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Accurate thresholding using a compound-Poisson-lognormal lookup table and parameters recovered from standard single particle ICP-TOFMS data

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The use of time-of-flight (TOF)-based instruments in single particle inductively coupled plasma-mass spectrometry (ICP-MS) is growing quickly. While these instruments have critical advantages over their quadrupole counterparts, they present new challenges when determining thresholding values in single particle analyses. One challenge is the need to analyse the single-ion area (SIA), which is essential for accurate thresholding in single particle data sets. However, the SIA is different for each element and changes across usage, time and during detector calibration. Rapid and effective algorithms are required to determine the SIA and predict thresholds automatically. Here we introduce new tools to investigate and fit the SIA with a lognormal distribution and, for determining background signal in single particle ICP-TOFMS. First, a lookup table of compound-Poisson-lognormal quantiles was computed using a simulation of 10^{10} random values. This improved accuracy of thresholds at large lognormal standard deviations and was significantly faster than our previous approach. To facilitate its use, we have implemented it into our data processing software, SPCal. We also present a method to recover the SIA parameters that are required for thresholding from both raw ionic and particle data, enabling on-site SIA fitting during normal data processing. This method was tested both in simulation and experimentally, across different instruments, conditions and masses. The limitations of the method are discussed and conditions required for successful recovery determined.

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Introduction

Accurately modelling background signal is critical for single particle analysis using inductive coupled plasma-mass spectrometry (ICP-MS) as false positive detections directly affect apparent particle concentration and size.[1] For quadrupole instruments generating moderate amounts of data, this is relatively simple, and backgrounds can be accurately modelled

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using either Poisson or Gaussian statistics. However, the fast analogue digital converters used in time-of-flight (TOF) detectors preclude the use of a pulse counting mode and instead reveal the full analogue response of the electron multiplier. The gain produced by an electron multiplier is not constant but is instead a distribution resulting from small statistical variations in electron trajectories and emission energies, among other factors.[2] The resulting 'pulse height distribution' or single-ion area (SIA) is the signal produced from single ions and must be statistically modelled to accurately determine the threshold for distinguishing particle event signals from background noise.

At low count rates, the signal obtained using ICP-TOFMS follows a complex distribution (Fig. 1) that arises from two separate physical processes. The first process is the arrival of k number of ions to the detector and can be accurately modelled using a Poisson distribution. The second is the sampling of the SIA by each ion. This combination of distributions creates the difficulties in establishing statistically valid thresholds for single particle ICP-TOFMS data.

Gundlach-Graham *et al.*[3] proposed the use of a compound-Poisson distribution to model electron pulses generated by the arrival of a Poisson-distributed number of ions. Previously, we demonstrated that the SIA can be accurately fitted with a lognormal distribution, and that a compound-Poisson-lognormal model can be used to simulate background signals in ICP-TOFMS measurements.[4] Crucially, this approach requires measurement of the lognormal shape (σ) and location (μ) parameters.

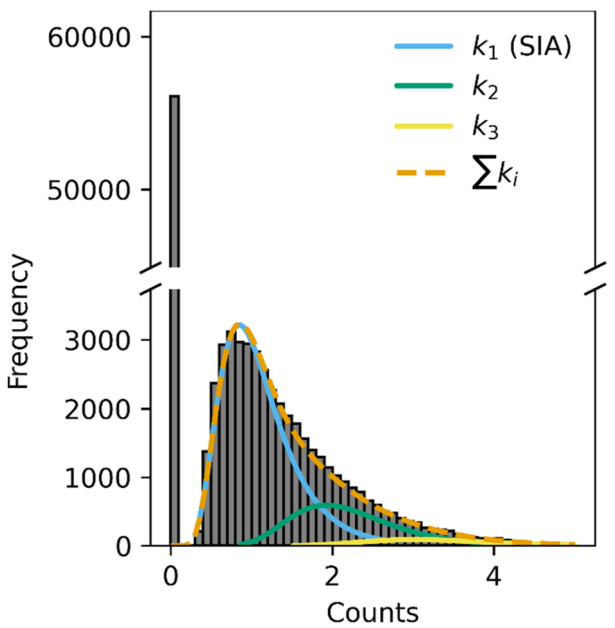

Fig. 1 Histogram of the ICP-TOFMS signal produced by a low concentration ionic standard. The non-zero signal is a sum of the distributions produced by both single and multiple ion events as they impact and are amplified through the electron multiplier. The probability for the number of ions per event k_i is itself drawn from a Poisson distribution.

Lognormal parameters can be determined under the same conditions as a detector calibration, by measuring an ionic standard under ion transmission conditions that yield predominantly single-ion events. This permits measurement of the SIA, which shows the response distribution of single ions and is used to convert raw detector responses into counts. The SIA varies across different elements and the variation has been attributed to several ion-specific and instrumental factors, including atomic number, mass, electronic configuration, ion velocity, electronic stopping power, ionic radius, and the composition and condition of the detector material.[5] Current practice involves an estimation of an average SIA which is applied without taking element-specific deviations into account.[6] Furthermore, it is worth noting that the SIA changes across usage, time and after detector calibration which is a result of deterioration and aging effects of the detector.[7] Taking typical abundance sensitivities of current ICP-TOFMS instrumentation into account,[8] high intensity signals of neighbouring masses could also impact the mass specific SIA. Consequently, periodic SIA analysis is essential for accurate SIA determination and threshold settings in single particle ICP-TOFMS.

In this work, a new and rapid approach is introduced which enables the determination of element-specific SIA from common ICP-TOFMS data files or, alternatively, from detector calibration files. It enables more accurate signal thresholding and accelerates the analysis of large and complex data.

Experimental

Materials

Certipur® ICP multi-element standard solution IV containing 23 elements (1000 mg L^{-1}; Ag, Al, B, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, In, K, Li, Mg, Mn, Na, Ni, Pb, Sr, Tl, Zn) was purchased from Merck (Darmstadt, Germany). Peak Performance multi-element standard P/N 4400-ICPMS1 (10 mg L^{-1}; Dy, Ho, Lu, Sm, Sc, Tb, Th, Tm, Y, La, Ce, Pr, Nd, Eu, Gd, Er, Yb) was purchased from CPI International (Santa Rosa, CA, USA). VHG Labs 68 element SM68 standards 1, 2 and 3 were purchased from LGC Scientific (100 μg mL^{-1}; Teddington, UK). An 80 nm gold nanoparticle suspension in 2 mM citrate was purchased from nanoComposix (San Diego, CA, USA). Up-conversion nanoparticles (UCNPs) containing Gd and Yb were obtained from a previous study.[9] All solutions were diluted to working concentrations using ultra-pure water (18.2 MΩ cm, Merck Millipore, Bedford, USA).

Instrumentation

A Vitesse ICP-TOFMS system by Nu Instruments (Wrexham, UK) was used to acquire the mass range from m/z 22 to 240. Three spectra were binned before baseline correction and subsequently saved at 12 193 kHz. The plasma was operated at 1.3 kW and the segmented reaction cell used He and H_2 gas flow rates of 14 and 8 mL min^{-1}, respectively. Data acquisition was conducted using Nu Codaq software (Nu Instruments) and data analysis was performed with the open-source python-based data

processing platform SPCal.[4,10] To test the general applicability of the approach, four different Vitesse ICP-TOFMS instruments (Nu Instruments) were used to investigate μ (location) and σ (shape parameter) across the mass range under similar settings as outlined above. All data was used in its raw form (integrations of the full mass spectrum) without converting to counts *via* the mean SIA value. During thresholding an α value of 10^{-6} was used.

Lookup table

A lookup table of zero-truncated compound-Poisson-lognormal quantiles was created from the simulation of 10^{10} randomly drawn values with a mean of 1. The simulation was written in C++ (gcc 8.5.0) using a *t*-digest to estimate quantiles from the stream of random values.[11] This simulation was performed for 71 λ values (geometrically spaced from 0.001 to 100) and 41 σ values (linearly spaced from 0.25 to 0.95), with 101 quantiles (inverse logistic spaced from 10^{-3} to $1\text{–}10^{-7}$) calculated for each. For each simulation the value of μ was chosen to give the distribution a mean of 1, $\mu = -\frac{\sigma^2}{2}$. The table was then converted to a NumPy array and exported.

To use the lookup table for non-zero-truncated, data, the quantiles (y) are first converted to their truncated form (y_0) using eqn (1).

$$y_0 = \frac{y - e^{-\lambda}}{1 - e^{-\lambda}} \tag{1}$$

The value is then linearly interpolated from the closest values in the table, with a maximum error of 0.2%. Finally, the quantile is rescaled to the desired μ by multiplying by $e^{\mu - \left(-\frac{\sigma^2}{2}\right)}$, where $-\frac{\sigma^2}{2}$ is the value of μ required for a mean of 1.

Recovery of compound-Poisson-lognormal parameters

Drawing a value from the compound-Poisson-lognormal distribution Y is performed by summing N samples from an underlying lognormal distribution (eqn (2)), where N is itself drawn from a Poisson distribution (eqn (3)).

$$Y \sim \sum_{i=0}^{N} \text{Lognormal}(\mu, \sigma) \tag{2}$$

$$N \sim \text{Poisson}(\lambda) \tag{3}$$

The first parameter that can be determined is the Poisson rate value, λ. Using the Poisson probability mass function, the probability that any value k is drawn from the distribution can be calculated. As a lognormal does not support zero values, any events in Y producing zero response must originate from the absence of ions. The probability that $k = 0$ (*i.e.*, $P(N = 0)$) is therefore equal to the probability that the compound-Poisson-lognormal is zero, $P(Y = 0)$. We can use eqn (4)–(6) to calculate λ from the fraction of zero values in the data.

$$P(N = k) = \frac{\lambda^k e^{-k}}{k!} \tag{4}$$

$$P(N = 0) = P(Y = 0) = e^{-\lambda} \tag{5}$$

$$\lambda = -\ln(P(Y = 0)) \tag{6}$$

The 95% confidence interval for λ can be calculated using the Wald method as in eqn (7).[12] For typical single particle ICP-TOFMS data sets where $\lambda > 0.01$ and the number of samples n is in the millions, the error will be less than 5%.

$$\lambda \pm 1.96\sqrt{\frac{\lambda}{n}} \tag{7}$$

Once λ is determined, the expected value and variance of the Poisson part of the distribution are known. The laws of total expectation and total variance are then applied to determine the expected value (eqn (8)) and expected square (eqn (9)) of the lognormal component, from which its variance can be calculated.[13]

$$\mathbb{E}[X] = \frac{\mathbb{E}[Y]}{\lambda} \tag{8}$$

$$\mathbb{E}\left[X^2\right] = \frac{\mathbb{V}(Y)}{\lambda} \tag{9}$$

Finally, the lognormal parameters were recovered using their method of moments, eqn (10) and (11).

$$\mu = \ln\frac{\mathbb{E}[X]^2}{\sqrt{\mathbb{E}\left[X^2\right]}} \tag{10}$$

$$\sigma = \sqrt{\ln\frac{\mathbb{E}\left[X^2\right]}{\mathbb{E}[X]^2}} \tag{11}$$

Comparison with lognormal fit of data

A 68-element standard mix (VHG-SM68 standard 1,2 and 3; 1 or 10 μg L^{-1}) was run on four ICP-TOF instruments. TOF integration data was filtered to contain only masses that had a Poisson probability $P(N > 0) > 10^{-2}$ and $P(N \geq 2) < 10^{-3}$, to limit analysis to elements containing mostly single-ion events. The λ value was calculated from the fraction of zeros as above, after which a lognormal distribution was fitted to all non-zero data using SciPy to obtain the optimal μ and σ values.

Iterative

Naïve parameter recovery in samples containing both ionic and particulate signals was unsuccessful. Particle signals lead to an underestimation of $P(Y = 0)$, and overestimation of both the mean and variance of the distribution. Consequently, particle events were filtered out to obtain the true compound-Poisson-lognormal parameters. This filtering was performed by iteratively thresholding the data, removing identified particle events

and repeating the process until the threshold no longer changed. The threshold was calculated in each iteration using the 99.9th quantile.

Results and discussion

This study aims to provide a more accurate and generally applicable method to determine the threshold over which a signal is identified as a single-event in ICP-TOFMS data sets. On the one hand, this required a thorough understanding of the SIA for different instruments and across the mass range, and on the other hand, an effective computational algorithm capable of analysing vast TOF-data sets rapidly, establishing thresholds based on the gained understanding.

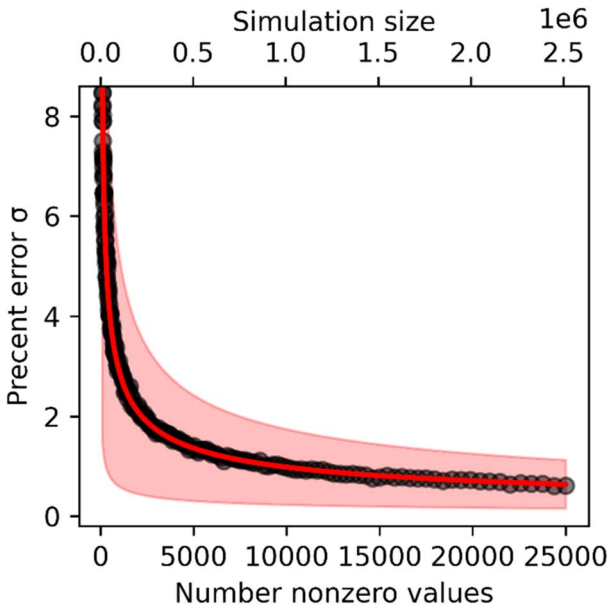

Fig. 2 The error in recovery of σ (0.6) at a λ of 0.01 when determined with increasing numbers of nonzero values. A log–log fit of the mean and standard deviation is shown in red, determined using 1000 iterations for each value.

The SIA can be fitted with high accuracy using a lognormal function facilitating the prediction of quantiles and providing a computational advantage when stipulating or calculating the α error. When fitting the SIA with a lognormal, only two parameters are required, σ (shape) and μ (location). Previously, we employed an approximation method based on a Fenton-Wilkinson approximation of lognormal sums, assuming a mean of 1.[4,14] While this method yields accurate results for low standard deviations, its performance deteriorates at standard deviations greater than 0.5,[15] resulting in reduced accuracy in predicted thresholds. Further, this approach was computationally more expensive, making it less suitable for datasets with many m/z of interest. To accelerate data analysis, a lookup table for thresholds was generated, consisting of 101 compound-Poisson-lognormal quantiles for 71 λ values and 41 σ values, covering a realistically expected range. Simulations of 10^{10} randomly drawn values were performed for each λ and σ value, with a location (μ) selected to give a lognormal mean of 1 (see method section for more information). Using interpolation, a threshold can be drawn for any realistic combination of λ, μ and σ, with a minimum alpha value of 10^{-7}.

Drawing quantiles from this compound-Poisson-lognormal lookup table instead of performing the previous lognormal approximation provided enhanced precision and accuracy at high σ and λ. The maximum deviation caused by linearly interpolating between tabled values was estimated to be 0.2%. Calculating thresholds using the lookup table was also

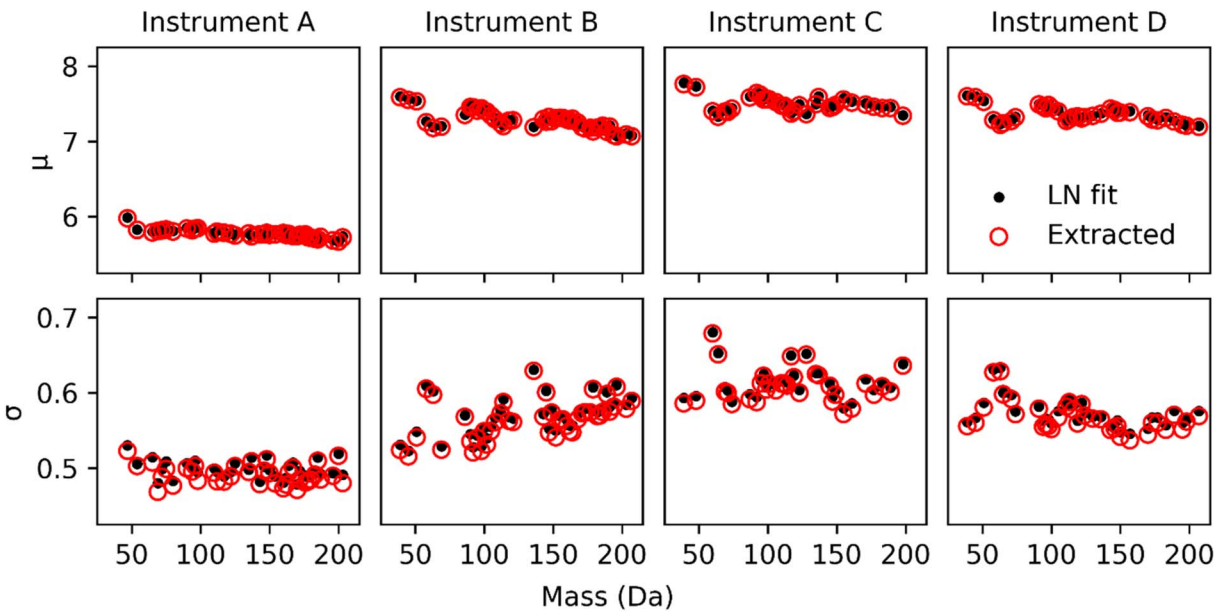

Fig. 3 Recovery of μ and σ from four ICP-TOF instruments using a lognormal fit of the data and the proposed extraction method. For clarity, only 50% of data points are shown.

significantly faster than the previous method (0.15 ± 0.02 ms *versus* 4.5 ± 1.5 ms). Vectorisation of the code further improved performance when simultaneously calculating multiple quantiles. This is particularly relevant for operations such as rolling mean thresholding (windowed thresholding) and non-target particle screening.[10,16] Computing 1000 quantiles across various λ, μ and σ values was more than 16 000 times faster. The lookup table has been implemented in our single particle analysis software, SPCal, as the default method for determining thresholds of ICP-TOFMS data. The speed-up from the previous approach enabled windowed thresholding for this data, which was previously disallowed due to the time required to calculate thousands of thresholds.

Once an effective method for determining quantiles was in place, the focus was set on accurately predicting critical Poisson λ and lognormal μ and σ parameters from common ICP-TOFMS data sets. The mentioned parameters are essential to use of the lookup table and are typically obtained separately by running a low concentration standard and fitting a lognormal distribution to the resulting data. As shown in Fig. S1, both μ and σ depend on the detector voltage and the element measured, and consequently, they need to be re-determined whenever the detector is calibrated and set at a new voltage. This process is time consuming, and difficult to apply consistently across the entire mass range.

Here, we suggest retrieving the λ value directly from common ICP-TOFMS data files by considering the fractions of zeros in the raw data using the Poisson probability mass function. With the value of λ determined, the mean and variance of the underlying lognormal distribution could be calculated using the laws of total expectation and variance. From these, the corresponding μ and σ values required for the lognormal fit were then derived using the method of moments. However, it is worth noting that when the data contain few or no zero values, λ cannot be reliably calculated. In these cases, the compound-Poisson-lognormal nature of the background approaches a normal distribution and Gaussian statistics may be used instead.[3]

The compound-Poisson-lognormal parameter extraction method must be reliable across different instruments and background signals, *i.e.*, a range of λ, μ and σ values. To demonstrate the performance of the compound-Poisson-lognormal parameter extraction method on a range of parameters, tests were conducted using λ values of 0.01, 0.1 and 1.0, combined with a range of realistic μ and σ using 10^6 randomly drawn values. Plots of the absolute error of the recovered μ and σ parameters are shown in Fig. S2–S4, with the highest errors for a λ of 0.01 observed at 0.008 ± 0.008 for both μ and σ. Most of this error occurred for σ values above 0.8, where a greater number of nonzero data points were required to determine the variance of the data. For small datasets with λ values less than 0.1, the number of nonzero points may be insufficient, highlighting the need for a minimum threshold of nonzero values to accurately determine μ and σ.

The required number of nonzero values to achieve a specific error in the recovered σ was determined by simulating distributions with a λ of 0.01 ($P(X = 0) = 0.99$) and a μ of 1 at increasing simulation sizes. After 1000 simulations at each simulation size, a trendline was fitted to the relative error (Fig. 2) and used to determine the minimum number of nonzero values required to achieve a 5, 2 and 1% error in recovering a σ value of 0.6. Recovery at these errors required 350, 2100 and 8900 nonzero values and would result in a shift in a determined threshold at an α value of 10^{-6} of around 3.0, 1.2 and 0.6 counts. When the experiment was repeated for a σ value of 0.8, the increases in variance meant that more nonzero values were required to achieve the same 5, 2 and 1% errors. Recovery required 550, 4300 and 20 500 nonzero values, with an implied shift in threshold of 8.6, 3.3 and 1.6 counts. For data with very low λ values (*i.e.*, a high percentage of zero values) this method may not be appropriate and the previous method of determining σ should be used. Determination of μ required approximately 50% the number of nonzero values as σ, suggesting the recovery of σ was the limiting factor.

Following the evaluation of simulated compound-Poisson-lognormal distributed data, experimental data was collected

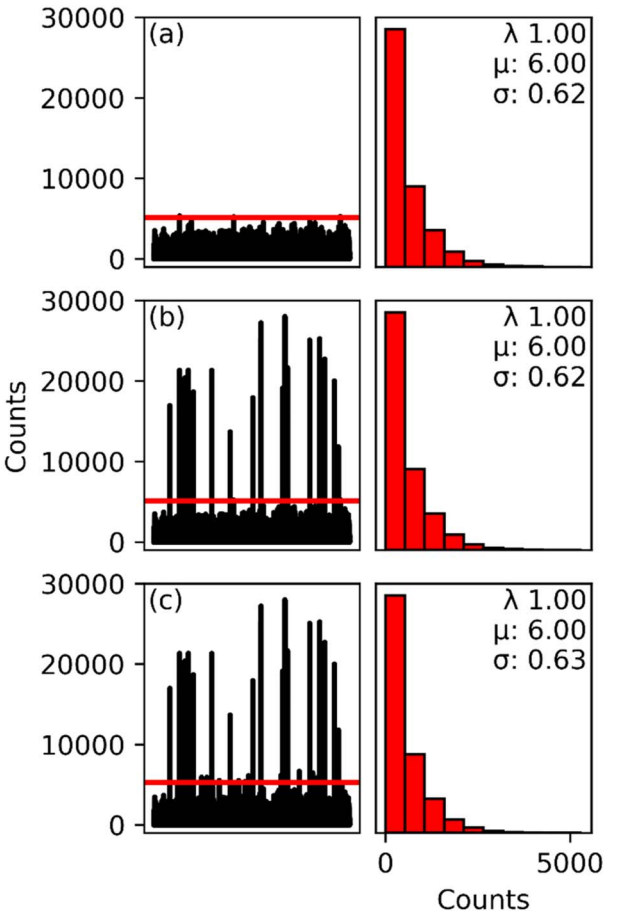

Fig. 4 Iterative extraction of parameters from compound-Poisson-lognormal data simulated using a λ of 1, μ of 6 and σ of 0.62. A section of the data is shown with the determined threshold in red and a histogram of remaining data points. Three different scenarios are illustrated, which simulate an ionic-only background (a), the addition of large particles (b) or both large and small particles (c) did not affect the accuracy.

across four different instruments. Both μ and σ values were determined across the mass range using both the proposed method and a lognormal fit of the data, as shown in Fig. 3. The absolute difference between the methods, over the four instruments, was 0.15 $\pm$ 0.05% and 1.0 $\pm$ 0.5% for μ and σ respectively. We argue that the observed differences in σ are caused by non-single-ion events affecting the lognormal fit. When the stringency for inclusion of two-ion events is relaxed and attenuation not used, a large shift is observed in σ values of the lognormal fit, while our proposed method remains unaffected (Fig. S5). Shape values varied from 0.45 to 0.68 across all instruments and masses. Instrument A used a detector that was close to the end of its operational lifetime and a significant deviation of the lognormal parameters from other instruments was evident. In contrast, the other instruments showed relative consistent μ values though variations in σ were still observed with the same elements measured on different instruments producing different SIA shape parameters. Both the longitudinal changes of SIA shape and position, as well as the element- and instrument-specific influences underpin the requirement to consider and fit the SIA routinely. This poses practical challenges and is time-consuming as it means that each instrument needs to monitor the SIA regularly and must adjust lognormal parameters for accurate thresholding. The method suggested here, allows this adjustment to be carried out in parallel during dataset analysis, without requiring additional calibration or measurements.

To demonstrate the method's robustness across varying ionic concentrations, and its ability to extract parameters even in cases with few single-ion events, parameters were extracted from samples containing 1 and 5 μg L^{-1} of a multi-element ionic standard mix and a lanthanide standard (Fig. S6). Particle contamination was observed for the elements Mg, Al, Fe and Bi and were excluded. The mean absolute difference for calculated μ and σ values were 0.025 $\pm$ 0.017 (0.4 $\pm$ 0.3%) and 0.005 $\pm$ 0.003 (0.8 $\pm$ 0.5%) respectively. This demonstrated the applicability of the method and its capability to extract the mean and variance of the underlying SIA distribution, even in cases where single-ion events were not prominent.

Thresholding in single particle analysis requires knowledge of the mean, which is not directly available in typical data sets due to the abundance of particulate events which increase the overall mean and variance of the data set. To extract parameters from data sets that do not exclusively contain ionic information, particle signals must be removed. Here, an iterative thresholding method was used to extract parameters, calculate a threshold using these parameters and then remove all data above this threshold. By repeatedly performing this process until no more data is above the threshold, all particle signals could be eliminated from raw ICP-TOFMS data, leaving only ionic signal. First, this method was tested on simulated particle data, generated by the addition of Gaussian peaks to a compound-Poisson-lognormal background with λ of 1, μ of 6 and σ of 0.62. Fig. 4 shows different scenarios, which simulate an ionic-only background (a), the presence of high particle signals (b) and the presence of low and high particle signals (c) and the critical parameters that were extracted in each case, as shown adjacently. In all cases, the developed method successfully extracted the parameters (within $\pm$0.01), which enabled the analysis of datasets containing ionic signals, particle signals or a mixture of the two.

The efficacy of this process was subsequently demonstrated using experimental data. Here, samples containing Au nanoparticles and UCNPs doped with both Gd and Yb were analysed across varying ionic background concentrations and resulting data sets were processed to extract the desired parameters.

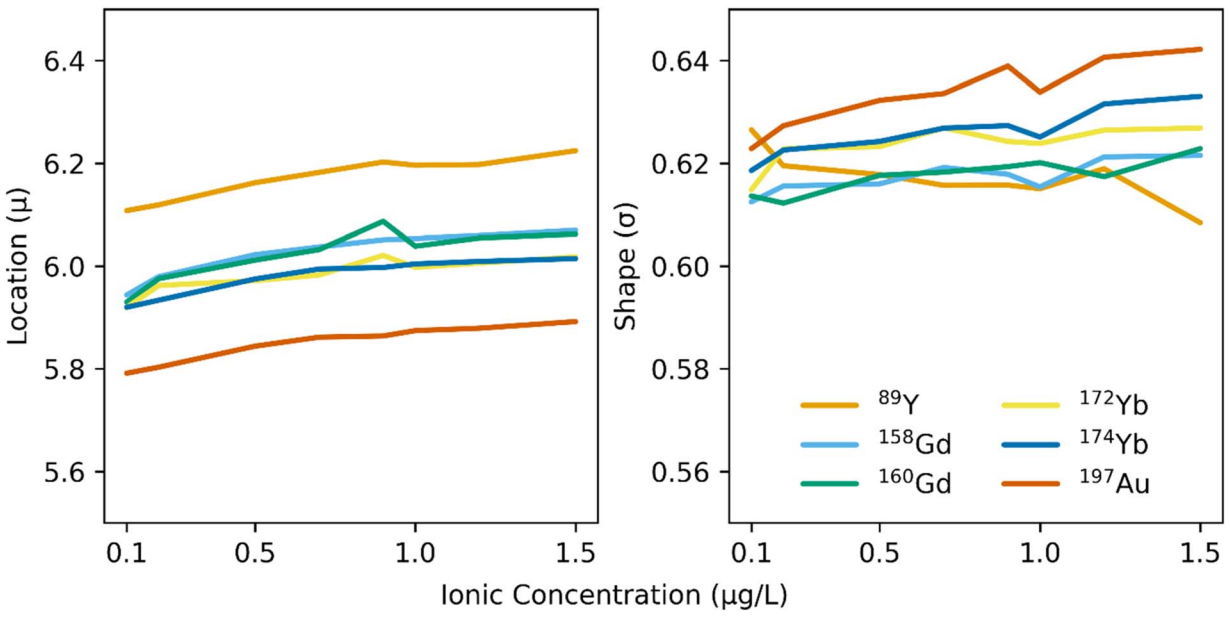

Fig. 5 Extraction of μ and σ from samples containing Au nanoparticles and lanthanide doped UCNPs. The recovery of parameters was stable over a range of spiked ionic concentrations.

Fig. 5 shows the extraction of μ and σ values from nine data sets with ionic background levels ranging from 0.1 to 1.5 μg L^{-1}. The values of μ and σ increased slightly with concentration, most likely due to increased similarity between the ionic and particulate signals, resulting in incomplete removal and the transition into a more normal distribution. In experimental conditions, this increase resulted in predicted thresholds at an α of 10^{-6} changing by less than 1 count. Even so, at the highest concentration (1.5 μg L^{-1}) Gaussian statistics would be preferred for ^{89}Y.

We have previously introduced an open-source single particle data processing platform, now widely used by various groups for both quadrupole and TOF-based particle analysis. To facilitate the application presented here, the lookup table has been implemented into the latest release. Extraction of compound-Poisson-lognormal parameters for thresholding will be included in an upcoming version. The source code is available online† with additional details on its integration into SPCal and usage provided in the online documentation.‡

Conclusion

The probabilistic detector response of single ions in single particle ICP-TOFMS as well as element and detector specific effects add significant complexity when attempting to carry out adequate thresholding. Furthermore, challenges related to current simulations/approximations are computationally expensive and obstruct the analysis of large data sets. This work presents a new approach for fast and accurate thresholding of single particle ICP-TOFMS data. An extensive lookup table of quantiles from simulated compound-Poisson-lognormal data was created and used to rapidly produce desired thresholds. This table has been incorporated into our existing open-source analysis software, SPCal, and is available in the SI of this paper.

A new method to estimate critical compound-Poisson-lognormal parameters from raw data was established and tested across different conditions, mass ranges, particle suspensions, simulations, experimental conditions, instrumental settings as well as different instruments. This method allowed the determination of parameters required for thresholding using existing data and without knowledge of the SIA whilst considering element-specific deviations. While the method is accurate across a range of ionic strengths and instruments, careful attention must be paid to the number of nonzero values in the dataset and its practicality in samples with very low or high backgrounds is limited. Once this method is implemented in SPCal, rapid and accurate thresholding will be available to other research groups.

Author contributions

Thomas Edward Lockwood: conceptualisation, formal analysis, software, writing – original draft, writing – review & editing. Raquel González de Vega: investigation, writing – review & editing. Lukas Schlatt: investigation, formal analysis, writing – review & editing. David Clases: conceptualisation, investigation, writing – review & editing.

Conflicts of interest

L. S. works for Nu Instruments.

Data availability

The lookup table is available on GitHub (**https://github.com/djdt/spcal/blob/v1.4.2/spcal/resources/cpln_quantiles.npz**) and in the supplementary information. The code used to generate simulated data and the lookup table, and to extract parameters, is included in the supplementary information. ICP-TOF data used in Fig. 5 and S6 are available on Zenodo at **https://doi.org/10.5281/zenodo.15631160**. ICP-TOF data used in Fig. 3, S1 and S2 are available upon reasonable request and with the approval of Nu Instruments.

Supplementary information is available. See DOI: **https://doi.org/10.1039/d5ja00230c**.

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