Experimental Validation of the Digital Tandem Mass Filter

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Abstract:

This work presents the experimental evaluation of a digital tandem mass filter that is composed of two digitally operated low-resolution mass filter in series whose mass windows are shifted with respect to each other. The overlap of the mass windows allows the resolution (Δm) of ions to be narrowed to provide better resolving power while the acceptance tandem mass filter is defined by the acceptance of the first low-resolution quadrupole. Our experiments show that digital operation fulfills the promise of the tandem mass filter for providing better ion transmission at the same or better resolving power as a single quadrupole mass filter. It allows the user to continuously adjust the resolving power and sensitivity to meet current needs. Most importantly, the observed resolving power/sensitivity characteristics are the same at any mass and m/z.

Introduction:

Theory of digital tandem mass filter operation:
A tandem mass filter (TMF) is created by placing two quadrupole mass filters in series approximately 1 to 5-mm apart without an intervening end cap electrode between them. The rods of the mass filters are spatially aligned and operated at the same frequency with their phases also aligned. The quadrupoles Q1 and Q2 are setup as low-resolution mass filters with relatively broad mass windows that are offset (see Figure 1). To be transmitted through both mass filters, the ion m/z must fit within the overlap of the two offset mass windows. This overlap is adjustable and defines the tandem mass window width as well as the ability of the mass filter system to transmit ions. In general, wider mass windows yield better ion transmission/sensitivity. The advantage of a tandem mass filter is that its acceptance is defined by the acceptance of the first mass filter in the series. In general, acceptance reciprocally correlates with the resolving power.[1-2] Consequently, the lower resolution of Q1 yields greater TMF acceptance (better sensitivity) while the smaller tandem mass window yields better resolution. As a result, the advantage of a TMF relative to a single mass filter (MF) is that it provides better sensitivity at the same resolution.

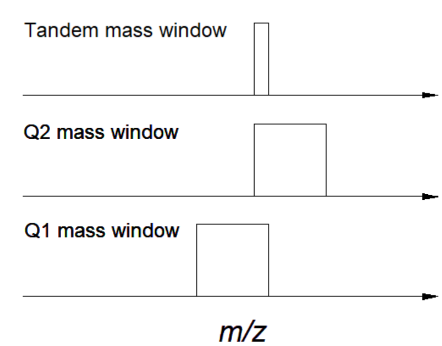

Figure 1: Illustration of the tandem mass window concept.

This concept was experimentally explored by Du and Douglas[3] using two sine mass filters (SMF). To shift the mass windows of SMFs, their operational AC voltage must be offset. The mass windows were moved during the scan by ramping the DC and AC voltages applied to the quadrupole electrodes with the same linear function[4] while maintaining the AC voltage offset between the filters. The AC offset creates a difference in the operational Mathieu parameter q of each mass filter and causes the ions to excite as they transition through the interface between the quadrupoles. Excitation occurs because the transmittance of the first quadrupole does not match the acceptance of the second when the operational q values are different. Mismatched transmittance and acceptance of the respective mass filters yield large ion losses. To mitigate the difference between transmittance of the first quadrupole and the acceptance of the second, Du and Douglas shifted the phases of the waveforms applied to each mass filter with respect to each other and thereby were able to minimize ion loss.[3]

Unlike SMFs that operate at constant frequency and scan the applied potentials, digital mass filters (DMF) operate at constant AC voltage and step the frequency to scan the mass windows. DMF windows are created by changing the duty cycle of the applied waveforms.[5-7] Tandem digital mass filters (TDMF) can offset their mass windows by offsetting the duty cycle applied to each quadrupole.[8] Because each DMF in the tandem pair operates at the same frequency, phase, and voltage, the operational value of the Mathieu parameter q does not change between the quadrupoles and so the ions do not excite when they transition through the interface between the DMFs. This assumes that the quadrupoles are precisely aligned and have the same radius. Consequently, unlike a tandem sine mass filter (TSMF), the ions should not significantly excite at the interface of a TDMF and so there is no need to offset the waveform phases to improve transmission.

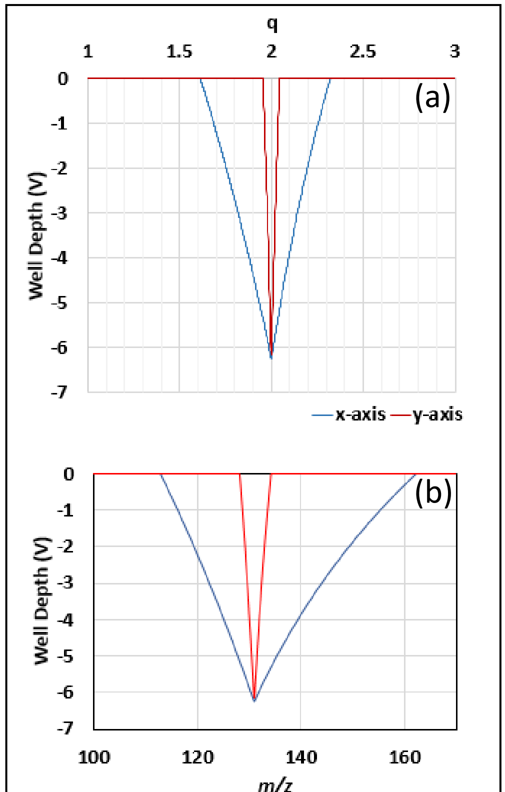

Figure 2: (a) axial well alignment at q = 2.00 for a 75.00/25.00 duty cycle waveform. (b) Axial well alignment at m/z = 131.

The duty cycle sets the positions of the axial wells with respect to each other. Our group has created spreadsheet programs that solve the Hill equation to provide stability and well depth profiles for sine and rectangular waveform operation of quadrupoles. These spreadsheet programs are available to the public at our group website: https://reilly.chem.wsu.edu/spreadsheet-stability-programs/. They have been used to calculate the axial well positions. For example, a 75.00/25.00 duty cycle centers the y-axis well within the wider x-axis well along the a = 0 axis in Mathieu space (see

Figure 2 (a)). This plot can be transformed to visualize the axial wells along the m/z axis using the definition of the Mathieu parameter q:

$$q = \frac{4eV}{mr_0^2\Omega^2} \qquad (1)$$

and specifying the frequency and radius for a given m/z value. Figure 2 (b) shows the axial wells at m/z = 131. The ions are only stable when they exist in both axial wells overlap. At optimal overlap, the stability well is mapped by the y-axis well. When the duty cycle is shifted away from the optimal overlap value, the axial wells shift in opposite directions, thereby reducing the overlap.

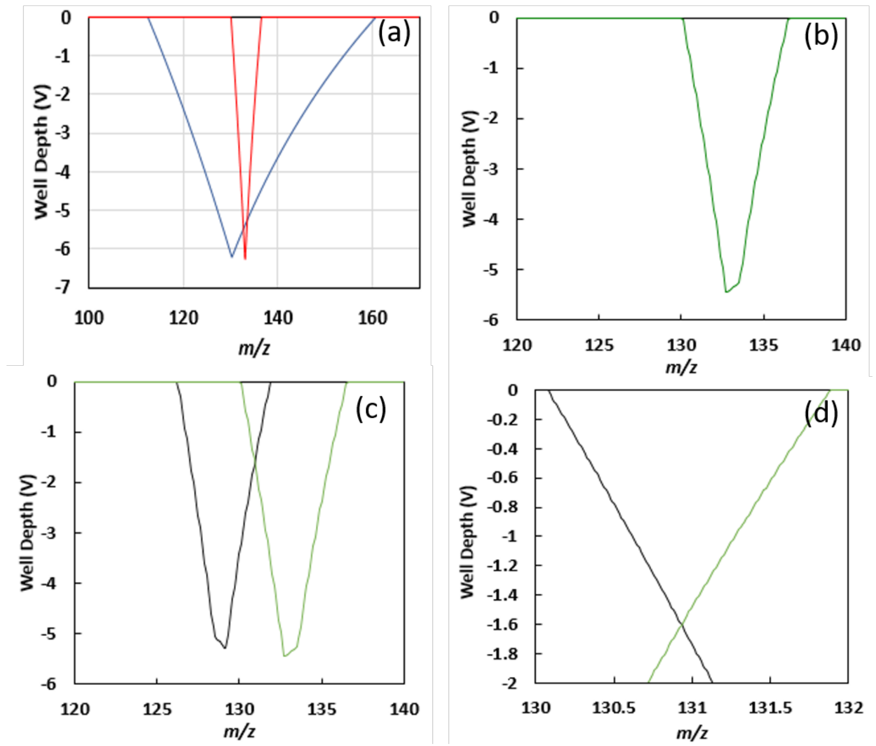

Figure 3: (a) axial well alignment at q = 2.00 for a 74.80/25.20 duty cycle waveform. (b) Axial well alignment at the same frequency and voltage as Figure 2 (b) for a 74.80/25.20 duty cycle. (c) Stability well overlap of 74.80/25.20 and 75.20/24.80 waveforms at the same frequency and voltage. (d) Blow up of the well overlap defines the tandem well.

Figure 3 (a) displays a small but significant shift in axial well alignment along the m/z axis at the same frequency as Figure 2 (b) by shifting the duty cycle 0.2% to 74.80/25.20. The stability map in Figure 3 (b) shows the well depth versus m/z for the ions that exist within both axial well simultaneously. It is no longer completely triangular because the x-axis well clips the bottom of the y-axis well. Greater duty cycle shifts reduce the stability well depth until one side of the well is defined by the x-axis and the other is defined by the y-axis with the eventual outcome of continuing the shift being zero overlap.

Shifting the duty cycles by 0.2% in the opposite direction creates equal but opposite well shifts. The stability wells of the 74.80/75.20 and 75.20/24.80 waveforms operating at the same 100 $V_{0\text{-}p}$ and frequency as Figure 2 (b) are shown in Figure 3 (c). By shifting the duty cycle by the same percentage in opposite directions, the wells intersect at same q = 2.0 and m/z 131 as the optimal alignment duty cycle shown in Figure 2. A blow up of the well intersection is shown in Figure 3 (d). The intersection of these wells defines the tandem well of the tandem mass filter. The small 0.2% shift created a tandem well with a baseline resolving power $RP_{BL} = q/\Delta q = m/\Delta m = 131/1.79 = 73$ and a full width half maximum resolving power $RP_{1/2} = m/\Delta m_{1/2} = 131/0.80 = 163$ from two low resolution quadrupoles with $RP_{BL} = 23$ and $RP_{1/2} = 44$. Another important feature of these pseudopotential well profiles is their well depth. The wells of the individual DMFs are in the vicinity of 4 to 6 V, whereas the tandem well at $RP_{1/2} = 163$ is 1.7 V. Relative to the well depth of a SMF operating at unit resolution ($\Delta m = 1.00$) whose well depth is $D_u = \sim 0.2$ V.[4] It is important to note that well depth directly correlates with ion transmission and sensitivity. At 0.2 V SMF operating at unit resolution are a standard for sensitivity. DMFs operating in zone 2,1 have well depth that are an order of magnitude greater than the $D_u = 0.2$ V industry standard.

It is an interesting exercise to project the achievable resolving power of the DTMF. With the comparison base method of rectangular waveform generation, our waveform generator can change the percent duty cycle at 10 ppm resolution; that is the 3rd place after the decimal. Therefore, there is more than enough duty cycle resolution to incrementally change the duty cycle to achieve any resolving power provided the tandem well has enough depth to transmit ions. If we conservatively assume a 0.2 V tandem well depth as the limit for ion transmission, then the spreadsheet used to calculate the well depth versus m/z plots in Figure 2 and 3 can be used to extract the achievable resolving power. Alternatively, the triangular shape of the tandem well can be used to project the resolving power with the recognition that triangular slopes of the y-axis wells do not noticeably change when the duty cycle is incrementally changed. The tandem wells created by shifting the duty cycle are therefore similar triangles and so if we know the height of the triangle (well depth) and its length along the baseline (Δm) or at full width half maximum ($\Delta m_{1/2}$), the length along the baseline or at the midpoint at different heights can be calculated by proportion. Consequently, it can be shown that $RP_{1/2b} = RP_{1/2a}*(D_{ua}/D_{ub})$. Then the approximate resolving power limit at $D_u = 0.2$V is given by $RP_{1/2} = 163*(1.7/0.2) = 1386$ at the same voltage. It should also be recognized that the well depth D_u is directly proportional to the applied AC voltage. This calculation was made at 100 $V_{0\text{-}p}$, so if the AC voltage were increased to 500 $V_{0\text{-}p}$, then D_u becomes 1.0 V at the same resolving power. Then the resolving power limit also increases by a factor of 5 to $RP_{1/2} = 6{,}930$. The advantage of the DTMF is that the resolving power and transmission can be adjusted with the operational voltage, are continuously variable, and can be set according to the user's need. This work applies the theory outlined above to experimental validation of the DTMF instrument and discusses the outcomes.

Experimental:

A generic schematic of the DTMF is shown in Figure 4. The test DTMF instrument was configured with an electron impact ion source (EI), two low resolution mass filters (Q1 and Q2) in series without an end cap electrode between them, and Channeltron detector.

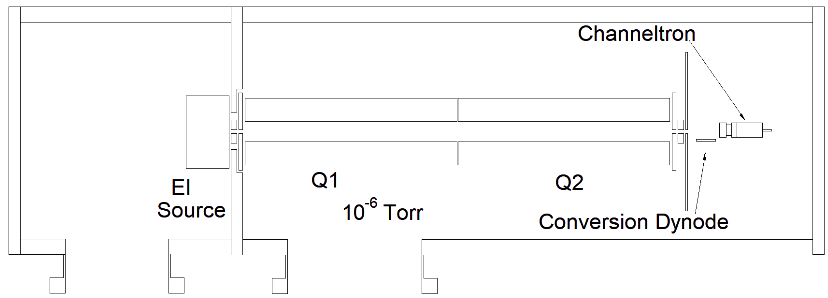

Figure 4: Generic schematic of the of the DTMF test instrument with an EI source, DTMF, and detector.

The image of the test instrument used in this work is shown in Figure 5. The instrument was designed on a rail system that can align Q1 and Q2 and maintain that alignment after changing their spacing. The instrument is pictured with an end cap electrode, labeled EC2, between Q1 and Q2. The rail system allows EC2 to be removed and Q1 and Q2 to be translated into proximity without loss of alignment. For the DTMF experiments shown here, the spacing between Q1 and Q2 was 1-mm. The small spacing was used to minimize perturbation and distortion of the applied fields.

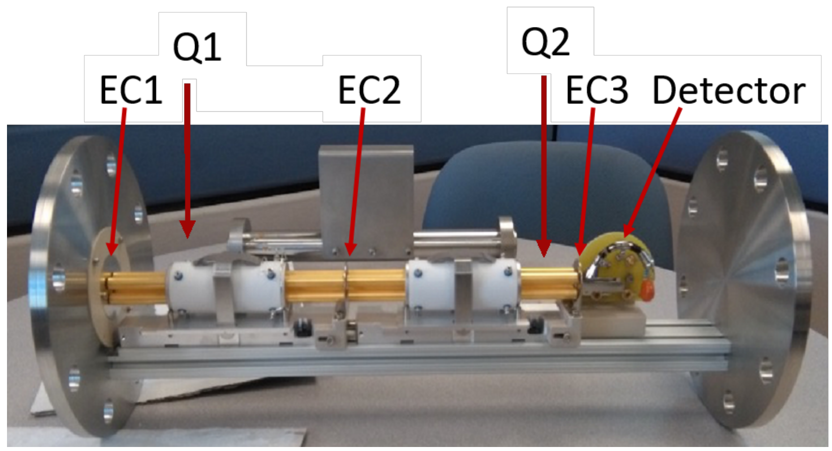

Figure 4: DTMF instrument image.

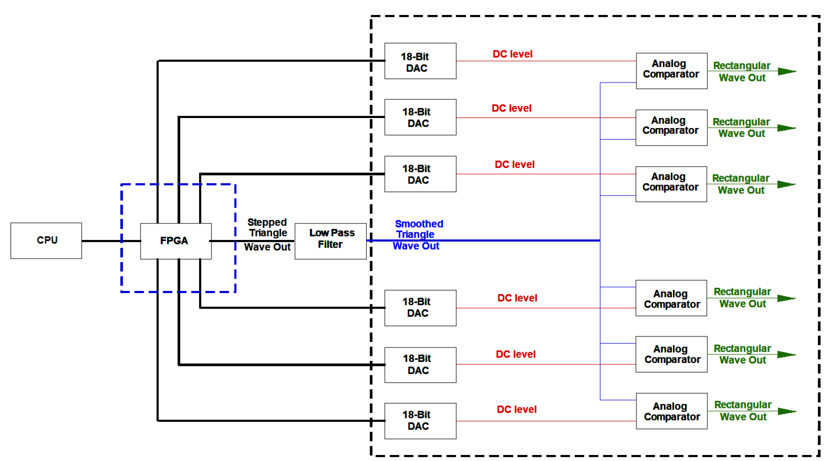

Figure 5: Low voltage digital waveform generator block diagram for creating high resolution duty cycle rectangular waveforms.

Care must be taken to ensure the adjacent rods of each quadrupole have the same phase while both quadrupoles operate at the same frequency. To this end a low voltage digital waveform generator was created using a field programable gate array (FPGA). The FPGA uses the direct digital synthesis method (DDS)[9-10] to create a stepped waveform, usually a sine or a triangular wave. An FPGA operating at 100 MHz will produce a minimum 500-point stepped waveform if the quadrupole frequency is ≤ 500 kHz. The stepped output then smoothed with a 7th order low pass elliptical filter to remove the steps in the waveform. The smooth waveform then enters the digital to analog convertor (DAC) analog comparator printed circuit board (PCB). The 18-bit DAC creates a constant potential with 15 μV resolution to compare with the smoothed waveform potential (0 to 4 V). When the DAC potential is greater than the waveform potential, the comparator outputs a high and when it does not, it outputs a low to create the rectangular waveform.[11] Sine comparison with this system allows 10 ppm duty cycle resolution. Each DAC/comparator PCB has six DACs and six analog comparators that create six different rectangular waveforms with six independent duty cycles that operate at the same frequency and phase. One DAC/comparator board can be used to control a mass filter or linear ion trap with pre- and post-filters. One PCB can also operate a single DTMF. The FPGA can create three independent stepped waveforms to operate three quadrupoles independently.

DTMF Operation Results:

A summation of the results of the Tandem Digital Mass Filter are shown in Figure 6. We have focused on the EI generated m/z 69 (CF_3^+) ion from PFTBA using $V_{AC} = 50\ V_{0\text{-}p}$. Column 1 shows the m/z 69 peak profile as a function of pseudopotential well overlap in zone 2,1. Column 2 shows the calculated well overlap versus m/z as a function of duty cycles settings. Column 3 catalogues the duty cycle settings of the tandem mass filters, transmitted ion intensity, measured and theoretical FWHM resolving powers, and well depth. As expected, the signal intensity decreases as the resolution (Δm) decreases. The limitation of the resolving power ($m/\Delta m_{1/2}$) that can be achieved is defined by the tandem well depth. To verify this claim, a plot of the signal intensity versus well depth is shown in Figure 7. There is a straight-line relationship between them until the well reaches approximately 1.5 V as can be seen from the trendline. After 1.5 V the signal intensity levels out at which point charge saturation of the mass filter occurs beyond 3 V.

We take the straight-line correlation of the well depth and the signal intensity to mean that our original claim that transition of the ions between the mass filters is not causing significant excitation because the signal does not precipitously drop as the wells move farther apart.[8] The plot also suggests that the well depth at the signal threshold is approximately 0.3 V. It is important to keep in mind that well depth is directly proportional to the operation AC voltage. Consequently, increasing the signal near the threshold should only be a matter of increasing the AC voltage. To test this concept, we have calculated the tandem well at 100 $V_{0\text{-}p}$ with a duty cycle combination of 75.27/24.73 and 74.73/25.27 in Figure 8 (a). At 100 $V_{0\text{-}p}$, the tandem well

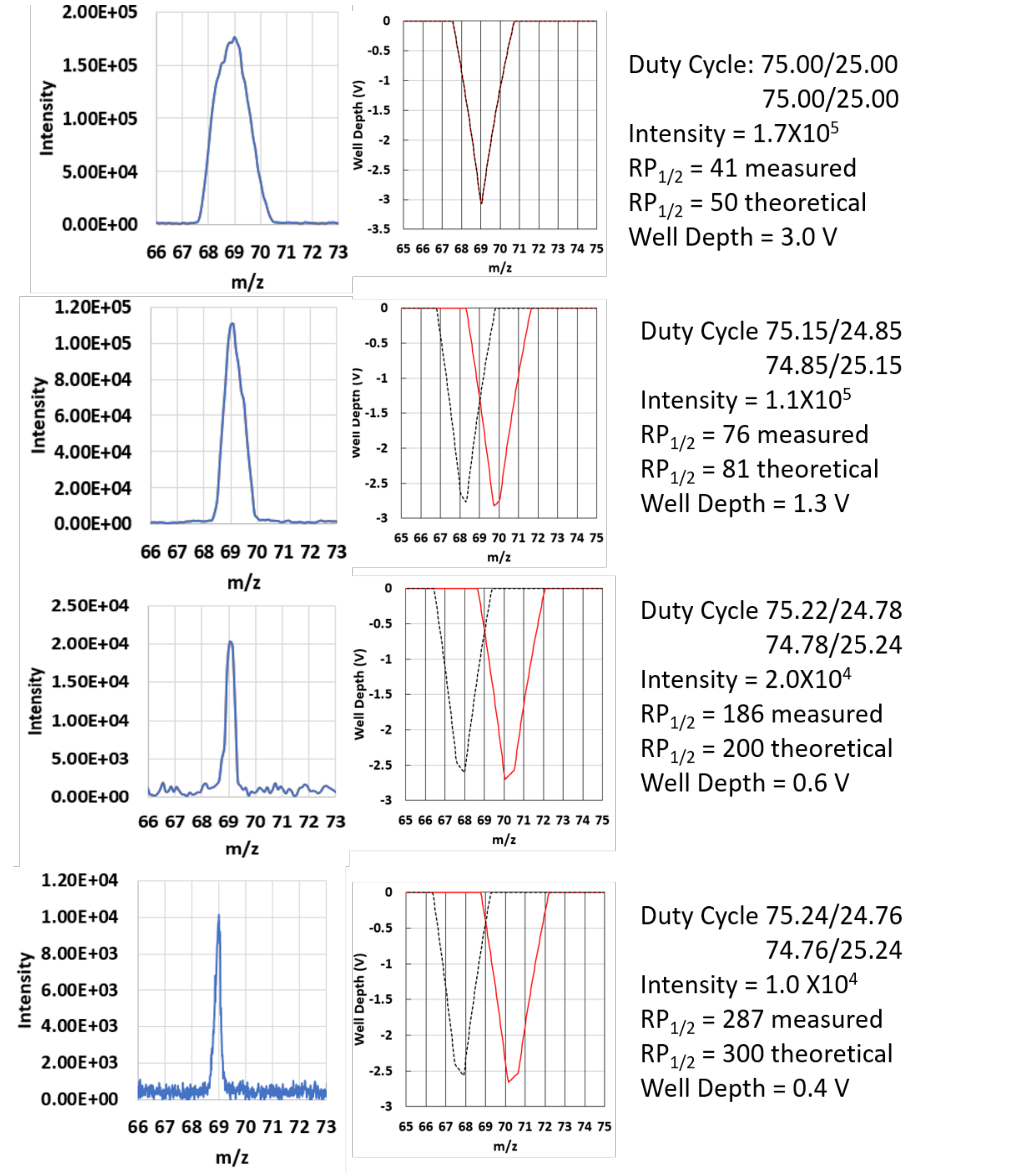

Figure 6: (column 1) m/z 69 peak of PFTBA generated by EI as a function of pseudopotential well overlap at 50 V_{AC}. (column 2) Well depth versus m/z overlap of the tandem wells. (column 3) Duty cycle settings of the tandem quadrupoles, signal intensity maxima, measured and theoretical resolving power at FWHM and tandem well depth.

depth is roughly 0.3 V and has a theoretical $RP_{1/2}$ = 825 while the individual wells are approximately 5 V deep. We also measured the m/z 264 peak of PFTBA near the signal threshold in Figure 8 (b) with a measured $RP_{1/2}$ = 850. Note that the well depth versus m/z plot in (a) maps the peak profile in (b) closely. Furthermore, at 50 $V_{0\text{-}p}$, this duty cycle combination would still yield the same tandem well based resolving power, but the well depth would be half at 0.15 V and the signal would not penetrate the baseline noise.

Given that the operational well depth of a sine mass filter at unit resolution is approximately 0.2 V where very good transmission occurs, why is the well depth at signal threshold approximately 0.3 V for the tandem mass filter? The theory suggests that the acceptance is defined by the 1st mass filter in the series. That mass filter has RP_{BL} = 22 and a well depth of roughly 5 V. If the theory is correct, then acceptance does not really change when the mass wells are displaced and so it is not an issue. That means that the transmission through the tandem mass filter is completely defined by the overlap of the mass wells (i.e., the tandem well). Increasing the ion flux into the 1st quadrupole does not change the transmission intensity. The only parameter that appears to affect that overlap is the waveform jitter by effectively reducing the mass window width and thereby reducing transmission. Recognize that jitter doubles for two mass filters operating in tandem. It is our belief that jitter will eventually limit the achievable resolving power at any operational voltage. The evidence to date from our lab and engineering experts consulted all suggest that the waveform jitter is a problem that is addressable and can be significantly reduced.

DTMF Evaluation Discussion:

Our work completely validates the concept of the digital tandem mass filter espoused in our recent paper on the theory of the DTMF.[8] DTMF acceptance appears to be defined by the

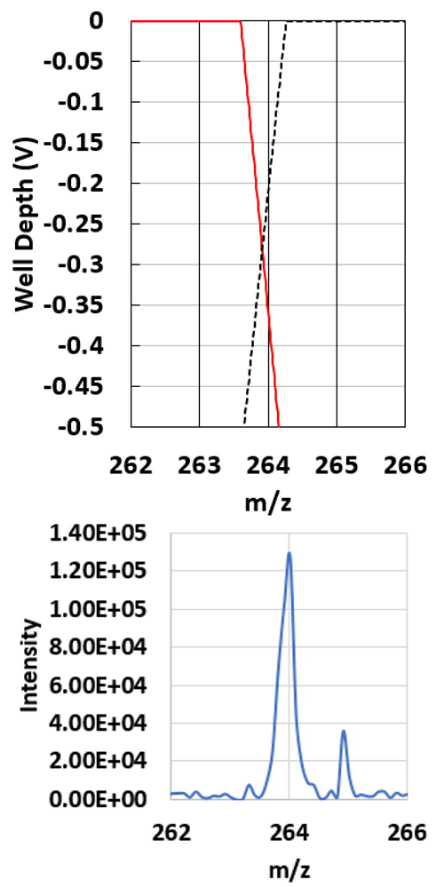

Figure 8: (a) Zone 2,1 tandem well depth vs. m/z and (b) the corresponding m/z 264 peak profile of PFTBA from a 75.27/24.73 and 74.73/25.27 duty cycle tandem combination.

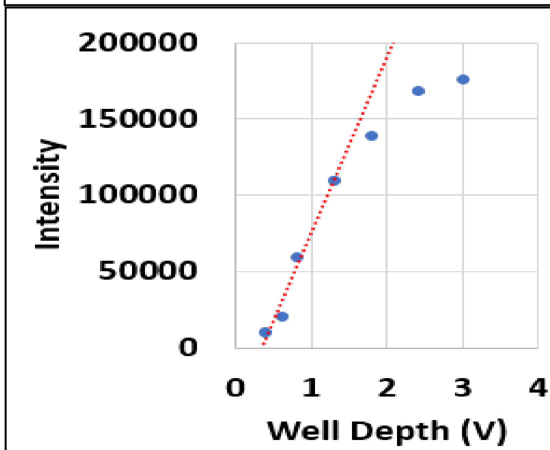

Figure 7: plot of intensity versus well depth.

acceptance of the 1st mass filter as suggested by and Du and Douglas.[3] Transmission through the DTMF seems to be completely defined by the pseudopotential tandem well depth. Greater well depth yields correspondingly greater transmission at least until charge saturation occurs (see Figure 7). Increasing the operational AC voltage correspondingly increases transmission and sensitivity and enables higher resolving power to be achieved. Unlike sine driven tandem mass filters, there is no need to phase shift the waveforms to improve transmission (as we previously suggested)[8] because the Mathieu parameter q does not change between the tandem quadrupoles. Only small duty cycle changes are required to shift the mass wells; these have no effect on q. Our results, so far, have been limited to zone 2,1 by waveform jitter. Zone 3,1, for example, did not yield tandem mass filter signal even though we are able to see strong signal with a single DMF, but we remain hopeful that jitter improvement will permit access to higher stability zones for the DTMF when much higher resolution is required.

DTMF Projections and Conclusions:

Assuming resolving power is not limited by jitter, if the operation voltage were increased to 500 $V_{0\text{-}p}$, a 0.2 V well would yield a tandem mass well resolving power limit of $RP_{1/2} = 5200$ at every value of m/z. Behlke (www.Behlke.com) makes push-pull pulser systems that can switch 5400 $V_{p\text{-}p}$ at up to 3 MHz and so the resolving power can be correspondingly further increased. It is our assertion that the DTMF can obtain resolving powers greater than $RP_{1/2} = 3k$ with good sensitivity just in zone 2,1 with the waveform generator that we currently have without improving its jitter specifications just by increasing the operation voltage. This will allow the user complete control of the resolution and sensitivity at every value of m/z well beyond the current mass range of any mass filter. Moreover, the performance of the DTMF will be correspondingly enhanced by any improvement in waveform jitter. Each factor of ten improvement of the waveform jitter will increase the achievable resolving power by an order of magnitude. Currently the waveform jitter is on the order of 1 ns. Theoretically, there is room for up to three orders of magnitude improvement in jitter (1ps) because the FPGA can operate with sub-picosecond jitter clocks. If significant jitter improvement by even a factor of ten can be obtained, then other higher stability zones such as zone 3,1 or 3,2 can be used to create the tandem wells and significantly higher resolving power can be obtained. Because the DTMF resolution and sensitivity are continuously adjustable, its use would be of great value for ion selection and preparation/activation for hybrid instruments such as the digital Q-TOF.

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