POPs, such as polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs), are environmental contaminants of concern due to their toxicity and persistence. Nagornov *et al.* (2020) applied an FTMS Booster in a gas chromatography (GC)-Orbitrap FTMS setup, demonstrating a significant increase in sensitivity for trace-level POP detection.<sup>[13]</sup> The FTMS Booster's transient acquisition allowed for transient averaging of multiple GC-FTMS runs (technical replicates), substantially increasing the SNR and allowing for the more accurate and confident quantitation of low-abundance POPs in complex environmental samples. Furthermore, acquiring extended transients with the FTMS Booster on this Q Exactive Orbitrap instrument allowed Nagornov and coworkers to achieve resolution levels exceeding 500,000 at  $m/z$  200, effectively separating and identifying trace contaminants despite matrix interference. These advancements demonstrate that FTMS Booster-enhanced Orbitrap systems can support accurate POP quantitation in environmental monitoring, public health assessments, and food safety.

### 3.5 Super-Resolution Mass Spectrometry

Transient processing in FTMS has traditionally relied on FT methods to convert ion time-domain signals into frequency-domain Fourier spectra, providing the mass-to-charge ratio ( $m/z$ ) information for identifying molecular species.<sup>[47]</sup> However, FT methods are not without limitations. FT methods require extended detection periods to achieve high resolution, which can slow acquisition rates and reduce throughput. Additionally, the accuracy of FT-based methods in peak  $m/z$  and intensity values determination can be insufficient. It compromises quantitative accuracy, especially in applications requiring rapid and precise quantitation. FTMS Boosters facilitate the use of advanced signal processing methods, such as super-resolution (SR) algorithms, which allow for enhanced resolution and quantification precision without the trade-offs associated with conventional FT methods.<sup>[47–49]</sup>

Integrating SRMS techniques with FTMS instruments may advance its key application - proteomics, particularly for multiplexed quantitative analyses involving isobaric tags like tandem mass tags (TMT).<sup>[47,50]</sup> In conventional MS2-based quantitative proteomics, isobaric tags enable the analysis of multiple biological samples in a single experiment by encoding each sample with unique isotopic labels.<sup>[47,51]</sup> However, co-isolation and co-fragmentation artifacts are common, which can lead to signal overlap and compromised quantitation.

Kozhinov *et al.* (2023) demonstrated the application of least-squares fitting (LSF) SR algorithms enabled by FTMS Boosters in an MS2-level quantitative proteomics workflow.<sup>[20,48]</sup> Using complementary reporter ions in the TMT approach (TMTc), the FTMS Booster-enhanced SRMS setup achieved resolution levels at data acquisition rates unattainable with conventional FT methods, allowing for the rapid and precise detection of isobaric tag fragments even at high  $m/z$  ranges. The LSF algorithm effectively resolves low mDa differences, a capability crucial for high-multiplexing proteomics applications, as it minimizes the need for extended transients while preserving the scan speed, making it compatible with high-throughput LC-MS/MS workflows.

Despite the enhanced resolution and quantitation accuracy SRMS provides, several technical challenges persist. Coulombic interactions, for example, can cause peak coalescence of ions separated by only a few mDa,<sup>[52,53]</sup> especially in highly multiplexed samples. To address these issues, Kozhinov and coworkers optimized automatic gain control (AGC) settings to minimize ion-ion interactions, effectively reducing signal artifacts and preserving quantitative precision. Additionally, the FTMS Booster-enabled SRMS setup allowed for an improved SNR in low-abundance channels, a welcome improvement for proteomics workflows dealing with broad concentration ranges.

### 3.6 Complex Mixture Analysis

Analyzing complex mixtures is challenging in environmental science, industrial chemistry, energy, and pharmaceutical research. Complex mixtures often contain hundreds or thousands of molecules with many of them having similar  $m/z$  values, making it challenging to resolve individual components and accurately determine their chemical composition. FTMS, particularly FT-ICR MS, has long been the gold standard for high-resolution analysis of such samples due to its ability to achieve ultra-high resolution.<sup>[2,5,54–56]</sup>

*High-Resolution Analysis of Dissolved Organic Matter.* Dissolved organic matter (DOM) is a vast, heterogeneous mixture of organic compounds found in aquatic environments, playing a crucial role in carbon cycling and climate regulation. Traditional FT-ICR MS instruments are widely used for DOM analysis due to their high resolution and mass accuracy, essential for chemical formula assignments and molecular characterization. In addition, Oliveira *et al.* demonstrated how FTMS Boosters can enhance FT-ICR MS performance in DOM analysis, enabling more detailed

insights into the molecular complexity of these environmental samples.<sup>[57]</sup>

By combining FT-ICR MS with trapped ion mobility spectrometry (TIMS), Oliveira and coworkers leveraged the FTMS Booster to extend the transient acquisition period for achieving higher mass resolution. This approach supported TIMS-FT-ICR MS that differentiates DOM components based on collision cross-section values, adding a new dimension to the separation process. The FTMS Booster facilitated aFT mass spectra generation, resulting in better noise reduction and increased accuracy in chemical formula assignment. The aFT mode improved peak complexity decomposition and sensitivity, enabling researchers to get a 24% increase in unique chemical formulas compared to mFT processing.

*High-Resolution MS for Industrial Chemical Analysis.* Chlorinated paraffins (CPs) are complex mixtures used in industrial applications as lubricants, plasticizers, and flame retardants. Their analysis is particularly challenging due to the presence of multiple carbon and chlorine isotopes, which result in overlapping isotopic patterns that are difficult to resolve. Masucci *et al.* used an FTMS Booster with an LS-APGD ionization source and an LTQ Orbitrap XL mass spectrometer to achieve high-resolution CP analysis.<sup>[58]</sup>

LS-APGD is a soft ionization technique that preserves molecular integrity, essential for detecting intact CP compounds in complex mixtures.<sup>[46]</sup> Adding an FTMS Booster allowed the LTQ Orbitrap XL, which traditionally supports only mFT processing, to perform aFT processing, substantially enhancing its mass resolution and dynamic range. The aFT mode enabled Masucci and coworkers to resolve isotopic distributions in CPs at various degrees of chlorination, beneficial for accurate compound quantification. This is particularly useful in industrial settings where CP composition analysis is required for quality control and regulatory compliance.

#### 4. Conclusions and Outlook

The recent introduction of high-performance DAQ systems has unlocked new opportunities for enhancing the capabilities of FTMS instruments. However, substantial technical challenges have limited the development of alternative solutions, which may explain why the FTMS Booster systems remain the only high-performance DAQ systems currently available for integration with FTMS platforms. This review demonstrates that incorporating these advanced and innovative DAQ systems into FTMS workflows enhances MS capabilities across various applications.

FTMS Boosters advance MSI analyses in spatial lipidomics and metabolomics by supporting ultra-high mass resolution and precise molecular imaging. In high-mass ion analysis, they enhance the performance of FTMS and CDMS approaches through extended transient acquisition and improved charge state determination, making them essential for large biotherapeutic and viral vector research. In biopharma, FTMS Boosters offer optimum (from ultra-low to ultra-high) resolution and enhanced sensitivity in top-down and middle-down mass spectrometry while streamlining AbDC/AbOC workflows. They also broaden FTMS applications in isotope ratio and trace-level analyses by enhancing spectral resolution, dynamic range, and isotope ratio accuracy, with growing potential in regulatory and environmental sectors. FTMS Boosters improve isotopic distribution decomposition and facilitate absorption mode FT data representation, enabling efficient analysis of complex mixtures and driving innovation in environmental toxicology and industrial applications. Integrating FTMS Boosters with super-resolution mass spectrometry (SRMS) transforms quantitative proteomics, addressing co-isolation and co-fragmentation challenges with potential applications in high-sensitivity fields such as single-cell, spatial, and glycoproteomics. Advances in SR algorithms further expand FTMS's capabilities, *e.g.* in spatial drug monitoring.<sup>[59]</sup>

Looking ahead, FTMS Boosters, and eventually other high-performance DAQ systems, are poised to expand their utility in routine and advanced MS applications. As the FTMS technologies evolve, FTMS Booster systems will help drive progress in fields from environmental science to molecular medicine, ensuring that high-performance FTMS continues to adapt to new scientific challenges and discoveries. Lastly, these systems support the continued use of legacy FTMS platforms, offering laboratories a sustainable, cost-effective pathway to modern, high-performance MS capabilities.

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