Multiplexing in Multi-Reflecting TOF MS

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Abstract: The paper presents an overview of original inventions, development and experimental results by the group of authors in the area of multi-reflecting time-of-flight mass spectrometry with Folded Flight Path (FFP®) (MR-TOFMS) with main focus on multiplexing methods for improving the analysis throughput, i.e. the amount of information per time unit. MR-TOF provides panoramic spectra (virtue of TOFMS), while significantly enhancing resolving power, thus, providing yet more information. Resolving power R=500,000 is demonstrated to resolve isobars and to improve mass accuracy to sub-ppm level. Encoded Frequent Pulsing (EFP™) method improves sensitivity, expands dynamic range and opens multiple incarnations of parallel and fast tandem methods of analysis based on using ion traps, TOFMS and ion mobility for rapid and lossless parent ion separations.

Keywords: Multi-reflecting TOF, multiplexing, N-dimensional separations, high throughput.

INTRODUCTION

Mass spectrometry is a very powerful analytical technique, which rapidly becomes the core method of analytical chemistry. High throughput is a very desirable feature for mass spectrometry analysis. The amount of information per time unit is the key metric for solving complex problems within a reasonable amount of resources and time.

Time-of-flight mass spectrometers (TOFMS) is a widely used MS method, chosen for sensitivity, rapid spectral acquisition capability and, lately, for high resolution and mass accuracy. In a sense, the TOFMS method implements multiplexing on its' own: panoramic spectra of all ionic species are acquired at once (at millisecond time scale) for a single ion ejection from an ion source.

Since introduction in 1948 [1], multiple improvements were made for improving TOFMS resolution, including a method of time-lag ion extraction [2], energy focusing by electrostatic sectors [3], energy focusing and trajectory folding with grid covered mirrors [4, 5] and gridless mirrors [6, 7]. TOFMS have been successfully adopted for intrinsically pulsed ion sources, like SIMS [8], MALDI [9, 10], or accumulating Electron Impact (EI). Application of TOFMS has been extended to continuous ion sources, like Electrospray, APCI and EI, with introduction of orthogonal acceleration (OA) converter [11, 12] being further improved with collisional cooling and accumulation of ions in radio-frequency ion guides [13, 14]. Nowadays,

TOFMS are widely used with MALDI ionization, and as a second stage of tandems like Q-TOF [15, 16].

Resolving power of TOFMS dramatically improves in multi-turn [17, 18] and multi-reflecting (MR-TOF) analyzers [19, 20]. However, performance of such analyzers were limited either by high aberrations of electrostatic sectors [18], or by narrow mass range in looped schemes [17,19] or by ion losses due to ion packet divergence [20].

The authors have conducted decade-long research and development with the goal to extend the resolving power and throughput of the MR-TOFMS in single MS and tandem MS-MS configurations. The review of these efforts is the main focus of this publication which details could be found in corresponding patent applications [21-50], published articles and conference presentations [51-112]. Though similar review on the whole area of high resolution TOF and high throughput multiplexing methods is highly desirable, authors excuse themselves for not writing the book-size manuscript but rather concentrating on the review of the own yet unpublished results.

The review does not present an detailed technical description of individual methods or techniques, but refers to original various publications. The goal of this review is to combine the related methods and to help readers in grasping the wide scope concept, understanding the unity of the overall approach and to get inspired for the further progress.

Discovering the method of indefinite ion confinement within an array of periodic lens [51-53] allowed solving the problem of ion losses in planar MR-

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TOFMS and to propose an effective ion optical scheme of planar MR-TOFMS [24-26, 54-59]. In our earlier experiments [60-64] we implemented the indefinite ion trapping regime within the MR-TOFMS analyzer and demonstrated the resolving power up to 1,000,000 [65]. The MR-TOFMS analyzer has been adopted for continuous ion beams via so-called double orthogonal acceleration approach to ion introduction [26, 66-75], which sensitivity was further improved with velocity modulation within ion guide [26, 28, 29, 76, 77]. In the described here experiments, the mass resolving power of the MR-TOFMS was brought to R=200,000 at full mass range, thus, providing wealth of mass spectral information and improving mass accuracy to sub-ppm level. Aberration limit of the MR-TOFMS was experimentally shown to reach R=500,000 in a so-called 'Zoom' mode, while trapping ions in MR-TOFMS for multiple passes.

Many proposed improvements are likely to push the MR-TOFMS resolution even further. The recent developments have brought isochronicity of ion mirrors to full third order focusing and fifth order energy focusing [38, 44, 78-80]. The so-called "quasi-planar" ion mirrors with curved electrostatic fields [30, 50, 80] are expected to compensate aberrations of the periodic lens. Cylindrical analyzers [33-35, 37, 41, 43] provide yet even more compact trajectory folding to reach ions' flight path of hundreds of meters within rather compact mass analyzers. An axial bunching [48] opens the way to generate sub-nanosecond ion packets and significantly improve the MR-TOFMS duty cycle.

Combination of high-resolution MR-TOFMS coupled with comprehensive GCxGC chromatography [81-83], and in particularly while combined with soft and quantitative ionization using 'conditioned glow discharge' source [32, 84-86], brings the effective separation capacity over 10,000,000, which is quite useful for analysis of ultra-complex mixtures. The utility of such approach has been demonstrated by detecting over 300,000 species in crude oils samples [83].

The MR-TOFMS was also considered for using in development of all-mass tandems MS-MS, avoiding ion losses due to scanning of precursor ions. At very early stages of MR-TOFMS based instruments development we have proposed a method of time-nested TOF-TOF or Comprehensive TOF-TOF (CTT) [22, 23, 61, 87-89], where the first MR-TOFMS separates precursor ions at 10 ms time scale, and the second TOF sequentially analyzes ion fragments at 10 us time scale. It was found that short high gas pressure CID cell was capable of transferring fragment ions at such short time scale [98-101]. Experimentally it was found [90-97] that intensive ion packets (up to 1E+6 charges per packet) produced by an axial trap, expand in MR-TOFMS, which limits the ion flux into a CID cell, thus, defeating the advantage of the parallel fragment analysis by CTT. The CTT approach was further advanced with proposal of using a surface induced dissociation [41, 102, 103] for fragmentation of the precursor ions, which could accept wide ion packets without gas load into MR-TOFMS. To improve the throughput, there was proposed a method of non-redundant parallel sampling of multiple parents, employing several levels of spectral encoding [41].

Complexity and limitations of Comprehensive TOF-TOF tandems drove our attention to alternative MS-MS schemes, where the first mass separator may employ either quadrupole filters, or ion traps, or ion mobility separators. This approach requires ultimate sensitivity and speed of the second mass analyzer. To overcome the low duty cycle properties of MR-TOFMS with orthogonal accelerators (OA), we proposed and tested axial trap converters [90-97] with trapping ions by radial RF and axial DC fields. Indeed, the scheme allows effective use of small ion fluxes in MS-MS tandems [94, 95], but being limited in MS-only analyses mode by space charge capacity of the trap pulsed converter and of MR-TOFMS [96, 97].

Introduction of the Encoded Frequent Pulsing (EFP) method [36] for robust orthogonal acceleration improves the duty cycle of the MR-TOFMS with OA and addresses space charge limitations. The EFP method improves sensitivity, dynamic range and speed of analysis by up to two orders of magnitude [104, 105]. This paper demonstrates detection and identification of minor target species at low femtogram amounts of analyte. The paper also presents an idea of applying the EFP method to so-called 'open traps' [35, 36], expected to further improve the dynamic range of MS-MS analyses.

The EFP method brings another advantage to the analysis: speed of ion flow tracking, useful, for example, for recording time profiles past mass or mobility separators. This opens the opportunity for very effective analysis using multiple parallel all-mass tandems. A moderate sensitivity improvement may be obtained at so-called two-dimensional MS-MS analysis [45, 47], experimentally tested on the Q-MR-TOFMS research-grade instrument. The quadrupole separator of precursor ions is smoothly scanned with a wide (10-

30amu) mass window. The effective dwell time is increased proportional to the mass window width, while accurate time profiles for parent and fragment masses, obtained at 10 us period in EFP method, allow the accurate reconstruction of fragment spectra and recover unit mass resolution of parent separation. The method provides all-mass MS-MS with sensitivity and dynamic range being improved proportional to the width of the parent mass window scan.

Yet even higher efficiency of MS-MS tandems is expected with lossless parent ion separations, proposed in [39, 42, 46]. To handle large (approaching 1E+9 ion/sec) ion fluxes commonly observed in the modern ion source, we proposed [46] using an array of parallel linear ion traps for all-mass MS-MS, followed by MR-TOFMS operating in the EFP mode.

Early experiments with double encoded IMS-MR-TOFMS [106] have demonstrated the feasibility of the method and have shown the correlation of ion mobility with ion mass defect. The early prototype had limited charge throughput capabilities of the ion mobility stage, which will be a subject of further experimental optimization. The parallel and lossless IMS separation may be used for either 3D-tag analysis (chromatographic retention time, mobility and accurate mass tags) or for a lossless all-mass MS-MS within the same instrument.

Use of multiplexed arrays of MR-TOFMS analyzers [33, 34] presents yet another dimension of multiplexing. The array of analyzers could use identical electrode structures and share the same power electronics and vacuum system.

Summarizing all above, the multiplexing approaches in MR-TOFMS technology bring an opportunity for substantial improvements in throughput of MS and MS-MS analyses. In addition to parallel spectra acquisition (i.e. 1st multiplexing dimension) the described multiplexing dimensions are:

- Multiple reflections in TOF MS analyzers for improving TOF resolution;

- Multiple stage chromatographic separation for higher separation capacity;

- Time-nested comprehensive TOF-TOF tandems for all-mass MS-MS;

- Parallel TOF-TOF tandems with non-redundant sampling of multiple precursor ions;

- Encoded Frequent Pulsing (EFP) for improving MR-TOF duty cycle and for higher speed and dynamic range in parallel tandems;

- An alternative EFP method for open traps for improving sensitivity in tandems;

- Two-dimensional MS-MS in Q-MRTOF with wide open quadrupole windows;

- Parallel IMS-MRTOF for acquiring tandem spectra for all precursor ions;

- IMS-MRTOF identification with three tags: retention time, mobility and exact mass;

- All-mass MS-MS with a lossless ion trap array, supported by EFP MRTOF;

- Array of MRTOF analyzers for yet higher throughput;

- Electrostatic traps and open electrostatic traps for higher ionic currents.

PLANAR MULTI-REFLECTING TOFMS WITH FOLDED FLIGHT PATH (FFP®)

In a singly reflecting TOFMS, the turn-around time originating in the ion sources is the sole first order aberration of TOF mass spectrometers and the primary limiting factor for TOFMS resolution. The turn-around limit of the resolving power may be expressed as [63]:

$$R < (\Delta K/K)*(L*V)/(\Delta X*\Delta V)/4,$$

where $\Delta K/K$ is the relative energy tolerance of the analyzer, $\Delta X*\Delta V$ – ion beam emittance before the pulsed acceleration, and $L*V$ – analyzer acceptance with L meaning the flight path length and V being the average ion velocity in the drift region. The expression highlights the least used resource for improving resolving power – longer flight paths in TOF analyzers. Obviously, some form of ion trajectory folding is required to reach a substantial increase in the flight path, say tens of meters, if we want to stay within laboratory-size instruments dimensions.

Various multi-turn and multi-reflecting schemes [17-20] have been explored in the past, with most of designs either being limited by a narrow mass range or high aberrations (e.g. in electrostatic sectors). Multiple reflections between planar mirrors, proposed by Yakushev *et al.* [20], allow both multiple mirror reflections (i.e. increased ion path length) and

arrangement of the ion path along the mirror symmetry plane (i.e. unlimited mass range). However, the practical use of that scheme was limited by the ion packet divergence along the drift axis.
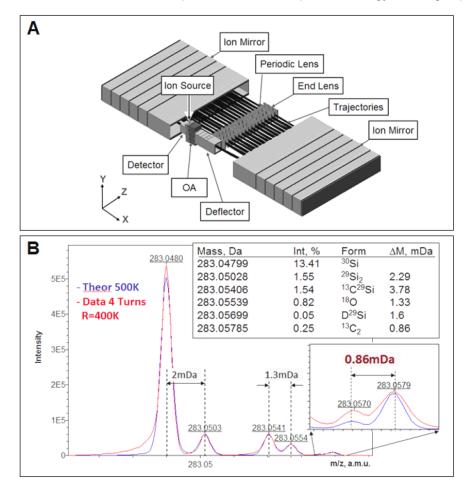
To address problems of the prior art multi-pass mass spectrometers [17-20], authors have developed a Multi-Reflecting Time-of-Flight mass spectrometer with Folded Flight Path (MR-TOFMS) [24, 25, 54-59], depicted in Figure **1-A**. The analyzer employs a pair of gridless electrostatic ion mirrors separated by a drift space. The ion mirrors are extended in the drift Z-direction to form a two-dimensional planar electrostatic field in the XY plane, similar to [20]. The mirror field is optimized to provide an isochronous ion motion in the X-direction and spatial ion focusing in the Y-direction, while providing the aberration limit of analyzer resolution exceeding one million [38, 44, 65]. Comparable resolution is theoretically predicted and is experimentally achieved in trapping coaxial MR-TOF employed in nuclear physics research [111, 112].

To avoid natural ion packet divergence in the drift direction, the MR-TOFMS scheme is further improved by using an array of periodic lenses [24, 25]. As it has been shown in [51-53], the periodic lens provides an indefinite ion packet confinement along the mean zigzag ion trajectory. Though the lens introduces aberrations, such aberrations are moderate for practical ion packet widths and divergences. These aberrations are further reduced when ion packets are created narrow in the Z-direction. For this goal, the so-called double orthogonal acceleration scheme [26, 66-75] arranges the incoming ion beam substantially along the Y-axis, i.e. orthogonal to the plane of the zigzag ion trajectory. Simulations suggest that such ion-optical geometry is capable to provide of up to R=500K.

The described ion optical scheme of the planar multireflecting TOF mass analyzer with periodic lenses and double-orthogonal acceleration was commercially implemented by LECO Corporation (St. Joseph, MI, USA) in the Citius LC-HRT [113] and Pegasus GC-HRT [114-117] mass spectrometers.

With implementation of ion mirrors providing overall third order TOF focusing and 4th order TOF focusing with respect to energy, the flight path in a 1 m long

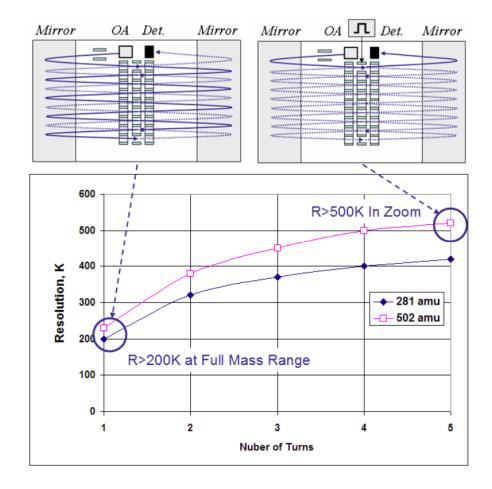| Mass, Da	Int, %	Form	ΔM, mDa
283.04799	13.41	^{30}Si	
283.05028	1.55	$^{29}Si_2$	2.29
283.05406	1.54	$^{13}C^{29}Si$	3.78
283.05539	0.82	^{18}O	1.33
283.05699	0.05	$D^{29}Si$	1.6
283.05785	0.25	$^{13}C_2$	0.86

Figure 1:

instrument is over 25 m. Further on, with repetitive passing ions through the instrument in the zoom-in mode as explained below, the 100 m long flight path was reached in an experimental test of the P-MR-TOF analyzer. In Figure **1-B** the obtained spectrum of an isotopic cluster of GC column bleed compound ($C_7H_{21}O_4Si_4$), ionized with electron impact source, is compared to the theoretical isotopic pattern (blue line). It is shown in particular, that the obtained high mass resolving power of 500K allows observing fine isotopic pattern with less than 1mDa mass difference.

As seen in Figure **2**, the same instrument provides resolution R>200K in the full mass range mode. Inserts A and B show the difference between modes of mass analyzer operation. In the full mass range mode (insert A) ions are flown for a single full pass: they leave the orthogonal accelerator (OA), follow multiple reflections in one drift direction (from top to bottom in Figure **2A**), then got reflected by the electrostatic electrical field of the end-lens and return by the same route to the detector. There is no trajectory looping, thus this mode allows acquisition of the full mass range. However, the ion path is not long enough to reach the aberration limit

of the analyzer and thus the dominant contributor into the time width of the ion signal peaks at the detector is the initial time spread of the ions when they leave the OA. When pulsing the voltage on the entrance lens (shown as "pulse" sign), ions could be "trapped" within the analyzer for a number N of full passes (turns), thus providing the so-called "zoom" mode. The ion flight path becomes longer and the resolving power increases, though at the expense of narrowing the admitted ions mass range. The plot on the Figure **2** shows that the resolution improves with the number of turns in the zoom mode, and reaches at least 500K after five turns and then increase in resolution is significantly slows down and essentially stays flat at the level of aberration limit R_A >500K.

FUTURE IMPROVEMENTS OF MR-TOF

Achieving yet higher resolving powers in MR-TOFMS would require a longer flight path, smaller aberrations of the analyzer and narrower ion packets. Figure **3-A** shows a concept of cylindrically wrapped planar MR-TOF analyzer [33, 34, 41, 43], which allows efficient folding of the ion trajectory within a relatively
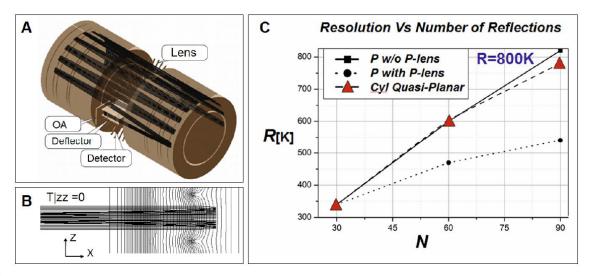

Figure 2:

Figure 3:

compact-size analyzer. Ion optical simulations suggest that 100 m long flight path is obtainable inside 1 m long mass analyzer placed in 0.3 m diameter cylinder. Optionally, the cylindrical analyzer could incorporate a periodic lens array in the drift region: with 10 mm lens pitch the design could provide almost 100 reflections in the single ion pass. The simulations also suggest that the tangential ion packet displacement within the cylindrical analyzer does not affect the MR-TOFMS resolution up to at least $R_A=1$ million level in case of injecting ion packets at a small inclination angles, sufficiently large radius to length ratio of the analyzer and if an additional radial displacement of ions is arranged to return the ion turning point onto the symmetry plane.

Figure **3-B** illustrates a concept of overcoming aberrations introduced by periodic lenses by arranging a so-called quasi-planar ion mirror [30, 80]. Small spatial modulations of the electrical field of the planar mirror could be achieved for example by incorporating auxiliary electrodes in the vicinity of ion reflecting point. Such electrodes help to create a small field curvature in the XZ plane. The curved mirror electrical fields are known to provide spatial focusing in the XZ plane with high order isochronicity as it has been demonstrated earlier for planar fields in the XY plane.

The plot on the Figure **3C** show results of ion optical simulations for the analyzer incorporating quasi-planar fields of Figure **3B**. It is shown that the resolution improves with number of ion reflections in all simulated cases. However, when using periodic lenses in the analyzer with planar or cylindrical ion mirrors, the resolution start being affected by lens aberrations at R>300000 and saturates at approximately R=500,000-

600,000 level. When using quasi-planar ion mirrors, the resolution keeps improving to at least R=800,000 at 90 turns and stays close to the aberration limit of the planar or cylindrical ion mirrors. Simulations suggest that resolving power of one million is achievable.

An alternative or complementary approach for achieving ultra-high resolution is shown on the Figure **4**. Ultra-short ion packets can be obtained by using an axial buncher [48]. The Figure **4A** describes the major steps of the method implementation: 1) A continuous ion beam is accelerated to high energies, thus strongly reducing an absolute velocity spread. Preferably, the beam is refocused for being a parallel; 2) The beam is pulse accelerated in the axial directions by a so-called axial buncher, where the moderate electric field strength is chosen to reach a sub-nanosecond turn-around time; and 3) An electrostatic energy filter selects ions accelerated in the middle of the buncher and thus, having a proper energy range, removes the continuous beam and excessive ions from edges of the axial buncher. Figure **4B** shows an example of the axial gridless buncher, terminated by an exit lens to form highly parallel ion packets. Figure **4-C** presents a simulated ion optical scheme, including an energy filter, simultaneously serving as a curved inlet into the MR-TOFMS analyzer [27]. Figure **4D** shows the simulated time profile of ion packets, formed by the arrangement of Figure **4C**, justifying an ability to form sub-nanosecond ion packets.

MULTI-DIMENSIONAL CHROMATOGRAPHY WITH MR-TOFMS

Authors have recognized tremendous separation capacity of high resolution MR-TOFMS, particularly
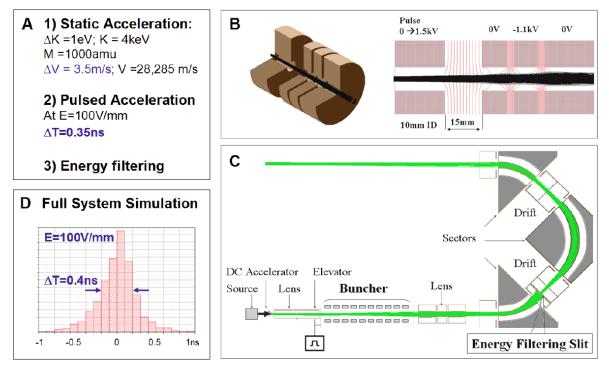
Figure 4:

when coupled with multi-dimensional chromatography and with soft ionizing sources to reduce the number of peaks per ion specie. Earlier [82-84], we reported the results of analysis of crude oils with MR-TOFMS while using soft ionization sources, like chemical photo-ionization (PCI) or conditioned glow discharge (CGD) [32, 84-86] sources.

The experimental setup is shown on the Figure **5-A**. The crude oil sample was diluted in CCl_4 to 1% concentration and injected into GC or comprehensive GCxGC. Time separated semi-volatile compounds were chemically ionized by hexane ions, produced by photo-ionization using Xenon UV lamp. The mass spectra were collected on MR-TOFMS with dual orthogonal acceleration with resolving power over 100,000. High resolution allows separation close isobars at 3 to 6 mDa difference (e.g. pairs like SH_4/C_3, $^{13}C/^{15}N$). Mass separated isobars allow accurate assignment of elemental compositions of the detected ions. In many cases very close isobars with 1-2 mDa mass difference (which is not enough to separate at the given resolving power) were eluted at different retention times and that accurate mass measurements were possible without isobar interferences.

After assigning elemental compositions, the spectra were analyzed with in-house software for extracting information about a set of detected compounds, corresponding to the same hetero-atomic class, for example, having single serum atom to be referred to as S-class. Within the set, the detected compounds were then differentiated by number of carbons C (CH_2 mass difference) and by number of effective double bonds DBE (H_2 mass difference). Figure **5B** shows an exemplar C-DBE plot for S-class ions with spot brightness corresponding to compound concentration in the sample. Notably, cyclic compounds with DBE=3, 6 and 9 are most intense, probably meaning higher stability of cyclic compounds in the nature-formed reactor baking crude oils.

The elemental compositions with exact mass were then plotted as SIC (single ion current) plots, demonstrating their chromatographic separation, as shown in Figure **5C**. The number of chromatographic peaks roughly corresponds to the number of possible structural isomers, confirming that the natural reactor creates all possible isomers. When comparing analyses results of different oils we have found that the isomeric distribution may be used for the fingerprint identification of the oil origin. The overall number of identified species, taking in account separated isomers was estimated in the 100,000 range.

While single stage gas chromatography (GC) is known to provide the separation peak capacity up to 1000, the comprehensive GCxGC is known to increase the separation capacity up to 10,000. In a typical setup, the first GC stage in GCxGC separates molecules by
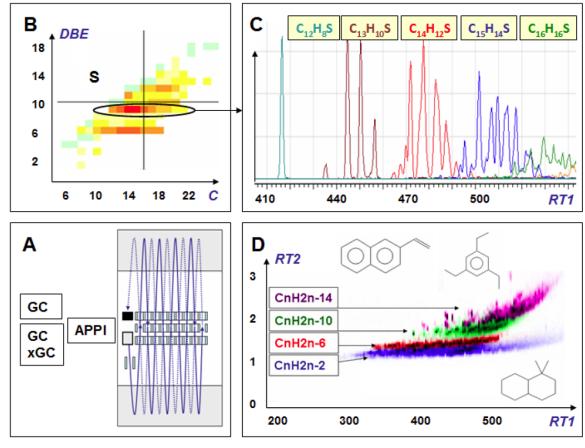
Figure 5:

volatility, while second GC by their polarity, thus providing characteristic patterns on the two-dimensional (2D) plot indicating chemical classes. A soft APPI ionization provides only molecular M+ or quasi-molecular ion peaks for most of the crude oil species and high resolution MR-TOFMS enhances the separation capacity by factor of 10,000, bringing the overall separation capacity to approximately 10^8. Figure **5-D** shows a color-coded overlapped GCxGC plots for different hydrocarbon series. Accurate mass measurements in MR-TOFMS allow extracting 2D GCxGC plots for individual compounds, each having rich isotopic composition. With GCxGC-PCI-MR-TOFMS we have detected over 10,000 elemental compositions and at least 300,000 species of crude oil, if accounting chromatographically separated isomers.

The PCI source has an advantage of selective ionization, which helps analyzing S-, N- and O-class compounds at the trace levels; however, the ionization selectivity turns into a drawback if quantitative measurements are desired. In order to achieve a uniform ionization efficiency across the compounds of interest and to detect non-polar species (e.g. saturated hydrocarbons), we have developed so-called

"conditioned glow discharge" ion source [32, 84-86]. The method employs Penning ionization in the argon atmosphere to provide exclusively M+ molecular ions accompanied by limited fragmentation, including such classes of compounds as for alkanes, phthalates, and nitro compounds. When in-source collisional fragmentation is applied, resulting mass spectra appear very similar to the corresponding spectra in the standard libraries (NIST, Willey, etc). A combination of soft ionization, NIST identification of fragment spectra, and quantitative analysis presents a novel opportunity in analytical chemistry. The method may be particularly suitable for the analysis of crude oils, for quantitative metabolomic measurements and analysis of other complex mixtures types.

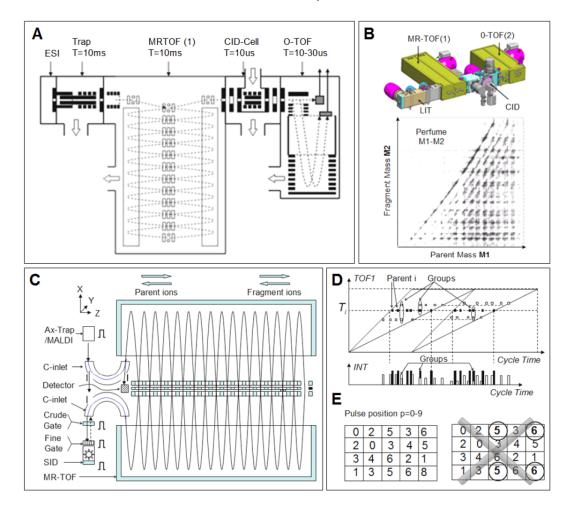**COMPREHENSIVE TOF-TOF MASS SPECTRO-METER (CTT-MS)**

The idea of all-mass MS-MS analysis has been long intriguing. Parallel MS-only analysis has been already known while using TOFMSs, ion traps and IMS, all operating with ion trapping and mass separation in time paradigm. The challenge was to make a tandem operation of two trapping "in-time" separators, with the

major technical challenge to make such a tandem truly lossless and handling realistically large ion fluxes, reaching 10^9 to 10^{10} ion/sec generated by modern ESI and EI ion sources.

Accumulating precursor ions in ion traps for sensitive MS-MS analysis was proposed in [21, 118]. This triggered an idea of using a three-dimensional ion trap for all-mass ion parent scan with downstream parallel fragment analysis by an orthogonal TOF [119]. The trap-TOF idea was then proposed in [120, 121]. However, it was quickly recognized that traps are too slow and their space charge capacity is too small. The limited charge throughput of the known ion traps would negate the sensitivity gain of the parallel MS-MS. The parallel IMS-TOFMS [122, 123] also might be considered too limited at the beginning. Based on the knowledge available in early 2000s, the scheme of time-nested TOF-TOF MS seemed being most prospective [22, 23].

The ion optical scheme of so-called Comprehensive TOF-TOF MS (CTT MS) [22, 23] is depicted in Figure

6. Ion flow is trapped in an axial RF trap, where ions are trapped by an RF field in the radial direction, and DC field of auxiliary electrodes helps trapping and pulse-ejecting ions in the axial direction. We have experimentally confirmed that the trap can operate at almost 1kHz frequency, while trapping up to 10^6 ions, i.e. the charge throughput of the axial trap is very adequate to the analysis requirements. All parent mass species are then separated in time within a first multi-reflecting TOF mass analyzer (TOF1) at relatively low sub-keV ion kinetic energy to extend the flight time to about 10 ms. The time-separated parents are then injected into the fragmentation cell (for example CID or SID type) and then are subjected to a rapid analysis in TOF2. The original idea was to use a short OA-TOF analyzer at high ion kinetic energies for a rapid TOF2 analysis. In a later proposition [41], the second TOF is a frequently pulsed MR-TOFMS.

The Figure **6** also depicts MS-MS spectra experimentally obtained in parallel all-mass analysis of a volatiles in perfume sample, ionized in APCI source. Experimental tests have revealed the challenging part

Figure 6:

of the CTT MS scheme. The charge throughput appears to be limited by ion packets expansion due to space charge inside the MR-TOF analyzer, causing ion losses at the fragmentation cell entrance. Such losses start to occur at ion packets containing more than few thousand ions and the loss factor may reach 100 at the full space charge load. Spatial ion losses then negate the sensitivity gain of parallel analysis. Thus, the scheme may be useful only at reduced ion fluxes at the CTT MS entrance, for example, for MS[3] analysis.

The issue of ion losses is expected to be solved in another MR-TOF-TOF tandem [41] reincarnation, shown in Figure **6-C**. The CID fragmentation cell is replaced for in-vacuum SID fragmentation cell, which has much wider entrance aperture and no need to introduce collisional gas flow into the MR-TOF analyzer. If one is using nonvolatile fluorinated polymers to coat the collisional surface of SID cell, the fragmentation efficiency of such SID cell was experimentally proven to be above 40%. To allow use of the same MR-TOF analyzer for both TOF1 and TOF2 stage, there was proposed a concept of so-called "non redundant sampling" [41]. The data acquisition experiment lasts for multiple (say 100 to 1000) pulses of an axial trap, or pulses of in-vacuum MALDI source. The set of crude and fine time gates samples multiple parents per every pulse of the source. The voltage on the SID cell is pulsed for obtaining delayed ion extraction, where the pulse timing is encoded similar to the EFP method.

The key concept of the non-redundant sampling method is to provide a high multiplexing gain of the MS-MS analysis. Multiple parents are sampled per every ejection from the ion source, and mass spectra for numerous precursor ions are multiplexed (combined) at the MR-TOFMS detector. To avoid the confusion during spectra decoding, the parents are multiplexed at different combinations, so that to combine the same pair of parents only once (Figure **6-D**). During the data acquisition, any single parent ion is selected multiple times, so that the corresponding fragment spectrum may be extracted by correlating the systematically occurring fragments. The method is constructed on pair-wise orthogonal Latin square matrices. Figure **6-E** provides a simplified example of orthogonal and non-orthogonal matrices for multiplexing samples 1 to 8 in multiple sequential experiments shown by horizontal rows. The second incorrect matrix repeats the pair of 5th and 6th samples.

The described method is expected to provide unusually high resolution of parent ion selection, in the order of several thousands, though at limited (5-10%) duty cycle. The method implementation would require developing of multiple novel hardware components and plenty of special software operating new algorithms.

ENCODED FREQUENT PULSING

It's been long recognized that sensitivity of TOF MS with orthogonal accelerator (OA) may increase at higher frequency of OA pulsing. However, that may cause spectral overlay, and for long time there was no effective solution for decoding of those overlapped spectra. The methods based on analysis of peak width [124], or single shift of pulsing frequency [125] can only work for high intensity peaks. Hadamard transformation (HT), earlier developed for IR spectroscopy [126], was proposed for mass spectrometry [127, 128], but the implementation was overlooking the fact that the HT method is suitable only for smooth spectra at narrow dynamic range. The automated addition and subtraction of peaks at "wrong" spectral position would leave the residual signal, if considering statistical variations only and not speaking of other artifacts.

We have departed from the "blind" mathematical algorithms and proposed a method derived from the "logical" analysis of spectra overlaps, occurring in MR-TOF MS FFP spectra, which characterized by sparsely populated sharp (well resolved with high resolution) ion signal peaks [33, 34]. High resolution spectra appear to be relatively low populated, particularly at short acquisition times, insufficient for revealing the chemical noise at 1E-4 to 1E-5 level relative to strong analyte signals. At the same time, a prolonged flight time in MR-TOFMS and a relatively small size of ion packets both reduce the efficiency of the double orthogonal accelerator (duty cycle) under DC<1%, as shown in schematic view of Figure **7-A**. In the exemplar case of 1ms flight time and 50eV continuous ion beam, the duty cycle is estimated as 0.25% for upper m/z range of detected ions.

In [33, 34] we proposed a solution for improving of the MR-TOFMS duty cycle – method of frequent pulsing of the orthogonal accelerator with unique time intervals (Encoded Frequent Pulsing – EFP). The key concept was that within overlaid mass spectra some overlaps are likely to occur between multiple peaks of various ion species. However, if time intervals between the OA pulses are unique, the overlaps will not be systematic! Figure **7-B** compares time diagram for rare
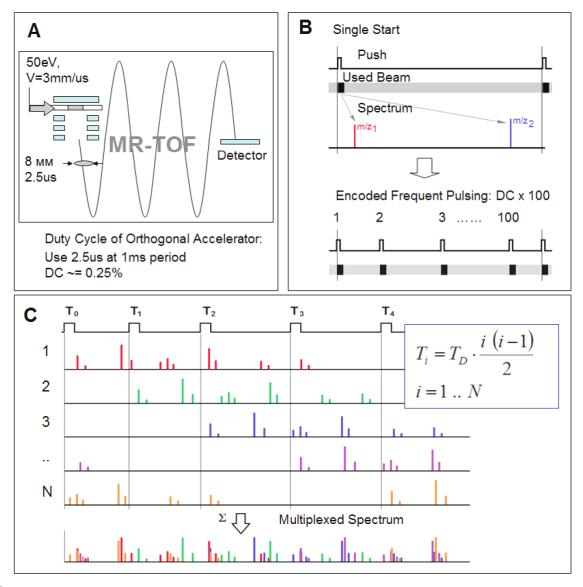
Figure 7:

pulses and encoded frequent pulsing (EFP). The grey bar represents a continuous beam with black sections denoting the used portion of the continuous ion beam. At frequent pulsing, the number of black portions rise dramatic, meaning that the continuous ion beam is sampled much more efficiently. In the presented example of 100 pulse sequences, the duty cycle is improved up to 25%, which is very comparable to best implemented singly reflecting TOFMS with notably lower resolving powers.

The concept diagram in Figure **7-C** shows how the multiplexed spectrum is composed from the multiple starts and from multiple ion species. The multiplexed spectrum looks like a mess, if trying to analyze it manually. However, the appropriate decoding algorithm knows the pulsing time sequence with one proposed example of pulse intervals as $T_i = T_D \cdot i \cdot (i-1)/2$, ensuring

unique intervals between any pair of pulses. By knowing the expected peak intervals, the decoding (de-multiplexing) algorithm collects all hypotheses into peaks of mass species, analyzes hypotheses for consistency of the intensity and accurate mass, and, optionally, analyzes the hypothesis for overlaps of the already detected mass species. There are multiple variations of the decoding algorithms, usually optimized for speed and efficiency.

Figure **8** presents an example of the sensitivity gain provided by implementation of EFP in MR-TOFMS operation. The trace amount of a drug is detected within a rich biological matrix and the results were compared between a single-start analysis data and data acquired with 68-pulse EFP. Expectedly, the absolute signal from the analytes grows proportional to the number of starts, as witnessed by the Total Ion
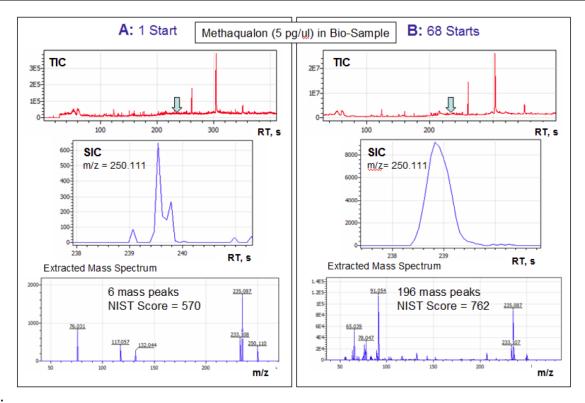
Figure 8:

Current (TIC) traces. Individual Single Ion Current (SIC) traces also grow proportional for strong mass components (not shown). For lower intensity components, the gain starts dropping, since the filtering part of the algorithm may reject very low signals, which potentially may be confused with signal composed of random overlaps. However, at 1 pg analyte amount level, the EFP gain is still high (at least 30 for m/z=250.111), as seen from the inserts in the middle of the figure. Most importantly, SIC traces have a good statistics, which allows their deconvolution by retention time and this way extracting representative EI spectra of the analytes, compared in the bottom plots. For example, in the shown data, while single start analysis allows reliably extract only 6 major peaks, the EFP analysis allows extracting 196 mass peaks within much wider dynamic range. As a result, the detection and identification is much more reliable. In the presented example, the NIST similarity score grows from 570 (no EFP) to 762 (with EFP).

The method of encoded frequent pulsing (EFP) does recover the duty cycle of MR-TOF and allows further extension of MR-TOF flight path (for example, in cylindrical analyzers as shown in Figure **3-A**) without compromising sensitivity. The duty cycle is defined by the frequency of OA pulsing rather than by the flight time in MR-TOF mass analyzers. The method extends the space charge limit of the analyzer and the dynamic range of TOF detectors. Finally, if analyzing the intensity distributions of the peak groups for any single ion specie, one can extract fine timing details and rapidly track time variations of ion flow in front of the MR-TOFMS. The fast signal tracking capability is particularly useful for accelerated profiling in surface image analysis, and in the fast parallel MS-MS and IMS-MS tandems as described below.

The drawback of the EFP method is in limitations due to high spectral population. According to our experimental tests, the method works very well for tandem mass spectra, which are usually scarcely populated. It also works well for MS-only analysis at short spectral acquisitions (under 100 ms per spectrum). However, the method fails when intense spectra are accumulated for seconds. However, in such cases, the single start spectra already provide detection down to chemical noise limit and there is no need to apply EFP. The switching between single start and frequent pulsing could be controlled in a data dependent strategy.

FREQUENT PULSING IN OPEN TRAPS

While choosing the methods of spectra multiplexing and de-multiplexing, the problem of low duty cycle in MR-TOFMS can be solved in an alternative way, being somewhat advantageous compared to the above EFP
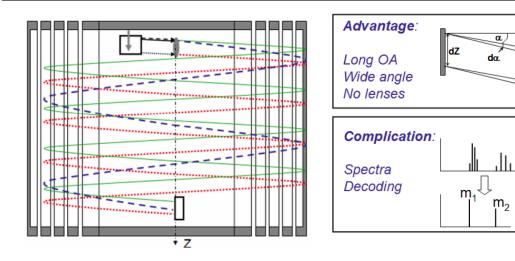
Figure 9:

method. In [35] we suggested Multi-Reflecting Open Traps (MROT), schematically depicted in Figure **9**.

To understand the concept of MROT in Figure **9**, they should be compared to multi-reflecting time-of-flight mass spectrometers of Figure **1**. In MR-TOFMS, the periodic lens confines ions along the mean trajectory, thus fixing the number of reflections and the length of ion trajectory and a single ion specie forms the single peak in the TOFMS spectrum. The peak multiplicity appears in EFP method (Figure **7**), when the double orthogonal accelerator is pulsed frequently. In the Open Traps (Figure **9**), the periodic lens is removed, and the number of reflections is not fixed because of the natural angular divergence of the ion packets and single specie rather forms multiple peaks corresponding to a span in the number of reflections. The ion peaks ensemble per single ion specie will have some intensity distribution per number of reflections (multiplexed peaks), expected to be a generic apparatus function for all mass species. The time period between ion peaks is proportional to square root of mass, thus, the systematic overlap between peaks of any two species is excluded, and open trap spectra can be decoded (de-multiplexed).

The multiplexing of MROT provides multiple advantages. Splitting single peak into multiple peaks and using wider ion packets overcomes space charge limitations of the TOF analyzer and improves the dynamic range of TOF detectors. Since ion packets are wide when they reach the detector, they can be formed wide in the orthogonal accelerator aligned in the drift Z-direction (see Figure **9**), this way substantially improving the OA duty cycle. Using an elongated and

dual side detector as described in [35] further improves the duty cycle and the dynamic range of the MROT. Finally, the MROT multiplexing may be combined with an encoded frequent pulsing of the OA, as described in [35].

The MROT is also a quite efficient way for enhancing the resolution, since the periodic lenses are removed, thus removing their aberrations. Besides, the ion beam is narrow in the Y- direction, thus strongly reducing ion mirror aberrations contribution into the peak width. The Open Trap mass analyzer may be cylindrically wrapped one as shown in Figure **3** to provide an extended flight path and high resolution. One should note that extension of the flight path does not compromise the sensitivity. The only seen drawback of MROT is an inevitable use of multiplexed spectra. In other words, contrary to MR-TOFMS with EFP method, the Open Traps operation is not capable of switching between single start and multiplexed spectra acquisition modes.

ION MOBILITY FOR PARENT SEPARATION

Mass scanning losses have been a significant concern for MS-MS tandems operation. In triple quadrupoles, both quadrupole mass filters select and pass single mass specie in a time. This is an effective strategy for ultra-trace target analysis, where the parent and fragment masses are known up-front and are mapped per the expected chromatographic retention times. The Q-TOF instruments [15, 16] employ "all-mass" TOF analyzer as MS2 to provide full information on all daughter (fragment) ions. However, first quadrupole separator as MS1, still spends time and
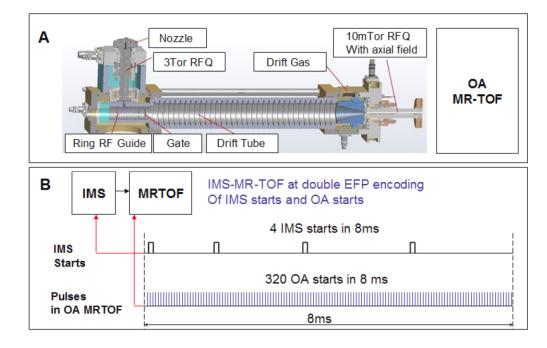
Figure 10:

loses other parent species when switching or scanning between parent masses. It is desirable to improve sensitivity while scanning or switching precursor ions.

One approach to parallel tandems has been proposed by Clemmer *et al.* [122, 123]. The precursor ions are trapped in an ion trap, pulsed-released, separated by an ion mobility spectrometer, optionally fragmented in a fragmentation cell, and then analyzed by a TOF mass spectrometer. Though the method was claimed to provide a parallel parent separation for all-mass MS-MS analysis, the originally implemented apparatus had multiple limitations due to spatial ion losses, space charge spreading, and restrictions of a counting TDC data system, negating overall the gains of parallel separation. Since then, the multiple advances of the IMS-TOF were proposed and implemented, truly enhancing the IMS-TOFMS tandems [129-131].

We have proposed yet further enhancements of IMS-TOFMS performance by much faster tracking of ion mobility profiles with MR-TOFMS with FFP and with EFP [39, 42]. Figure **10-A** shows a corresponding apparatus [106]. Electrospray ions are sampled via nozzle, delivered through the RF ion guide at 3 Torr and enter an accumulating RF ring guide. The RF ring gate [39] is used to release fast (100 us) ion packets into the electrostatic drift IM cell. Ions are gathered by an ion funnel and enter into an MR-TOF via orthogonal accelerator using transfer RF ion guide at 10mTor. The IMS-MR-TOF tandem employs the double encoding

method [39, 42, 106], where the intervals between IM pulses are not even and the orthogonal accelerator of the MR-TOF is pulsed with a much more frequent and also non-uniform string of pulses (Figure **10-B**).

A time section of the doubly multiplexed mass spectrum is shown in Figure **11-A**. Envelopes of at least two major mass components are visible. By knowing a predetermined non-uniform pulse sequence of the OA, the decoding algorithm extracts mass spectrum, as shown in Figure **11-B**. Tracking intensity profile for any single mass specie provides the multiplexed ion mobility profile. The IM profiles are then decoded based on the information of the predetermined pulse sequence of the IM gate. As a result, each 8 ms spectrum simultaneously provides the information on mass and mobility. A multiplicity of detected pairs - m/z and mobilities - provide total mass spectrum 2D plot of Figure **11-C**. In the tested example, most of the peaks are singly charged and mobility is heavily correlated with m/z, still, however, separating hydrocarbon and fluoro-hydrocarbon series. Surprisingly, mobility correlates with mass defect (Figure **11-D**). For hydrocarbons it may explained by the effect of double bonding: each double bond removes a pair of hydrogen atoms (strong mass defect), while making the structure more compact, i.e. shortening the drift time in IMS.

Let us estimate the charge throughput of the IM-MR-TOFMS tandem. The MR-TOFMS stage is limited to 300 ion/packet due to space charge effects in the
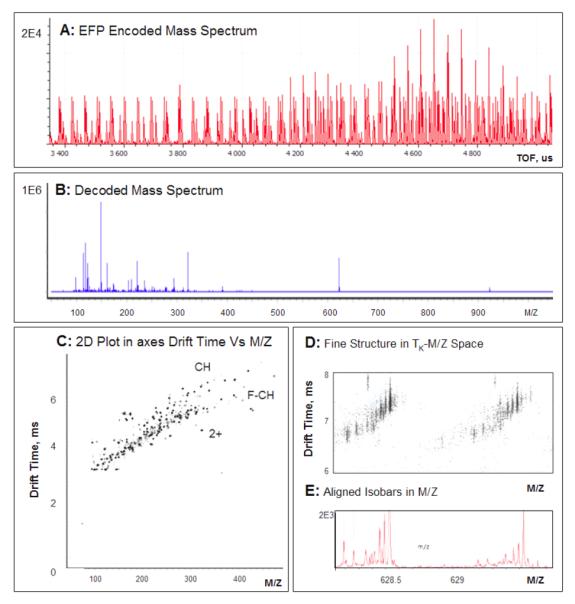
Figure 11:

analyzer and due to the limited dynamic range of the TOF ion detector. Accounting 100 kHz average pulsing rate of the OA, and assuming somewhat denser (than was experimentally implemented) pulsing of the IMS stage, the total charge throughput of the MR-TOFMS per ion specie can be estimated as 3×10^7 ions/peak/sec at the detector [129, 130].

The throughput of the IM stage has been measured as 150 pA (10^9 ion/sec at IM exit, i.e. 2×10^6 ions per IM packet at 2 ms period of IM pulsing), before the space charge starts affecting IMS resolution. Accounting approximately 10% duty cycle of the OA in the EFP regime, and accounting multiple species in MS spectra, the IMS separation stage is expected to be then the limiting stage. If using a cylindrical coaxial IMS as

proposed in [39, 42, 134] it is expected to further increase the charge throughput of the IMS stage and to bring the overall throughput to approximately 10^{10} ion/sec in the IMS stage, corresponding to 10^9 ion/sec at the MR-TOFMS detector. The expected dynamic range (minor component per total spectral content) is then expected up to 10^8 per second.

The described IM-MR-TOFMS provides an opportunity for a rapid 3D-tag analysis (LC retention time, mobility and exact mass) of complex mixtures. The same apparatus may be switched to MS-MS mode, where the IMS serves as a parent ion separator. In-spite of moderate IMS resolution (30 to 50), the fragment spectra may be then extracted and correlated to precursor ions by time correlation in both time
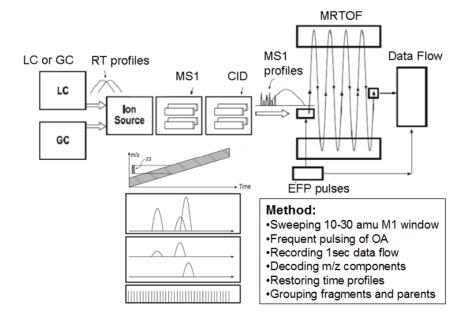
frames - chromatographic separation and mobility separation. The MS-MS regime may be used at discovery stage, where MS-MS spectra are used for reliable compound identification. Once the discovery is completed, the 3D-tag method is expected to be a very robust characterization method, identifying the target compounds at more sensitive measurements, since parent ion signal is not split between multiple fragments.

2D MS-MS IN Q-MR-TOFMS

The method of Frequent Encoding Pulsing (EFP) in the MR-TOFMS with FFP provides an immediately available opportunity for improving the efficiency of Q-TOF tandems if using the method depicted in Figure **12** called 2D-MS-MS [45-47, 135]. A quadrupole filter is smoothly scanned with a wide open M1 window of 10 to 30 amu, this way reducing scan losses at parent ion separation stage compared to standard 1-2 amu Q1 window in Q-TOFMS tandems. Fast pulsing of the OA at mean 100 kHz rate does allow to recover mass spectra and to track the time profile for every ion mass specie. This in turn is used to reconstruct fragment mass spectra, apparently assigned to parent masses at about 1 amu precision. Thus, the method provides approximately 10 to 30 fold gain of sensitivity without sacrificing the resolution of the parent ion selection.

Figure **13** shows experimentally obtained data with 2D-MS-MS method on a research grade Q-MR-TOFMS instrument with ESI source operating in the infusion mode. The analyzed solution contains 100 uM of reserpine and 0.1uM of Bovine Serum Albumin (BSA) digest. Quadrupole filter was scanned once for 5 second scan time in a mass span from 300 to 1100 amu and with 20 amu wide window. Mass separated precursor ions were then fragmented at 30 eV collisional energy. The OA was pulsed at ~100 kHz rate at the periodically repeated EFP pattern. Figure **13-A** shows a total (TIC) signal at MR-TOFMS detector as a function of mean parent mass M1. The vertical scale is expanded 10-fold in order to see peaks of BSA peptides. The signal was EFP decoded to recover mass spectra for multiple wide time intervals (wider than time per M1 peak), and then the analytical ion current (AIC) plots were produced for each mass specie. The appearance of the fragment and precursor ions was correlated with the mean M1 mass to produce the 2D plot shown on the Figure **13-B**. Vertical patterns of fragment spots correspond to the same M1 centroid which allows grouping the mass spectral peaks into fragment spectra, apparently assigned to precursor ions with $\Delta M1=1$ amu accuracy, in spite of using wider (e.g. 20 amu) MS1 quadrupole window. A single 5 second analysis revealed 112 BSA peptides present at 0.1uM concentration in the sample. An example of minor peptide fragment spectra is shown in Figure **13-C**. The mass spectrum corresponds to overall 500 ions, however, because of ~ppm mass accuracy in MR-TOFMS, the fragment spectrum still allows peptide identification. De-novo sequencing allows assignment of several peptide fragment peaks. The SIC of the same peptide is shown in Figure **13-E**. The detected specie is minor and is at least 3 orders of magnitude smaller than the major reserpine specie shown in Figure **13-D**.
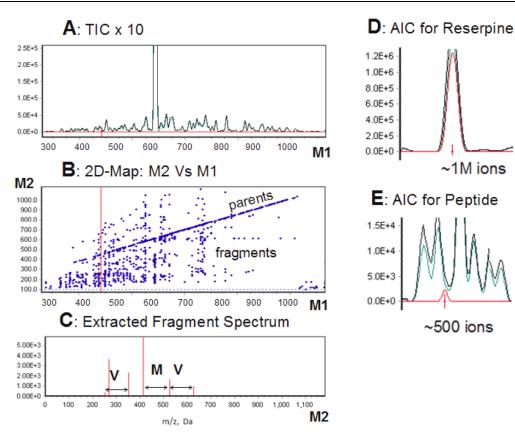

Figure 12:

Figure 13:

The presented 2D-MS-MS method of analysis is data independent acquisition type, meaning that the same robust scan may be used independent of the sample composition. It provides MS-MS spectra for all parent species at 1 amu parent mass resolution. The measurement is accomplished in a single and fast quadrupole scan (0.3-3 sec), compatible with LC separation times. Using wide (from 10 to 30 amu) M1 mass window proportionally saves on parent scan duty cycle, comparing to stepping of individual 1 amu windows, used in the typical way of MS-MS operation. The obtained MR-TOFMS fragment spectra are usually low populated, which allows reliable decoding of the EFP encoded spectra. High resolution of MR-TOFMS helps with interpreting spectra of minor species at minimal ion statistics.

The sensitivity and dynamic range of the method could be further enhanced if employing an ion trap upstream with sequential ion release and with a humongous space charge capacity of approximately 10^9 ions [46]. The resolution of precursor ions selection may be improved with a synchronously scanning downstream quadrupole, still, the sensitivity gain would be proportional to resolution of the mass sequential ion release of the trap.

TRAP ARRAY FOR PARENT SEPARATION

The lossless parent scan for all-mass MS-MS is expected to be reached with a trap array, described in [46] and conceptually shown in Figure **14-A**. To increase the charge throughput up to 10^9 ion/sec, the trap array is composed coaxially, employs multiple (30-50) linear traps being fairly long (10-30 cm). Further enhancement of the charge throughput is to be achieved by faster (10 ms) mass selective ejection at a moderate resolution (30 to 50). The mass selective ejection is arranged by opposing quadupolar DC and RF fields, which is less sensitive to space charge effects than resonant excitation methods.

Overall the apparatus (Figure **14-B**) combines fast and lossless parent separation in the trap array with rapid mass spectral acquisition in MR-TOFMS, aided by frequent encoded pulsing of the orthogonal accelerator. Within 10 ms separation, each MS1 peak lasts for approximately 200 us, with time profile being detected during approximately twenty OA pulses.

Three operational methods are envisioned for the proposed apparatus. In one method, major spectral components are acquired in the MR-TOFMS with FFP, optionally with EFP. In the second, so-called dual MS
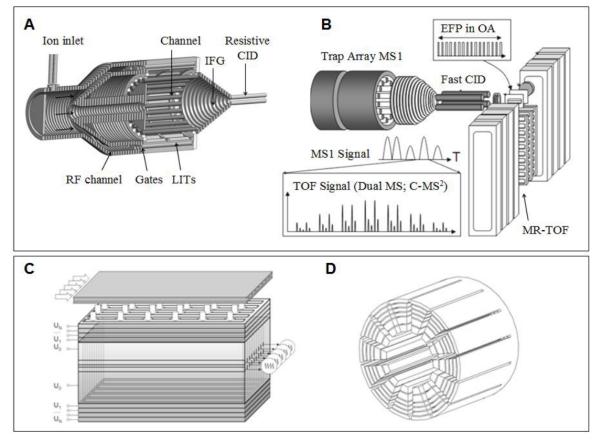
Figure 14:

method, the CID cell is setup for transmitting precursor ions without any significant fragmentation. As a result, EFP spectra are acquired for momentarily narrow mass range, this way fully avoiding spectral overlaps with EFP in OA. In the third method, comprehensive MS-MS method, mass separated precursor ions are subjected to fragmentation in the CID cell and then fragment spectra are analyzed in the MR-TOFMS. In spite of a relatively wide (10-20 amu) mass window for precursor ions, the window is smoothly scanned and time centroids are recovered from TOF signal profiles. Fragment spectra are then reconstructed and related to parent masses at about 1 amu precisions, similarly to previously described 2D-MS-MS method. Contrary to 2D-MS-MS, the trap-array method is expected to completely avoid the parent ion losses.

In case of yet higher ion fluxes (potentially reaching 10^{10} ion/sec), the resolution of the trap array is likely to fall to approximately R=10. Then it may be beneficial to use a downstream synchronized quadrupole at somewhat higher resolution from 50 to 100. In this case, the trap array is still expected to enhance the parent selection sensitivity and the detection limit of the tandem MS by a factor of 10.

MR-TOF ARRAYS AND ELECTROSTATIC TRAPS

An effective, though probably expensive, way of improving the MS throughput is to build multi-channel MS, employing multiple parallel TOF mass analyzers. The cost of building an MR-TOFMS array can be notably reduced with the method shown in Figure **14**. The array of planar MR-TOF mass analyzers may be constructed by making a set of parallel slots in plane electrodes (Figure **14-C**) or making radial slots in cylindrical electrodes (Figure **14-C**). The analyzers then can share the same vacuum chamber and the same set of high voltage power supplies.

The MR-TOFMS array may be used to enhance the analyzer charge throughput when detecting large ion flows from a single bright ion source. In this case, it may be also convenient to multiplex the planar analyzer with rotation. Then electrode windows are to be made as radial slots. The pulsed converter may be diverting ion packets between analyzers, this way reducing space charge effects in the analyzers and also reducing the spectral overlaps if using the EFP method. Alternatively, high throughput analysis can be arranged with multiple chromatographic columns, ion source arrays, and multi-channel interfaces, feeding

ions to individual MR-TOFMS channels. Source arrays and multi-channel interfaces may share common pumping system and common electronics to provide significant cost saving compared to a set of individual single channel mass spectrometers. Such system may be worth using for applications requiring high thoughput analyses, such in clinical applications, proteomics, etc.

CONCLUSION

Throughput of mass spectrometric analysis, expressed as the amount of information per analysis time (and which can be measured as product of main characteristics like analysis speed, sensitivity, and resolution) in the past two decades has been growing faster than the productivity of personal computers. Mass spectrometry has multiple resources to sustain such rapid growth for dealing with true complexity of real-life samples and to support the large-scale programs like proteome or fast and high volume clinical studies.

TOF mass spectrometry provides high speed analysis by its nature of parallel analysis. MR-TOF mass spectrometers dramatically enhance resolution and provide more spectral information at the enhanced mass accuracy, i.e. with better reliability. Frequent encoded pulsing improves MR-TOFMS sensitivity and opens opportunity for effective analysis by MS-MS and IMS-MS tandems. All-mass parallel separators, like high capacity IMS or trap arrays, are potentially suited to deliver lossless and fast scans to enhance the sensitivity and dynamic range, as well as providing robust strategies for data independent MS-MS acquisition. MR-TOFMS arrays are capable of delivering yet higher throughput at lower cost per single MS channel.

The development of novel instrumental principles and yet more efficient hardware is well supported by fast evolution of computers, data acquisition systems and TOF detectors. The supporting industry started paying more attention to the arising and further spreading TOFMS technology.

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