IN SEARCH OF THE PERFECT NOTCH: A NOVEL APPROACH TO THE OPTIMIZATION OF DIPOLE EXCITATION WAVEFORMS IN QUADRUPOLE MASS FILTERS

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OVERVIEW

PURPOSE: We investigate a novel method for excluding a target m/z range ('notch') in a quadrupole mass filter. Classical methods used in ion traps are also discussed.

METHOD: Optimisation of phases and amplitudes of a set of dipole excitations using a Markov Chain Monte Carlo algorithm.

RESULTS: High quality notch profiles can be created in simulated data. Many solutions can be found for a given notch profile and some of these are tested in a more realistic SIMION™ [1] model.

INTRODUCTION

In Tandem MS/MS experiments, transmission of a target m/z range using a quadrupole mass filter, followed by dissociation, can produce highly specific fragment information for a selected precursor. Only a single precursor may be transmitted at a given time. Therefore, if multiple co-eluting analytes are targeted, sensitivity will be reduced in proportion to the number of precursors that are sequentially transmitted.

Mass-to-charge ratio (*m/z*) dependent attenuation (notching), using dipole excitation, can be used to create more arbitrary transmission profiles. Modulation of transmission with time encodes precursors and fragments with the same time-dependence, allowing fragment information to be recovered simultaneously for multiple precursors[2]. We describe a method for designing waveforms to produce desired target transmission profiles, particularly those containing sharp edged notches.

METHODS

Quadrupole / Dipole Excitation Model

We begin with a simple 2D model of a perfect quadrupole of internal radius r_0 with applied RF of angular frequency Ω and amplitude V_{RF}. This produces an effective quadratic confining potential in which, in the absence of any excitation, an ion of mass *m* and charge *z* would oscillate radially with simple harmonic motion of angular frequency *k* where

$$k = \frac{\sqrt{2}\,V_{RF}}{\Omega\, r_0^2}\,\frac{z}{m}$$

with an amplitude A_0 and phase δ_0 that depends on its position r_i and velocity v_i on entering the quadrupole where

$$A_0 = \sqrt{r_i^2 + \frac{v_i^2}{k^2}} \qquad \delta_0 = \tan^{-1}\frac{k r_i}{v_i}$$

N sinusoidal dipole excitations with amplitude V_n, angular frequency ω_n and phase δ_n, $1 \le n \le N$, are superimposed on this potential, and the resultant radial equation of motion is

$$\frac{\mathrm{d}^2 r(t)}{\mathrm{d}t^2} = -k^2 r(t) + \sum_{n=1}^{N} A_n \sin(\omega_n t + \delta_n)$$

where

$$A_n = \frac{V_n}{r_0}\frac{z}{m}$$

This differential equation can be solved using a Green's function, and solution written in the form

$$r(t) = A_0 \sin(kt + \delta_0) + \sum_{n=1}^{N} A_n \left[\frac{1}{2k}\left(\frac{\sin(kt+\delta_n)}{\omega_n - k} + \frac{\sin(kt-\delta_n)}{\omega_n + k}\right) - \frac{\sin(\omega_n t + \delta_n))}{\omega_n^2 - k^2}\right] \quad (1)$$

A single dipole excitation of angular frequency ω causes resonant excitation (and ultimately ejection) of ions having angular frequencies k≈ω. At low *q*,

$$\frac{m}{z} \simeq \frac{\sqrt{2}\,V_{RF}}{\Omega\,\omega\, r_0^2}$$

Frequency Sweep or Quadratic Phase Dependence

Our objective is to eject ions lying in a continuous m/z range (equivalently a range of *ω*), so it is natural to consider sweeping a single dipole excitation through this range. This method is appropriate in trapped-ion mass spectrometry[3], in which every ion experiences all frequencies in the range. However, we must also take into account the finite length *L* of the quadrupole mass filter. With an ion energy *E*, time of flight through the quadrupole is

$$T = \sqrt{\frac{1}{2E}\frac{m}{z}}\,L \quad (2)$$

The portion, or number of cycles, of the waveform experienced by every ion will depend on the time that it enters the quadrupole and its individual time of flight *T*.

A natural alternative to consider is to attempt to utilise all frequencies simultaneously, replacing the sums over dipoles in the above expressions by integrals. **Figure 1** shows the type of waveform that results when dipoles with a continuous range of frequencies (100<*ω*<200) and the same phase are combined. Although all of the required frequencies are present, the information in the waveform is spread over a high dynamic range, making its use impractical.

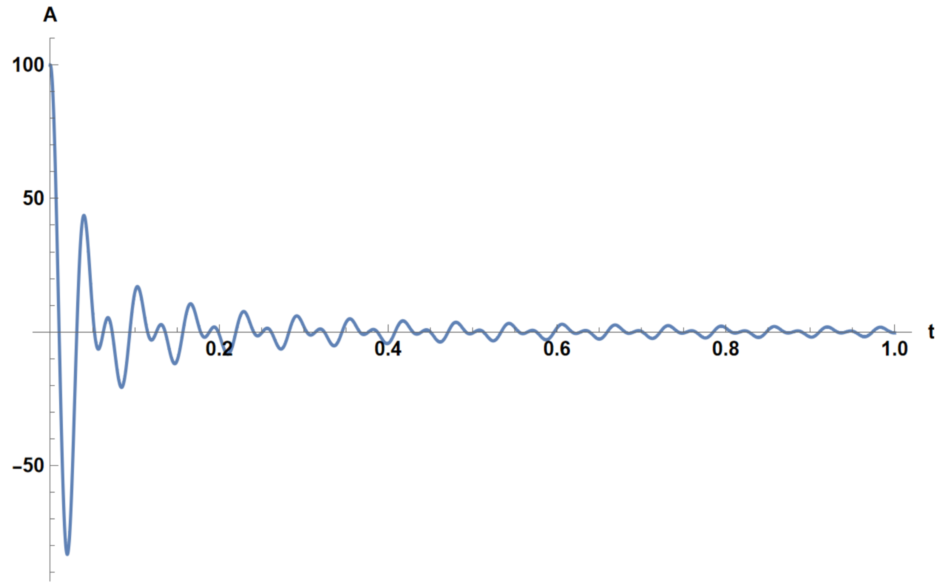

Figure 1. *Waveform resulting from integrating all dipole waveforms in the frequency range 100<ω<200 (arbitrary time units).*

This is a well-known problem that has been addressed in trapped-ion mass spectrometry by allowing the phase of the excitation to vary quadratically with frequency[4]. A typical resultant waveform is shown in **Figure 2**. Although the dynamic range is much improved, it is clear that the correlation between frequency and time has returned.

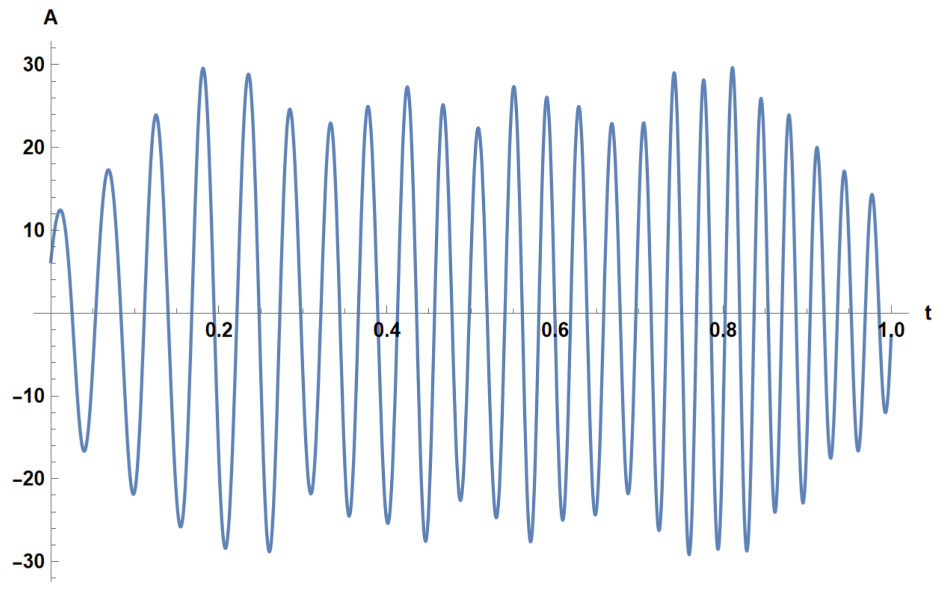

Figure 2. *The waveform resulting from integrating dipole contributions with a quadratic phase dependence δ(ω)=ω-ω²/200 over the angular frequency range 100<ω<200. Frequency increases steadily with time.*

In fact the emergent frequency dependence is linear. This can be understood qualitatively by considering **Figure 3** which shows the waveforms that contribute to the integral as a function of angular frequency and time. **Figure 2** was obtained by integrating this function over the range 100<*ω*<200. At any particular time, the integrand oscillates with frequency, except at the turning points of *ω t + δ(ω)* considered as a function of ω , where the integrand varies slowly. These turning points lie on the straight red line *t=ω/100-1*. The oscillating contributions away from this line tend to cancel, while contributions close to the line reinforce and dominate the integral. Linear frequency variation is therefore a natural consequence of quadratic phase functions.

Aside: This is somewhat similar to the argument used to explain how classical trajectories (at a stationary point of the action) emerge from Feynman path integrals in quantum mechanics[5].

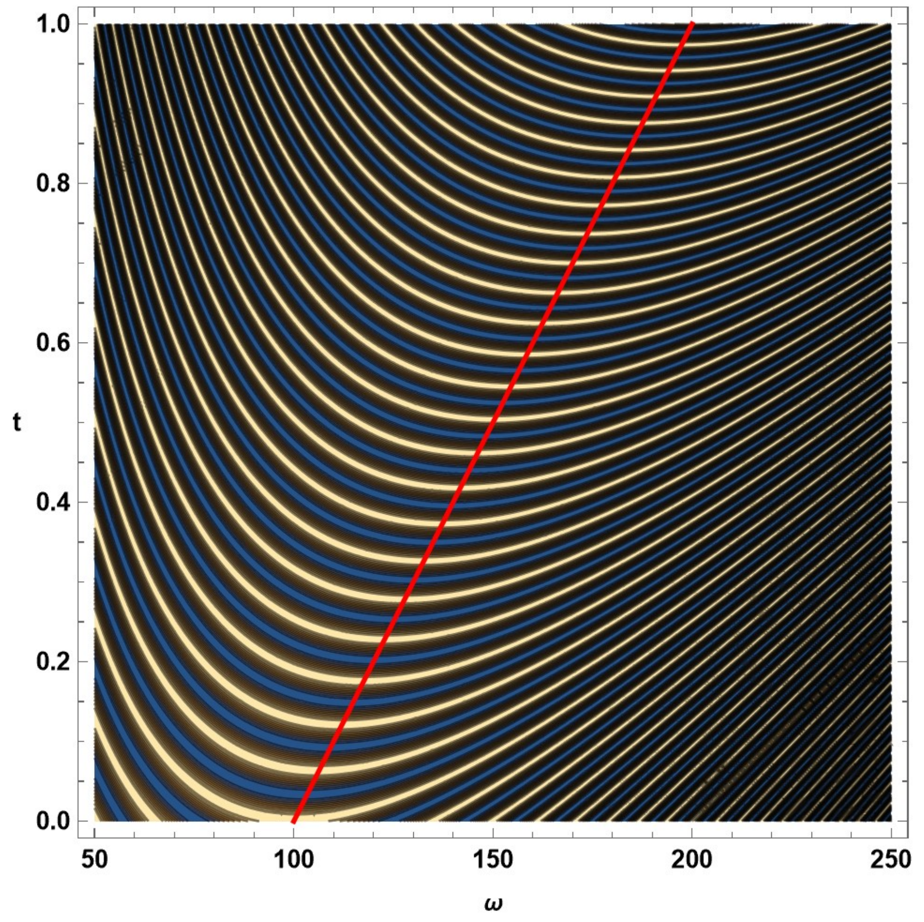

Figure 3. *A continuum of dipole waveforms of equal amplitude with a quadratic phase function sin(ωt+ω-ω²/200). The waveform in **Figure 2**. was obtained by integrating this function over the range of angular frequencies 100<ω<200.*

Numerical Notch Optimization

It is reasonable to consider alternative frequency sweeps or continuous phase functions. However the interplay between the applied waveform, radial ion motion and the m/z and phase dependence of the waveform experienced by ions during their limited time in the device is complex. It seems unlikely that a purely analytic approach will find an optimal & general notch design strategy for quadrupole mass filters. We decided instead to investigate whether the superposition of a finite number of dipole waveforms with individually chosen amplitudes and phases would be capable of producing the desired notch profiles.

A quadrupole simulation was written in C++ to track the motion of ions with specified initial radial positions and velocities. An ion is given a random start time and is then exposed to a repeating waveform produced by a set of dipoles having specified frequencies, amplitudes and phases. The resulting radial motion is given by **Eq. (1)** and the time spent in the quadrupole is given by **Eq. (2).** An ion is considered to be lost if its radial position exceeds r_0 at any point during its trajectory or exceeds a threshold r_f at the exit aperture. Note that, in practice, the ion trajectory is randomly sampled at a large number of points during the time of flight to determine whether the radius exceeds r_0.

For a given set of dipole parameters, a large number of ion trajectories are simulated with initial radial positions and velocities sampled from realistic thermal distributions. A histogram of transmission probability (*T*) versus m/z is created, and a Gaussian quality *Q* is assigned relative to a perfect notch model (*U*).

$$Q(T \mid U) = \exp \sum_i \frac{(T_i - U_i)^2}{2\sigma^2}$$

where U_i*=0* inside the notch *m/z* range and U_i*=1* otherwise and *σ* sets tolerance to deviations from ideal transmission.

The amplitudes and phases are then optimised using a Markov Chain Monte Carlo (MCMC) algorithm, using simulated annealing to help prevent the exploration becoming trapped during early iterations.

RESULTS

A simulated quadrupole with the following configuration was used:

- Quadrupole Length: 130mm
- RF amplitude V_{RF}: 300V
- RF frequency: 830kHz
- Internal radius r_0: 5.3mm
- *m/z* range 170-600Th
- Target notch *m/z* range: 200-400Th
- 16 frequencies with variable spacing proportional to the width of a single-frequency notch
- Parameter ranges: 0V<A_n<2V, 0< δ_n<2π
- *σ* = 0.005

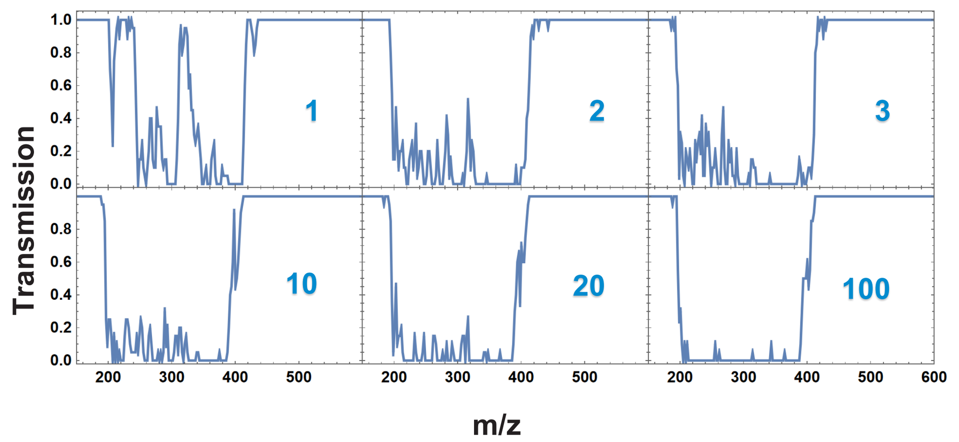

Figure 4. *Six iterations of the MCMC algorithm selected to illustrate its progress from initially randomly chosen dipole amplitudes and phases **(1)** towards a final set of parameters **(100)**.*

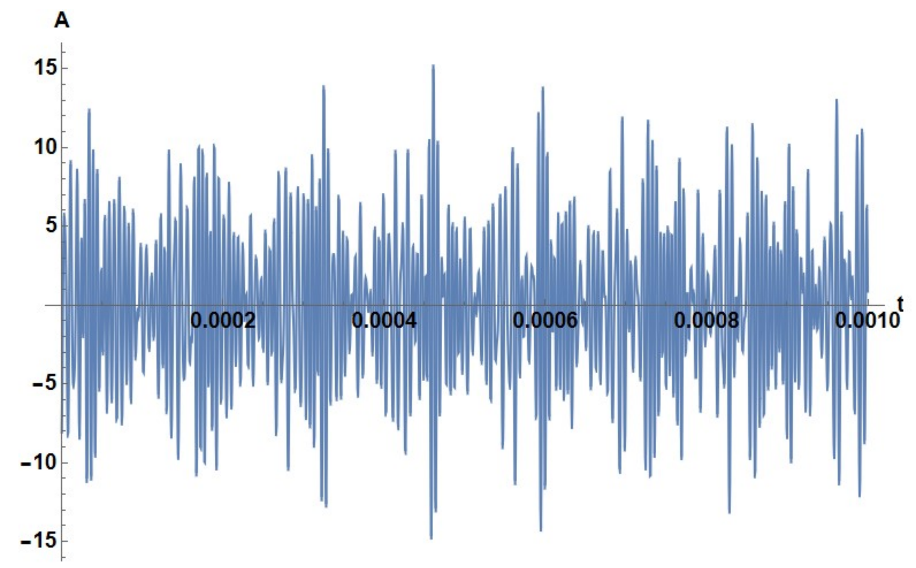

Figure 5. *The waveform (length 1ms) resulting from the optimised dipole parameters in the final iteration of the MCMC method.*

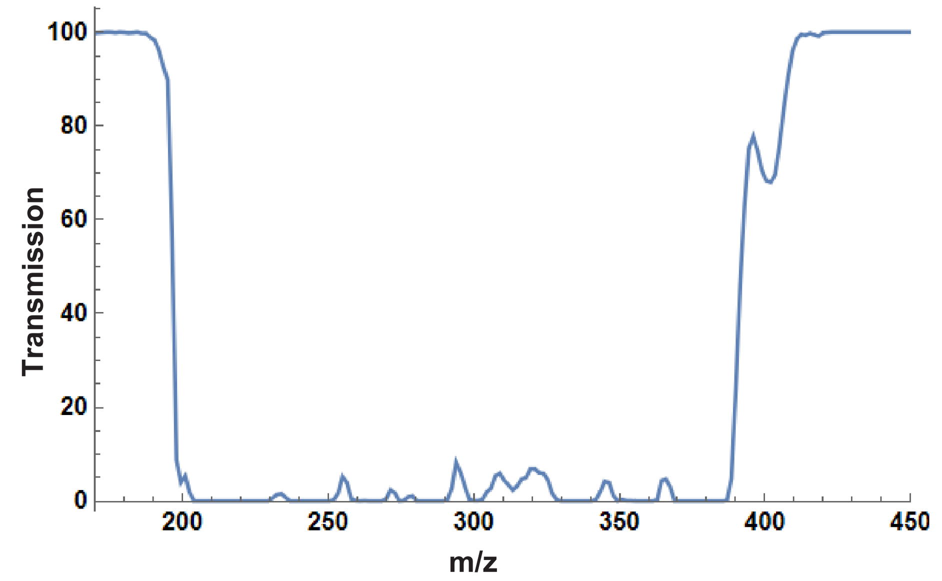

Figure 6. *The result obtained by utilising the final waveform shown in **Figure 5** in a SIMION™ simulation that reproduces more of the physics of a real quadrupole than the relatively simple simulation used during the optimisation.*

Figure 4 illustrates the progress of the algorithm from a randomly chosen starting point in the 34-dimensional parameter space of amplitudes and phases towards an optimized solution producing a high-quality notch profile. The resulting waveform is shown in **Figure 5** and the transmission profile obtained using this waveform in a more realistic SIMION™ simulation is shown in **Figure 6**.

DISCUSSION

MCMC exploration of the dipole amplitudes and phases produces notch profiles closely resembling the target profile, and significantly better than result obtained with randomly chosen values for the parameters. A SIMION™ simulation shows very similar results. More complicated target notch profiles, including multiple notches and regions with intermediate transmission can also be produced. For any problem of this type, many solutions of similar quality can be produced which could prove useful if their performance on a real instrument varies. Further work might involve systematically investigating limits in the sharpness of the edges than can be produced, and optimising other parameters such as the length of the repeating waveform record. The optimum length of the waveform might involve a balance between the need to reduce the frequency of discontinuities and avoiding destructive interference. Apodisation of the start and end of the waveform might also be beneficial. It might be possible to reduce the size of the parameter space by fixing phases and optimising amplitudes (or *vice-versa*).

CONCLUSION

- **A versatile optimisation tool has been written that can produce dipole excitation waveforms that yield a wide variety of target quadrupole transmission profiles.**
- **This has been demonstrated by optimising dipole parameters in a simulation of a quadrupole mass filter to produce a high-quality 200-400Th notch.**
- **SIMION™ simulations using the resulting waveforms, including more realistic physics, yield similar notch profiles.**

References

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