



This discussion paper is/has been under review for the journal Atmospheric Measurement Techniques (AMT). Please refer to the corresponding final paper in AMT if available.

Statistical precision of the intensities retrieved from constrained fitting of overlapping peaks in high-resolution mass spectra

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Received: 24 October 2014 – Accepted: 24 November 2014 – Published: 17 December 2014

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Published by Copernicus Publications on behalf of the European Geosciences Union.

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Abstract

Least-squares fitting of overlapping peaks is often needed to separately quantify ions in high-resolution mass spectrometer data. A statistical simulation approach is used to assess the statistical precision of the retrieved peak intensities. The sensitivity of the fitted peak intensities to statistical noise due to ion counting is probed for synthetic data systems consisting of two overlapping ion peaks whose positions are pre-defined and fixed in the fitting procedure. The fitted intensities are sensitive to imperfections in the m/Q calibration. These propagate as a limiting precision in the fitted intensities that may greatly exceed the precision arising from counting statistics. The precision on the fitted peak intensity falls into one of three regimes. In the “counting-limited regime” (regime I), above a peak separation $\chi \sim 2$ to 3 half widths at half-maximum (HWHM), the intensity precision is similar to that due to counting error for an isolated ion. For smaller χ and higher ion counts (~ 1000 and higher), the intensity precision rapidly degrades as the peak separation is reduced (“calibration-limited regime”, regime II). Alternatively for $\chi < 1.6$ but lower ion counts (e.g. 10–100) the intensity precision is dominated by the additional ion count noise from the overlapping ion, and is not affected by the imprecision in the m/Q calibration (“overlapping-limited regime,” regime III). The transition between the counting and m/Q calibration-limited regimes is shown to be weakly dependent on resolving power and data spacing and can thus be approximated by a simple parameterisation based only on peak intensity ratios and separation. An approximate graphical diagnostic can also be used to find potentially problematic ion pairs when evaluating results from fitted spectra containing many ions. Longer integration times can improve the precision in regimes I and III, but a given ion pair can only be moved out of regime II through increased spectrometer resolving power. Studies presenting data obtained from least-squares fitting procedures applied to mass spectral peaks should explicitly consider these limits on statistical precision.

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1 Introduction

Spectra acquired using techniques such as mass spectrometry (MS) can contain large amounts of information, but are inherently complex in nature and can represent a significant challenge for data analysis. The identification and separate quantification of overlapping peaks in measured spectra is often required in order to extract the maximum possible information content. Computational approaches to this deconvolution problem have been extensively reported in the literature, in both mass spectroscopy fields such as Liquid-Chromatography MS (LC-MS, see e.g. Jaitly et al., 2009; Yu and Peng, 2010), Matrix-Assisted Laser Desorption/Ionisation MS (MALDI-MS, see e.g. Sun et al., 2010; House et al., 2011), Proton-Transfer-Reaction MS (PTR-MS, see e.g. Tritzmänn et al., 2010), Electrospray-Ionisation MS (ESI-MS, see e.g. Horn et al., 2000; Strittmatter et al., 2003) and other techniques with similar analysis procedures such as chromatography (see e.g. Fraga et al., 2005; Krupcik et al., 2005) and gamma-ray spectroscopy (Hammed et al., 1993; Uher et al., 2010; Gardner et al., 2011). Assessing the precision in the fitting parameters resulting from such deconvolution procedures is important to demonstrate the reliability of the technique and understand the information content of the retrieved data (Hammed et al., 1993). However the quantification of this precision is not always discussed in the literature.

The primary goal of many mass spectrometry applications is the correct identification and quantification of ions present in the mass spectrum. Several studies probe the sensitivity of deconvolution algorithms to perturbations in the measurement parameters by applying them to synthetic data (Laeven and Smit, 1985; Blom, 1998; Lee and Marshall, 2000; Sun et al., 2010; Hilmer and Bothner, 2011; Müller et al., 2011). Some studies are also concerned with quantifying the overlapping ion signals, in fields such as proteomics (Link et al., 1999; Mirgorodskaya et al., 2000; Bantscheff et al., 2007, 2012) and atmospheric science (DeCarlo et al., 2006; Tritzmänn et al., 2010; Müller et al., 2011; Jokinen et al., 2012; Yatavelli et al., 2012). Quantification of such ion signals is difficult and may be confounded by unconstrained peak position parameters, or

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through the use of falsely-constrained peak centroids arising from an automated peak-finding algorithm. The peak intensity and position parameters and their precisions are clearly not independent. The quantification process is thus complex and assessing the precision of the retrieved intensities is difficult.

5 Correct identification of unknowns below the limit where two overlapping but non-coincident peaks no longer maintain an inflection point in the derivatives of the measurement profile is difficult. However, effects such as peak width broadening may point to the presence of unknown ions. For example, Meija and Caruso (2004) use peak width measurements from a calibration standard to compare with that of a spectrum
10 containing two overlapping peaks, showing that Gaussian deconvolution as well as shifts in the peak centroid position can be used to predict the ratio of the intensities of the ions. Blom (1998) considers the impact of a weak overlapping interference on two quantities describing peak shape, variance and skew. That study shows that deviations in the peak shape can point to the presence of an unknown interfering peak at separa-
15 tions well below those which would be required to separate it visually. However, Blom also concluded that an interfering peak with relative abundances of only a few percent could cause significant shifts (of a few ppm) in the centroid m/Q position, even though analysis of the peak shape would not point to the presence of the unknown peak in the spectrum.

20 Given the challenges encountered by such studies to correctly identify unknown peaks in the MS, it is unsurprising that the uncertainties arising during peak identification are often expressed simply by confidence metrics (such as mass accuracy/mass error, and relative ion abundance as compared to theoretical isotope patterns, e.g. Kilgour et al., 2012) rather than, as would generally be preferred, reporting the estimated
25 precision of the fitted intensities.

Similar confidence metrics are also reported for studies attempting to quantify the intensity of known overlapping peaks. Haimi et al. (2006) qualitatively split fits into reliable and unreliable categories by comparing peak ratios for successive measurements at different concentrations. Fits were considered reliable for a standard deviation (SD)

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in the peak ratio $< 25\%$ for eight successive measurements, an arbitrary but consistent metric. This is a useful guide when interpreting experimental results but does not address the intensity precision in a quantitative manner, limiting the scope of applicability. Müller et al. (2011) reported on a more systematic approach to quantify the expected attainable precision of the peak intensity for an example synthesised system subject to counting and estimated calibration errors. Their approach was however not extended from a single example to the general case. A generalised metric to describe the performance of such deconvolution procedures is desired.

This study aims to present a quantitative, systematic analysis of the statistical precisions arising during the deconvolution of overlapping peaks for the special case where the peak positions are known a priori and held fixed in the fitting procedure. This technique is widely employed by the atmospheric science community during analysis of data from field and also laboratory instrumentation (e.g. Farmer and Jimenez, 2010), for example the High-Resolution Time-of-Flight Aerosol Mass Spectrometer (HR-ToF-AMS, DeCarlo et al., 2006), the Proton-Transfer-Reaction Time-of-Flight Mass Spectrometer (Cappellin et al., 2009, 2011; Müller et al., 2011), the Atmospheric Pressure Interface Time-of-Flight Mass Spectrometer (APi-TOF, Junninen et al., 2010) and the High-Resolution Time-of-Flight Chemical-Ionisation Mass Spectrometer (HRTof-CIMS; Jokinen et al., 2012; Yatavelli et al., 2012). The ionisation techniques used in the instruments ionize and fragment the molecules in a very consistent manner. This leads to the presence of specific ions in a very reproducible manner, which is well documented for many systems of. Thus, one degree of freedom can often be removed from the ion fitting procedure, which is then based upon a comprehensive list of ions and their exact m/Q that define the fitted centroid values. Although analysis of the measurements from the above instrumentation motivated this study, the techniques and conclusions are directly applicable to other mass spectrometry or even optical photon-counting systems, as they are based on the spectra only and make no further assumptions about the instrumental details.

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Imprecision in such a constrained fitting procedure may arise from (i) noise in the measurement distribution, particularly from counting statistics of the ions of interest, (ii) the m/Q calibration, which is limited itself by statistical noise on the reference ions used to determine it, (iii) the discrete nature of the measurements, i.e. the spacing of the discrete measurement points; and (iv) the instrument transfer function (“peak shape”), errors in the determination of which propagate directly into retrieval of ion signals from the fits, but yet must still be empirically determined and thus will contain errors. The influence of this spacing on peak fitting results is discussed in detail in Hilmer and Bother (2010). In this work, the limitations of the fitting procedure are explored with respect to measurement noise and imperfections in the m/Q calibration, i.e. items (i)–(ii) above. Item (iii) is briefly discussed. Since the errors from (iv) are not included, our results represent a best-case scenario for the precision of the retrieved parameters.

Müller et al. (2011) conducted an error analysis on such a constrained hypothetical system using a peak model and specifications for a typical lower-resolution TOF spectrometer used (amongst other fields) in atmospheric science, and demonstrated that the precision in the fitted peak intensities is sensitive to the ratio of the peak intensities. The precision with which the less-intense peak intensity can be retrieved becomes extremely poor for peak separations less than the full-width at half-maximum. Müller et al. also concluded that a precise analysis could only be performed for well-separated peaks. We extend this analysis from a single example to the general case for a wide range of measured intensities, separations and resolving powers (peak widths). We investigate the relationship between peak separation and achievable peak intensity precision, and develop a parameterisation to quantify the latter.

2 Methods

A synthetic measurement distribution was constructed consisting of one or two Gaussian peaks of known width and centroid position. Unless stated otherwise, the synthetic peaks were generated for a fixed ion time-of-flight (iToF) resolving power $t/\Delta t = 2000$

and a sample interval that gives approximately 10 discrete measurement points within 2 full-widths at half-maximum (FWHM) of the peak centre. This could be obtained for example with 0.2 ns data acquisition point spacing at 2000 ns (as in this study), or 1 ns spacing at 10 000 ns. These metrics were chosen to correspond to realistic hardware specifications for current mass spectrometer and data-acquisition systems. Figure S1a shows an example of a peak using these specifications with a centroid flight time of 2000 ns and hence peak width 1 ns. It is chosen to state the peak parameters in i ToF space, in which the peak-fitting should be conducted, for the conversion to m/Q space is non-linear and the peak shapes are thus slightly non-Gaussian. Translation to the normally-specified spectrometer mass resolving power in m/Q space is given simply by $m/\Delta m = t/2\Delta t$, and thus the mass resolving power in our default case is 4000. From here on we refer to the mass resolving power unless otherwise stated.

To address counting-error (item (i) above), the synthetic measurement distribution was degraded, point-by-point, with Poisson-distributed error of magnitude \sqrt{N} (where N is the number of ions counted during the spectrum acquisition). In time-of-flight mass spectrometry, i ToF is converted to m/Q space by fitting a function, usually proportional to the square root of i ToF, which is determined by fitting isolated ions of known m/Q . To simulate the propagation of uncertainty of this calibration into the fitting procedure (item (ii) above), the constrained centroid values in the fits were also additionally perturbed during each fit by a randomly-assigned value from a Gaussian distribution of appropriate SD, as discussed below. This perturbation was applied consistently to both fitted peaks for a given fit (i.e. the calibration parameters remain equal for all peaks), but varied from one fit iteration to the next.

The peak shape model (item (iv)) was removed as a degree of freedom by utilising Gaussian shapes to represent the instrumental peak shape; the influence of the peak shape on fitted parameters is difficult to assess (Yu and Peng, 2010, and references therein) and is thus not considered here, although its relative impact should be the focus of future studies. The separation of the discrete data points (item (iii)) is held fixed unless otherwise noted. Further sources of uncertainty in the measurement distribution

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such as electronic baseline noise are not considered, as for modern data acquisition systems they are typically small compared to ion counting noise.

After application of the Poisson-distributed noise and of the m/Q calibration errors, least-squares Gaussian peak fits were applied to the measurement distribution, where only the peak intensity parameters were determined. This procedure was repeated for 10 000 randomly-generated cases, resulting in a histogram of the fitted peak intensities. The width of the histogram, reported as the SD of a Gaussian curve fitted to the histogram distribution, thus expresses the precision with which the peak intensities can be fit.

For the case of a system with two overlapping peaks, we define a normalised separation parameter $\chi = dt/HWHM$, dt is the separation of the known peak positions in $iToF$ space and $HWHM$ is the half-width-half-maximum of the peak (i.e. $\chi = 2$ is the case where the peaks are separated by one $FWHM$).

3 Results and discussion

3.1 Precision of retrieved signal intensities due to ion counting error for an isolated ion with perfect m/Q calibration

Precision theory offers a calculable method to describe the best precision with which the peak intensity of an isolated ion can be retrieved from a discrete spectrum with Poisson-distributed noise (Lee and Marshall, 2000). Lee and Marshall ran simulations of least-squares fits to Gaussian peak shapes and were able to demonstrate the application of precision theory to mass spectra, giving the relationships for the SDs in fitted

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peak amplitude, σ_A , and centroid iToF position, σ_t :

$$\sigma_A = c_A \sqrt{\frac{A\delta_t}{W}} \quad (1)$$

$$\sigma_t = c_t \sqrt{\frac{W\delta_t}{A}} \quad (2)$$

where A is the peak amplitude in counts, W the FWHM of the peak, δ_t the separation of the discrete data points in iToF space and c_A and c_t are constants. It is noted that δ_t is not varied in our study. This result is used as the starting point for the analyses in this work and a simulation of this simple system is demonstrated in Fig. 1. Histograms are shown for the distribution of the normalised deviation in the retrieved intensity, $\Delta = (I_{\text{fitted}} - I_{\text{true}})/I_{\text{true}}$, over 10 000 fits of an isolated ion for logarithmic steps in the peak intensity I_{true} . The peak position and shape are known a priori and the observed width of the histogram, σ_N , thus represents the precision in Δ arising purely from counting-error on an isolated ion. σ_N is inversely proportional to the square root of the number of ions detected ($1/\sqrt{N}$), as predicted by the Lee and Marshall equation and shown in the inset. The precision arising from counting error, σ_N , is unavoidable (i.e. $\sigma_l \geq \sigma_N$, where σ_l is the width owing to all sources of error). Figure 1 thus represents the best-case scenario for the system, in the absence of other contributing sources of uncertainty. For the example system of $I_{\text{true}} = 1000$ counts, centroid iToF $t_0 = 2000$ ns, $\delta_t = 0.2$ ns and $W = 1$ ns (i.e. resolving power of 4000, as shown in Fig. S1), the precision on the retrieved intensity owing purely to Poisson-distributed counting error is thus $\sigma_N = 3.2\%$. Regardless of data point spacing or resolving power, this value of σ_N remains fixed for this peak intensity, since the dependencies of A , W and δ_t upon one another cancel out. For example, doubling data-acquisition rate halves the peak amplitude for the same total number of ions (ignoring non-linear effects from the detector which are outside the scope of this paper). Thus σ_N is in this case given simply by $\sqrt{1000}/1000 = 3.2\%$, matching the value resulting from the simulations.

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3.2 Precision of retrieved signal intensities for two overlapping ions with perfect m/Q calibration

Repeating the process for a system with two overlapping but non-coincident Gaussian peaks leads to histograms that must be at least as broad as those shown in Fig. 1. Although the centroid positions of the two Gaussians are still fixed during both generation of the synthetic distribution and the fitting procedure, the combined Poisson-distributed uncertainties from the two peaks and the mix of information in the area of peak overlap leads to increased imprecision in the retrieved peak intensities. Figure 2 demonstrates this tendency for a pair of equally-intense peaks with various different peak separations (χ , in units of HWHM). As χ increases, the predicted histogram width, σ_C , tends towards the limiting uncertainty for an isolated ion σ_N , as reported by Müller et al. (2011) for a similarly-posed set of simulations. For ions of equal intensity, for $\chi < 1.6$ the presence of the neighbouring peak results in an appreciable increase of the normalised deviation in fitted peak intensity, consistent with the results of Müller et al.

A further example where one peak is 1/10th as intense as the other is shown in Fig. S2. In this case the results are starkly different for the parent (more intense) vs. child (less intense) ions. σ_C of the parent ion is reduced (more precise) relative to the equal-intensity case, as the influence of the less-intense neighbouring ion is weaker, and the influence of the neighbouring peak is only appreciable for $\chi < 1.2$. In contrast, σ_C of the child ion tends to a value of σ_N that is $\sqrt{10}$ higher than the equal-intensity case, and is appreciably higher than this limit as soon as $\chi < 1.6$.

These results are generally observed for other examples: the precision due to ion counting on an isolated ion σ_N for a given system will vary as per Eq. (1), but the total precision owing to counting-error, σ_C , can be much larger than σ_N when the peak separation χ is of the order of 1, with higher separation needed for the child and less separation needed for the parent.

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3.3 Estimation of the precision of the m/Q calibration

For the constrained fitting procedures investigated in this study, which constrain a priori the positions of the fitted ions, correct determination of the m/Q calibration is a prerequisite for retrieval of the ion intensities, for the m/Q must be translated to the constrained iToF values to be used in the fits. The determination of the m/Q calibration is, however, inherently subject to imprecision due to statistical effects, i.e. the fitting of the peak position of each ion (which is then used as the input of the m/Q calibration) will be subject to imprecision arising from statistical effects, as per precision theory. We will estimate this imprecision in this section. Additional sources of error can be present but are not considered here. These include possible contributions from surrounding ions to the shape of the calibration ions, and incomplete knowledge of the peak shape. Additionally, the m/Q calibration curve is likely to have worse precision in regions of m/Q space distant from the calibration ions.

The following procedure was used to obtain a quantitative estimate of the imprecision introduced on the m/Q calibration by ion counting error. We simulated the calibration procedure using synthetic data consisting of four Gaussian peaks at equally-spaced iToF values (4, 8, 12 and 16 μ s) translating to a set of corresponding known m/Q values using a pre-defined representative set of calibration constants. The width of each peak was defined by the use of a constant resolving power 4000, i.e. with the actual width in iToF space increasing linearly with iToF. The centroid position of the four calibrant peaks was then varied randomly according to the expected SD in the peak fitting procedure according to Eq. (2). As noted by Lee and Marshall (2000), this defines the theoretical upper limit to which the centroid position of the calibrant peaks in iToF space can be defined, since other possible sources of error are not accounted for. The imperfections in the fitted positions of the calibrant peaks propagate into the m/Q calibration equation (a square-root relationship between iToF and m/Q). In our numerical experiment the perturbed m/Q calibration was used to calculate the corresponding deviation in iToF for a set of 10 iToF positions across the calibrated

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range, from 2 to 20 μs in 2 μs steps. It is noted that the peaks used to assess the calibration are thus not always identical to those used to define it. This was done to reflect real MS analysis, where peak fits are more often than not applied to MS regions away from the calibration points. This procedure was repeated 10 000 times to build up a set of histograms of the deviation between the known and calculated *i*ToF values; and again repeated for resolving powers of 2000, 8000 and 16 000 using a constant acquisition time interval. As a longer flight path is generally required to achieve greater resolving power, the flight times of the calibrant and test peaks were also adjusted to be correspondingly shorter or longer (ie., for resolving power 2000, using calibrants at 2, 4, 6 and 8 μs).

As a result of the imprecision in the calibrant ion fits, for each iteration of the calibration procedure, each of the calibrated peak positions is subject to an error, the magnitude of which depends on the goodness of the fits to the calibrant peaks and the relative positions in *m/Q* space of the calibrants and the test peaks. Iterating the calibration procedure many times thus builds up a distribution of this error for each calibrant peak, whose SD we take as the precision in the calibrated peak position. The mean normalised precision in the peak position for all the test peaks is then taken for the best estimate of the calibration precision as a whole (i.e, quantitative description of the imprecision in the calibration over all *m/Q*). The resulting relationships are demonstrated in Fig. 3, which shows this estimate of calibration precision for four different resolving powers and for calibrant peaks of equally-intense I_{true} from 10 to 10^7 counts, as given on the *x* axis.

The limiting calibration precision, where all peaks exhibit identical signal-to-noise, can be less than 0.1 ppm for high signal-to-noise situations. This unrealistic scenario exceeds the performance attainable using current mass spectrometry systems of similar resolving power, indicating that other sources of error than purely counting statistics may play a significant role in determining calibration precision. Lee and Marshall (2000) note that the relative error in *m/Q* calibration could potentially improve by up to an order of magnitude when such sources could be eliminated. The simulations where one of

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the calibrant peaks suffers from poorer counting statistics (only 20 counts) also exhibit much greater calibration imprecision. Although an exhaustive investigation would be outside of the scope of this study, Fig. 3 thus highlights an important feature when using 4 ions for m/Q calibration as is often typical of actual applications. If only one calibrant peak suffers from poor ion counting statistics, then even if all the others exhibit strong signal-to-noise ratios, the m/Q calibration precision will be substantially degraded, by factors of 1 or 2 orders of magnitude. It is therefore important when determining the m/Q calibration using some lower intensity ions to integrate measurements for as long as possible, as long as the calibration does not drift over the averaging periods due to temperature variations or other effects.

In Sect. 3.4 we incorporate the impact of the limited precision of the m/Q calibration in the overlapping peak-fitting simulations discussed in Sect. 3.2. A quantitative estimate of the precision of the m/Q calibration is required. Assuming a typical case in which all calibration ions have at least 1000 counts while one ion has 20 counts, in Fig. 3, precisions of 9, 5, 3 and 1.8 ppm for the m/Q calibration were used for resolving powers of 2000, 4000, 8000 and 16 000 respectively. Whilst larger than the limiting precisions for calibration mass spectra with high count rates, these are actually of the same order or better than values reported for real instruments of these resolving powers, both in atmospheric science (DeCarlo et al., 2006; Junninen et al., 2010; Jokinen et al., 2012) and other fields (e.g. Strittmacher et al., 2003).

3.4 Precision of retrieved signal intensities in an overlapping two-ion system with realistic m/Q calibration error

We now estimate the achievable precision for the peak intensities resulting from the constrained fitting procedure. We combine the precisions from counting- and calibration-errors in an overlapping two-ion system, as summarised in Fig. 4. These simulations use synthetic data consisting of two overlapping peaks as was demonstrated in Fig. 2 for peaks of equal intensity. However, in Fig. 4 the peak intensities are different, with a dominant “parent” peak of intensity I_p and a smaller “child” peak of

intensity I_c , with $R_I = I_p/I_c = 2$. The precisions in the normalised deviation in retrieved peak intensity of the parent and child peaks, σ_p and σ_c , respectively, are shown. The values of σ_N (the counting-error limit) for an isolated ion are also shown for comparison.

Three regimes are apparent in this plot:

1. For large χ (well-separated peaks), the precision in the normalised deviation in retrieved peak intensity, σ_I , for both peaks is limited by counting-error and tends to the σ_N values for isolated ions. I.e. as the ion separation increases both ions are retrieved with similar precision as individual isolated ions. This region we term the “counting-error regime”. Note that for well-separated peak the imprecision in the m/Q calibration at the realistic levels used here does not result in an appreciable increase in the precision.
2. For smaller values of χ ($\lesssim 3$, overlapping peaks) and higher signal levels, σ_I is observed to increase rapidly above the counting-error limit σ_N . This region we term the “ m/Q calibration-limited regime”.
3. For the special case of low signal-to-noise and small χ ($\lesssim 2$, strongly overlapping peaks), the overlapping nature of the peak distribution increases σ_I above σ_N in a manner which is dominated by the overlapping peak effect (as in Sect. 3.2) and not affected by the m/Q calibration error. As discussed above, the effect is stronger for the weaker child peak than it is for the stronger parent peak. This region we term the “overlapping counting-error regime”, and $\sigma_I \sim \sigma_C$.

In summary, for low signal-to-noise ion pairs (in our particular examples for peak intensities of order 100 counts), the influence of the m/Q calibration imprecision on σ_I is negligible, and the counting and overlapping effects discussed in Sects. 3.1 and 3.2 dominate. Indeed, in the absence of m/Q calibration imprecision, σ_C (σ arising only from counting-error) for a given separation χ increases for both ions simply as the square-root of the respective peak’s intensity. The same relationship is, as expected, also true for σ_I in the counting-error dominated regime. However, the introduction of

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m/Q calibration imprecision in the simulations leads to a higher σ_I for small values of χ that sometimes greatly exceeds (e.g. > 10–100 times larger) the precision introduced by counting-error for overlapping ions alone.

3.5 Parameterisation of the intensity precision for overlapping ions with m/Q calibration error

Since our simulations are complex and time consuming, a parameterisation of the value of χ at which σ_I is observed to diverge from the counting-error limit of an isolated peak, χ_d , due to the presence of a neighbouring peak and m/Q calibration uncertainty, is desirable in assessing fitting precision. Such a parameterisation could be used to evaluate results while performing peak fits for real data.

First we consider the parameters from which χ_d is independent, noting that the data-point spacing in this study is fixed. Firstly, the imprecision in the m/Q calibration only weakly influences χ_d (Fig. S3). Thus, whilst the m/Q calibration precisions applied in the fits in this study are only estimates and may be lower than the real values, quantification of χ_d is not too sensitive to them. Secondly, χ_d is also independent of the spectrometer resolving power (under constant δ_t as assumed here), as the separation parameter χ is normalised to the peak width (Fig. S4).

However, from Fig. 4, it is clear that χ_d is dependent on the intensity of the ions I_p and I_c , as the lower limit in intensity precision imposed by the imprecision in the m/Q calibration, σ_B , becomes gradually more dominant as the precision due to counting statistics improves.

Further sets of simulations showed the consistency of χ_d over a wide range of intensities (Fig. S5). Changing the discrete data acquisition time interval (for constant peak amplitude and resolving power) also has no influence on χ_d , as this simply changes the counting limit σ_N according to Eq. (1) (Fig. S6). The same lack of effect on χ_d for fits at different iToF positions. Furthermore, σ_B is also only weakly sensitive to a doubling or halving of the resolving power whilst keeping the data sampling rate constant (Fig. S7).

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We thus propose that χ_d in the resolving power range considered in this study ($< 16\,000$) can be empirically parameterised by fitting a polynomial in $\log\sigma$ -space to the m/Q calibration-limited regime section of the results for high signal-to-noise (Fig. S8). In this region $\sigma_l \sim \sigma_B$. χ_d is then simply the point at which this line intersects the value of σ_N appropriate for the values of I_p , R_l , W and δ_t . With this information, the required χ to achieve a certain value of σ_l can be approximated and described for the smaller peak as a function of R_l , as shown in Fig. 5 for $I_p = 10^5$ counts. This shows that for two peaks separated by their FWHM ($\chi = 2$), R_l may be as large as 100 and the measurement of the intensity of the small ion still has a precision of $\sigma_C = 25\%$. However, only R_l of up to 25 may be tolerated if a precision of less than 5% is needed. In addition, precisions of 5% can never be reached for $R_l > 250$ (and $I_p = 10^5$ counts as in this example) for the counting-error limit is reached and σ_C described simply by Eq. (1).

This parameterisation, whilst predominantly generally-applicable for the resolving power range considered in this study, does break down in the overlapping counting-error regime (low signal-to-noise and small peak separation). This is apparent studying Fig. 4, which demonstrates that a maximum underestimate (at very low χ) in σ_l of 2 and 5 would be expected for $I_p = 10$ and 100 counts respectively. The parameterisation described here thus describes the best-case scenario and should be regarded as an estimate of the lower-limit of σ_l expected for a given system.

As a guide for the practical application of this parameterisation to a given overlapping peak distribution, we note that the 5 and 25% error lines in Fig. 5 can be roughly approximated by normalised Gaussian peak shape distributions. These are plotted inversely against the peak intensity ratio (i.e. at an x axis value of $\chi = 1$, the intensity is the inverse of that of a normalised Gaussian 1.0 half-widths from the peak centre, i.e. $1/0.5 = 2.0$). The inverse Gaussian curve roughly follows the $\sigma_l = 5\%$ line, and the inverse of a Gaussian with peak height 0.1 roughly follows the $\sigma_l = 25\%$ line. We thus propose that, in the absence of numerical error estimation, the magnitude of the precision on the fitted intensity of a child peak in an overlapping two-ion system can be estimated by representing it in the space shown in Fig. 5 and comparing it to the

inverse Gaussian peak shape. Whilst not providing a truly quantitative description of the error, this technique could be easily applied and would at least be able to estimate whether it is appropriate to utilise the fitted intensity of a child peak to draw conclusions from the data.

5 An example of this approach is given in Fig. 6, where the lines of Fig. 5 are plotted together with markers representing the peak separation and intensity ratios for the less-intense (child) peak of all pairs of peaks in a fixed- m/Q list applied in the analysis of real experimental data for the CalNex dataset (Hayes et al., 2013). The peak separation values can be calculated directly from the list; the intensity ratios are however calculated from the fit results for a representative average spectrum taken from the campaign dataset and are therefore subject to the same sources of imprecision discussed in this study. The influence of additional overlapping peaks is also ignored. Nonetheless, representation of the fitted peak pairs in this space provides a useful overview of the reliability of the fitted intensities. The precision in fitted peak intensity from counting statistics alone is represented by colouring the data-points similarly to the predicted lines of precision when accounting for both counting statistics and m/Q calibration error. The estimated precision is thus the larger of the two. In this example, the peaks fitted mostly exhibit good separation and counting-error is the limiting factor. It is noted that the region for $\chi < 0.4$ was not explicitly studied as part of this work, and the lines of estimated precision would have no meaning as χ approached zero. This region is thus not shown on the plot. The Gaussian peak shape can again be used to approximate the 5% precision line, while Gaussian shapes shifted by factors of 8 and 30 approximately delimit regions of precisions of 25 and 100%, respectively. It is noted that the real empirically-determined peak shape is slightly non-Gaussian, especially for larger values of χ . The influence of non-Gaussian peak shapes, in particular for features such as the “tail” seen in Fig. 6 to the left of peak centre, would be a useful extension to the work presented here.

25 The results shown in Fig. 5 for $I_p = 10^5$ counts are generalised for a range of peak intensities and $R_l = 8$ by representing σ_l in an image plot as shown in Fig. 7 (top).

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The parameterisation for the transition between the two regimes at $\chi = \chi_d$ is shown superimposed as the black line over the image. For $\chi < \chi_d$, the areas of similar σ_I appear predominantly as vertically-orientated rectangles. This shows how integrating to higher ion counts does not change σ_I in the calibration-limited regime. The only case for $\chi < \chi_d$ where integrating improves σ_I is for the overlapping counting-error regime (small signal-to-noise and small χ), seen by the small change in σ_I just above and left of the $\chi = \chi_d$ line for $\chi \lesssim 1$. In contrast, for $\chi > \chi_d$, the areas of similar σ_I appear as horizontally-orientated rectangles. This is the counting-error regime and integrating to higher ion counts will improve σ_I . So long as $\chi > \chi_d$, peak separation is unimportant for determination of σ_I for both the parent and child peaks.

The same results are shown in Fig. 7 (bottom) when normalising σ_I against the counting-error precision limit σ_N . This highlights again how the parametrisation of χ_d is successfully able to split the calibration-limited and counting-error regimes, showing how for $\chi > \chi_d$, the entire space is a single colour shade corresponding to $\sigma_I/\sigma_N \sim 1$. Figures S9 and S10 give two further examples for $R_I = 2$ and $R_I = 32$, respectively. The principle of separation into two regimes is clear, but the position of χ_d shifts according to the intensity ratio R_I . In all cases, the vertically-orientated rectangles for $\chi < \chi_d$ show how increasing ion counts does not help reduce imprecision on fitted intensities for ions in the calibration-limited regime, other than for very low signal-to-noise. The optimal experimental setup for a given ion pair is where $\chi = \chi_d$, for then intensity imprecision due to m/Q calibration is negligible but the number of points measured across the peak, is maximised.

To demonstrate the application of the parameterisation to a problem relevant to the atmospheric-science community that provided motivation for this study, we take three commonly observed ions in HR-ToF-AMS spectra as an example; $\text{C}_2\text{H}_3\text{O}^+$ ($m/Q = 43.015$ Th), C_3H_7^+ (43.054) and $\text{C}_2\text{H}_5\text{N}^+$ (43.043). Müller et al. (2011) concluded that $\text{C}_2\text{H}_3\text{O}^+$ and $\text{C}_2\text{H}_5\text{N}^+$ were distinguishable applying fits to a spectrum with mass resolving power 1000 (i.e. $\chi = 1.3$); from our parameterisation, a constrained fit to these peak positions would retrieve the peak intensity to within a precision of 5%

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only for $R_l < 6$ (assuming sufficient counting statistics), even though the presence of both the peaks may be evident in the spectrum for higher R_l (the overlapping peaks for this scenario are exemplified in Fig. S11). For the closely-separated C_3H_7^+ and $\text{C}_2\text{H}_5\text{N}^+$ ions, Farmer et al. (2010) concluded that a mass resolving power of 5000 would be desirable; this would result in $\chi = 2.5$ and thus a 25 % precision on I_c for R_l as high as 400. Up to 1 % precision would be achievable for $R_l \sim 15$ (the overlapping peaks for this scenario are exemplified in Fig. S12). With half this resolving power the same precision can only be expected for R_l less than ~ 20 .

4 Conclusions

A simple statistical simulation-based approach has been used to demonstrate the precision to which the intensities for a pair of overlapping mass spectral peaks can be ascertained using least-squares multi-peak fitting. Synthetic measurement distributions containing imprecisions from counting statistics and m/Q calibration were used in a fitting process where peak centres and widths were constrained. Three principal regimes appear: (1) the counting-limited regime: for well-separated and/or dominantly-abundant ions, the best precision on the retrieved peak intensity follows the theoretical limit imposed by counting statistics. (2) The m/Q calibration-limited regime: for closely-separated ions, the influence of the imprecision in the m/Q calibration dominates and the achievable precision on peak intensity degrades rapidly. (3) The overlapping counting-error regime: at low signal-to-noise, the imprecision arising from counting error still dominates and the imprecision in the m/Q calibration makes no additional impact. The transition between the counting-error and calibration-limited regime depends on the intensity of the peaks, but is only weakly sensitive to their absolute width. Thus a general parameterisation can be developed which describes the lower limits in peak separation and intensity that are required for a given precision in the fits. Except for cases of poor signal-to-noise ($\lesssim 100$ counts), integration to longer measurement time-scales for an ion in the calibration-limited regime cannot improve the precision with

which its peak intensity can be retrieved; in order to move the ion into the counting-error regime, higher resolving power would be required.

The results are demonstrated as applied to a typical instrumental setup employed in atmospheric science, but make no assumptions about ionisation or spectrometer type and can thus be generally applied. Further investigations to include the effect of imprecisions in peak width, non-Gaussian peak shape and systems with greater than two ion peaks should form the basis of future work.

**The Supplement related to this article is available online at
doi:10.5194/amtd-7-12617-2014-supplement.**

Acknowledgements. This work was partially supported by NSF AGS-1243354 and AGS-1360834, NOAA NA13OAR4310063, NASA NNX12AC03G, and DOE (BER, ASR) DE-SC0011105. We thank Marc Gonin for useful discussions on this topic.

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Table 1. Glossary.

χ	Peak separation normalised to half-width at half-maximum (HWHM)
χ_d	Peak separation below which ion would be considered to be in the m/Q calibration-limited regime
I	Peak intensity (in number of ion counts)
I_{true}	True peak intensity
I_{fitted}	Fitted peak intensity
Δ	Normalised deviation in fitted peak intensity $(I_{\text{fitted}} - I_{\text{true}})/I_{\text{true}}$
I_p	Peak intensity of parent (dominant) peak in an overlapping pair
I_c	Peak intensity of child (non-dominant) peak in an overlapping pair
R_I	Ratio of parent-to-child intensities for an overlapping ion pair (I_p/I_c)
σ_I	Normalized precision of the fitted peak intensity owing to all sources of error (%)
σ_C	Normalized precision of the fitted peak intensity owing to counting error only (%)
σ_N	Minimum achievable σ_I owing to counting error for an isolated ion (%)
σ_B	Minimum achievable σ_I owing to m/Q calibration imprecision (%)
W	Peak width (ns)
δ_t	Data point spacing (ns)
dt	Separation of the known peak positions in time-of-flight space

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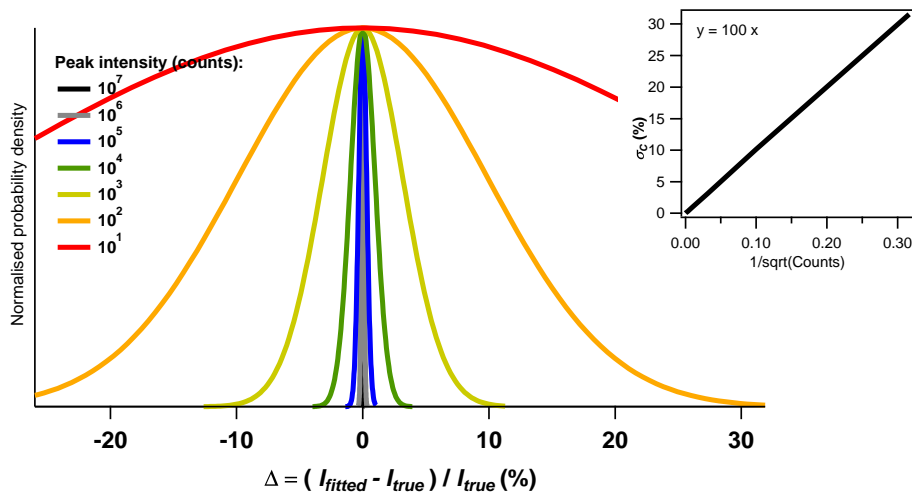


Figure 1. Histograms of the normalised deviation in fitted peak intensity, Δ , for 10 000 simulations of peak-fitting to an isolated Gaussian ion peak degraded with counting error and centred at 2000 ns, data-point spacing 0.2 ns and peak width 1 ns. Shown inset, the SD in Δ , σ_{Δ} , for all histograms.

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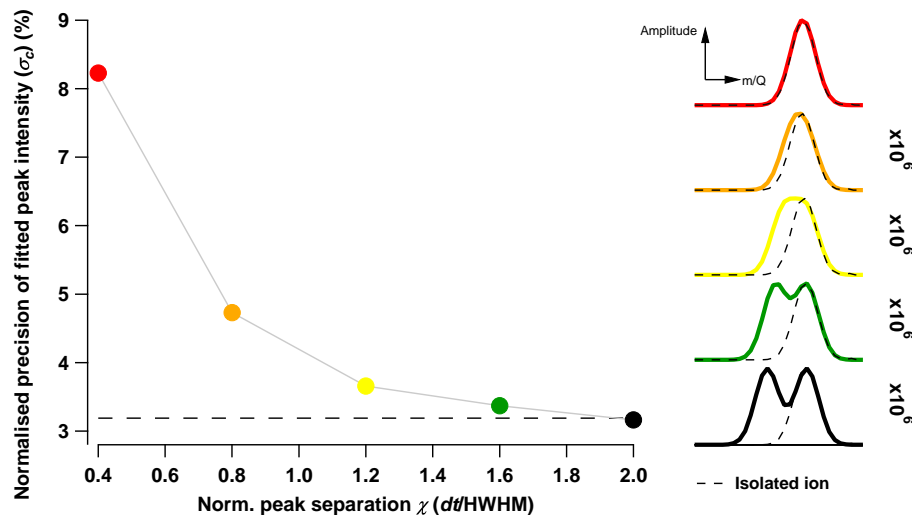


Figure 2. Relative precision in fitted peak intensity, σ_C , for 10 000 simulations of peak-fitting to a pair of overlapping Gaussian peaks degraded with counting error. Peak intensity = 1000 counts, peak width = 1 ns, peak centre = 2000 ns and point spacing = 0.2 ns. Schematics demonstrating the appearance of the measurement distributions are shown on the right, with dashed-lines showing the measurement distribution of an isolated ion for comparison.

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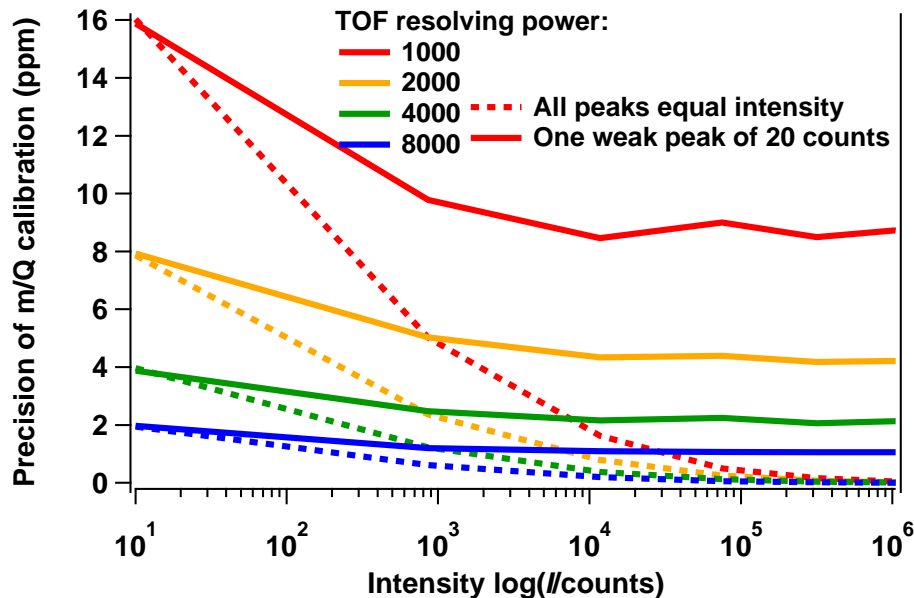


Figure 3. Mean precision in peak position arising from m/Q calibration as a function of the intensity of the calibrant ions. Dashed lines: all calibrant ions of equal intensity and as given on the x axis. Solid lines: as dashed, except one calibrant has peak intensity of only 20 counts.

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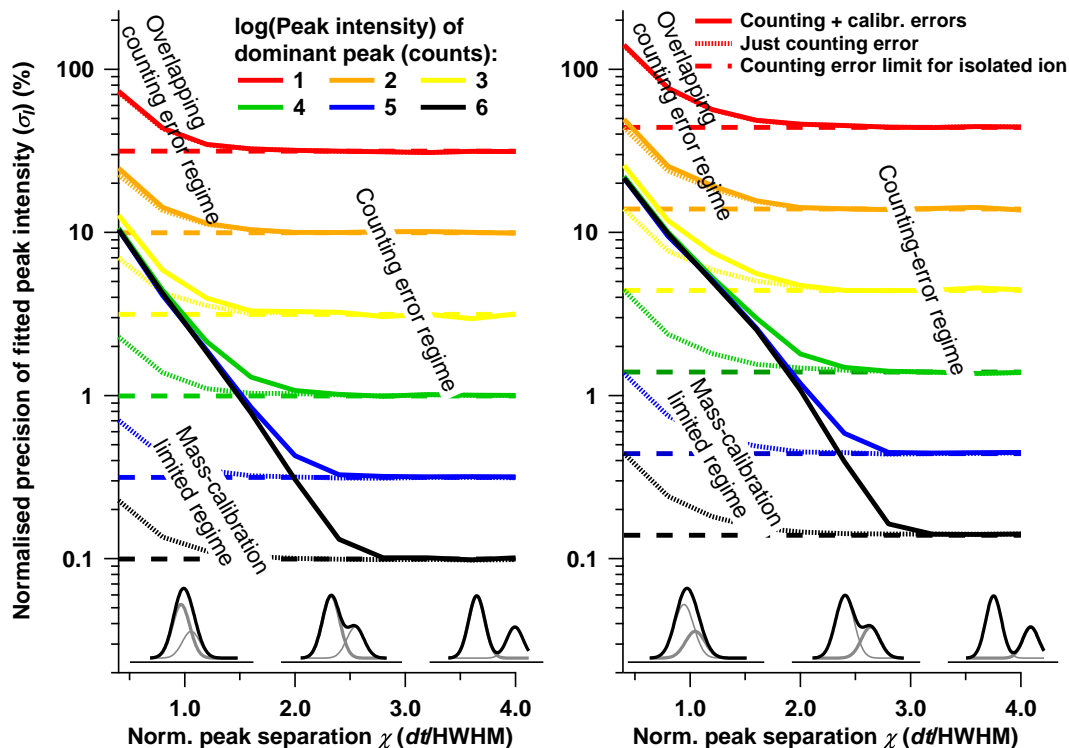


Figure 4. Precision on fitted peak intensity, σ_I , as a function of peak separation for an overlapping ion pair. Colours: peak intensity of the dominant ion (left); the weaker ion (right) is half as intense. The dominant peak is centred at 2000 ns; both have a width 1 ns and the data-point spacing is 0.2 ns.

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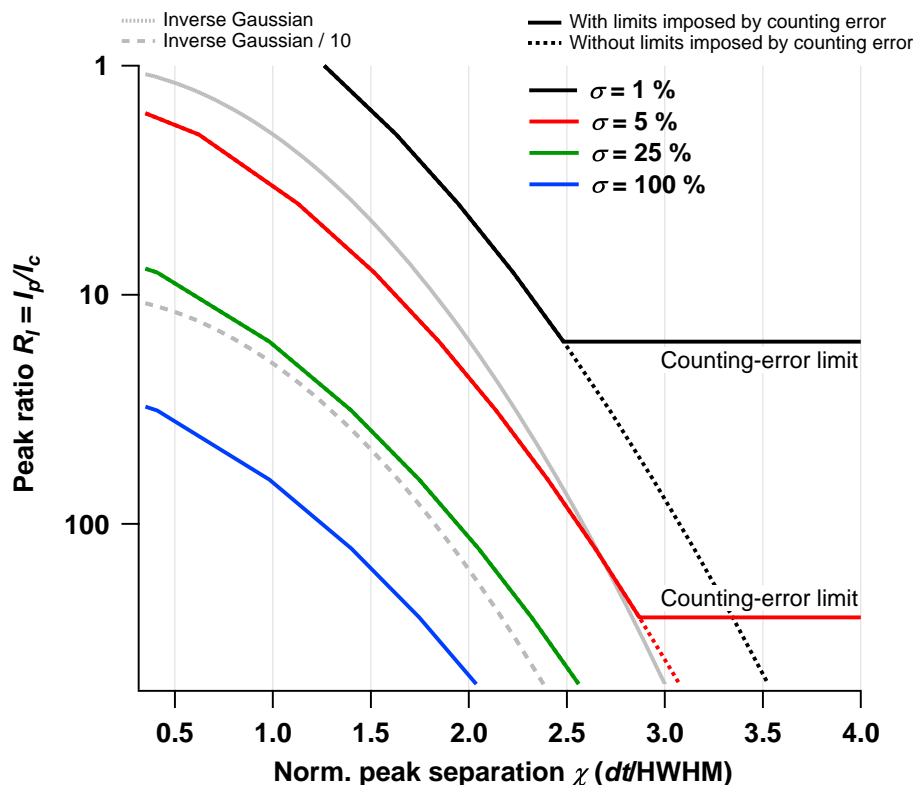


Figure 5. Estimated peak separation required to achieve the indicated precision on fitted peak intensity for the less-intense peak of an overlapping ion pair. Solid lines: dominant ion has a peak intensity of 10 000 counts. Dashed-lines: assuming no limit imposed by counting statistics. The data-point spacing is 0.2 ns and peak width = 1 ns. The lines for the inverse of two normalised Gaussian distributions of height 1 and 0.1 counts are shown for comparison.

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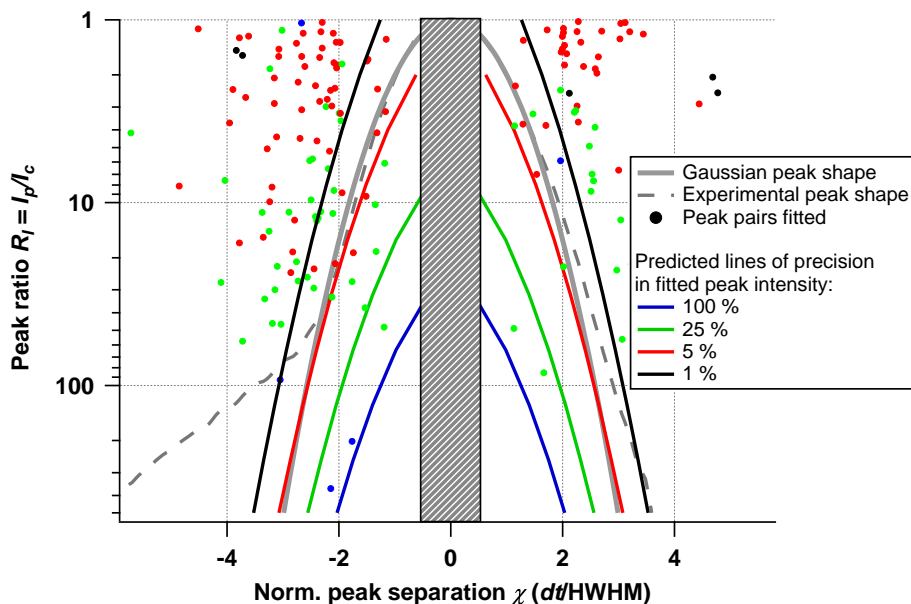


Figure 6. Ratio of fitted peak intensities vs. true peak separation for the smaller ion from all pairs of ions used in analysis of the CalNex field campaign data from a High-Resolution Aerosol Mass Spectrometer (Hayes et al., 2013). Superimposed are the lines of constant estimated precision on fitted peak intensity shown in Fig. 5. The data points are coloured according to the precision in fitted peak intensity expected from counting statistics. The Gaussian and experimental peak shape are shown in grey. The data-point spacing is 0.2 ns and peak width = 1 ns.

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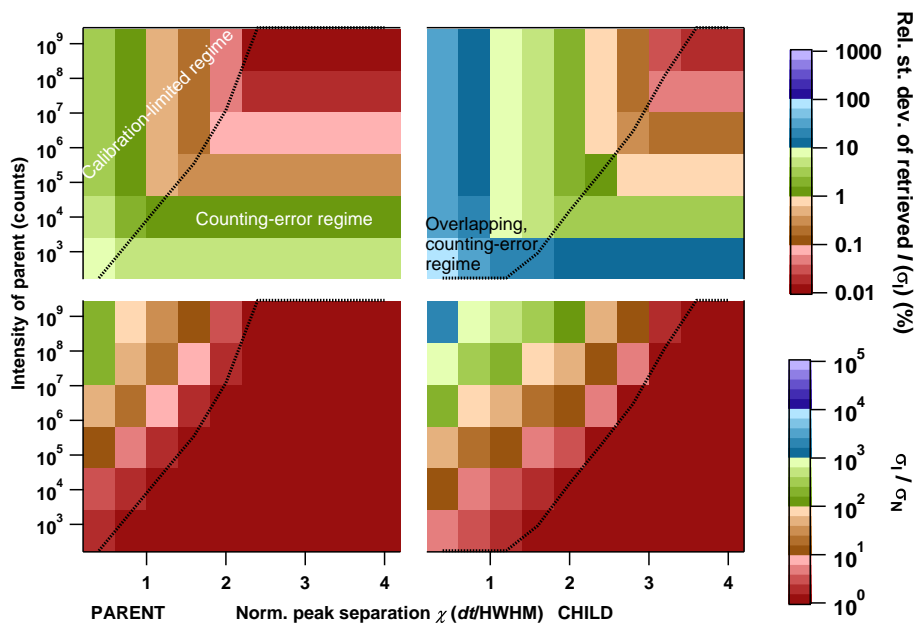


Figure 7. Actual precision in the normalised fitted peak intensities (σ_I , top) and normalised to the counting error limit (σ_I/σ_N , bottom), for an overlapping ion pair. The stronger (parent) peak is 8 times as intense as the weaker (child) peak. The precision is represented by the colour scale and shown for a range of peak intensities and separations. The black lines denote the peak separation at or below which an ion would be considered to be in the calibration-limited regime.