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Dead-time correction for time-of-flight secondary-ion mass spectral images: a critical issue in multivariate image analysis

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Abstract

Dead-time effects result in a non-linear detector response in the common time-of-flight secondary-ion mass spectrometry instruments. This can result in image artifacts that can often be misinterpreted. Although the Poisson correction procedure has been shown to effectively eliminate this non-linearity in spectra, applying the correction to images presents difficulties because the low number of counts per pixel can create large statistical errors. The efficacy of three approaches to dead-time correction in images has been explored. These approaches include: pixel binning, image segmentation and a binomial statistical correction. When few pixels are fully saturated, all three approaches work satisfactorily. When a large number of pixels are fully saturated, the statistical approach fails to remove the dead-time artifacts revealed by multivariate analysis. Pixel binning is accurate at higher levels of saturation so long as the bin size is much smaller than the feature size. The segmentation approach works well independent of feature size or the number of fully saturated pixels but requires an accurate segmentation algorithm. It is recommended that images be collected under conditions that minimize the number of fully saturated pixels. When this is impractical and small features are present in the image, segmentation can provide an accurate way to correct for the detector saturation effect.

Keywords

multivariate analysis; hyperspectral imaging; dead-time correction; simulation

Introduction

Imaging time-of-flight secondary-ion mass spectrometry (ToF-SIMS) is becoming an increasingly important technique for the analysis of biological and organic materials. ToF-SIMS is a hyperspectral imaging technique. Every image pixel (or voxel in the three-dimensional, 3-D, case) contains a complete mass spectrum. It is this hyperspectral quality which makes ToF-SIMS imaging such a powerful technique, but it also presents substantial challenges with data handling and interpretation. A variety of multivariate techniques, including principal components analysis (PCA), multivariate curve resolution (MCR), varimax rotation and maximum auto-correlation factors (MAF) have been shown to be powerful tools which can aid in interpretation of ToF-SIMS images.^[1-7]

All of these factor analysis techniques presume linear relationships within the data, that is, they presume that the intensity of peaks arising from the same chemical species will have a

constant ratio independent of the concentration of that species in the sample or the absolute intensity of those peaks. If random noise is the only cause of non-linearity in the data, then these multivariate techniques will reduce the data set into a small number of factors arising from chemical and topographical effects with the remainder of factors showing featureless images (noise). Unfortunately, because of dead-time effects, the ToF-SIMS intensity scale is only acceptably linear below approximately 10% percent detector saturation. This non-linearity of the intensity scale results in image artifacts that are highlighted by the multivariate analysis and can complicate the interpretation of results. The dead-time effect differs significantly from noise because variations in detector saturation across an image are not random. Image features that result in changes in the ion yield, such as topographic features, will result in changes in the percent detector saturation. As a result, factors that describe only noise generally result in featureless images, while those that arise from dead-time effects show false features.

Although the enhanced signal provided by cluster ion sources has greatly expanded the usefulness of imaging ToF-SIMS, the resulting higher secondary ion yields have exacerbated problems associated with detector saturation, resulting in significant image artifacts. An example of these artifacts can be seen in Fig. 1, which shows MAF analysis of a negative ion image from a HeLa cell.^[8] MAF factor 2 scores and the corresponding inverted factor loadings are shown. The inverted factor loadings reveal an anti-correlation between the PO_3^- peak and the other phosphate peaks. Because these peaks all arise from the same chemical moiety, the image features associated with the anti-correlation of these peaks can only be the result of detector non-linearity arising from dead-time effects.

Because ion generation is very well described by Poisson statistics, it is possible to correct for this dead-time effect on uniform samples with very high accuracy at over 95% detector saturation^[9] using Eqn (1), proposed by Stephan et al.^[10]

$$I_c = N \ln \left(1 - \frac{I_m}{N} \right) \quad (1)$$

where I_c is the corrected intensity, I_m is the measured intensity and N is the number of primary ion pulses. Making this correction on images, however, can be problematic because the low number of pulses per pixel results in large statistical errors. In fact, in many cases, the correction will result in an infinite corrected intensity because of the high probability that the measured intensity will be equal to the number of pulses per pixel (100% saturation) for at least some pixels. The fewer pulses/pixel that are used in acquiring the image, the greater this problem will be, as is illustrated in Fig. 2. The curve shows the point at which there is a 50% probability of having at least one fully saturated pixel in a 256×256 pixel image, as a function of the percent detector saturation and the number of pulses per pixel. Below this curve, one should expect that some pixels will be fully saturated, and thus some modification will be needed to Eqn (1) in order to correct for detector dead time. Note that for less than 20 pulses per pixel, a common case when imaging, one should expect some fully saturated pixels even when the average percent saturation is below 50%. The number of pulses per pixel required to avoid full saturation increases rapidly with the average percent saturation and reaches into the hundreds for a very high percentage saturation. This presents something of a conundrum for the analyst. High count rates are desirable to reduce the image acquisition time necessary to obtain satisfactory signal to noise. However, the high count rates also result in a higher percent detector dead time that will require longer acquisition times in order to eliminate fully saturated pixels. To resolve this problem, a reliable method is needed to correct for dead time in the presence of fully saturated pixels. In this paper, we consider three different approaches to dealing with fully saturated pixels in ToF-SIMS images and compare their efficacy under different conditions.

Experimental

Synthetic 256×256 pixel images with varying levels of detector saturation, number of pulses per pixel and feature size were generated using a binomial random number generator. The images consisted of two chemical species arranged in a checkerboard pattern on the surface. The size of the squares was varied from 2 pixels to 128 pixels. Superimposed on this checkerboard pattern was a pattern in which the total ion intensity was intended to mimic a topographic effect. On the right half of each square, the total ion intensity was double that on the left half of each square. A sample pair of the chemical and topographical images used is shown in Fig. 3. Two chemical cases were considered: a case where there was a very high degree of similarity between the spectra from the two species ($R^2 = 0.93$) and a case where the spectra for the two species were highly dissimilar ($R^2 = -0.05$).

Three different approaches to correcting for dead-time effects were considered. Method 1 utilized image binning. In this approach, it is assumed that the true detector saturation can be estimated for each peak at each pixel by binning over an $n \times n$ area surrounding that pixel. Every peak at a given pixel is then scaled by the percent correction calculated for the surrounding $n \times n$ region. The size of the bin, n , is selected to be the smallest possible number required to eliminate all fully saturated pixels. Method 2 was an image segmentation approach. A combination of MAF and a mixture model were used to segment the image into regions that were most similar in terms of both chemistry and total ion yield. A percent correction was calculated for each peak from the combined spectra from a region, and then each pixel within the region was scaled by that percent. The final approach was a statistical approach suggested by Keenan *et al.*,^[11] in which the measured intensity I_m for all fully saturated pixels is modified based on knowledge of the binomial distribution. All three approaches were compared based on two criteria: first, their ability to recover the correct peak ratios in the region with the highest total ion intensity (i.e. highest dead-time error), and second, their ability to eliminate the dead-time artifacts observed in multivariate analysis.

Results

Figure 4 shows the accuracy of each of the methods for recovering the correct ion intensity ratios, as a function of the number of pulses per pixel, for a case with 90% detector saturation and highly dissimilar spectra. The black line is the true intensity ratio. Method 1 (the binning approach) is able to recover accurate intensity ratios when the size of the image features is much greater than the size of the bins, but becomes increasingly inaccurate for small feature sizes. Its accuracy is also worse for a low number of pulses per pixel because a larger bin size is required. Method 2 (segmentation) is able to recover the accurate intensity ratios, regardless of feature size and nearly independent of the number of pulses per pixel. Method 3 (statistical) under-corrects when the number of pulses per pixel is low, and thus the number of fully saturated pixels is high. It then over-corrects when the number of pulses per pixel is high enough that there are few fully saturated pixels. Trends for methods 1 and 2 are nearly identical in the case where the spectra are highly similar, but method 3 performs worse for highly similar spectra. At lower levels of detector saturation, there is improvement in the recovered intensity ratios with all three methods. The segmentation method (Method 2) remains very stable up to 99% detector saturation, but further investigation is needed to determine the sensitivity of this approach to inaccuracies in the image segmentation. With the other two methods (binning and statistical), there is significant deterioration at high saturation and low pulses per pixel.

Figure 5 shows the results of MAF analysis of synthetic images with 90% detector saturation for the highest peaks, 64 pixel squares and highly similar spectra. The true

chemical and topographic features are those shown in Fig. 3. Similar results are observed for the dissimilar spectra and different feature sizes. MAF results are shown because they are insensitive to scaling, but very similar effects were obtained with PCA and MCR if optimal scaling was employed. In all cases, MAF factor 1 shows the variation in total ion yield, and MAF factor 2 highlights the chemical variation. In the absence of detector dead time, these would be the only features identified by MAF analysis. Without any dead-time correction, an artifact is clearly visible in MAF factor 3. If 100 pulses per pixel are used, there are no fully saturated pixels, and it is possible to correct for dead time directly using Eqn (1). Using this unmodified pixel-by-pixel correction, the artifact disappears from MAF factor 3, and the correct peak ratios are recovered. If only 20 pulses per pixel are used, approximately 10% of the values are fully saturated, and it is necessary to apply one of the modified methods. The artifact is no longer detectable in MAF factor 3 when either the binning method or the segmentation method is used, but the artifact is still clearly visible when the statistical method is used. It should be noted, however, that when using the binning method at higher degrees of saturation, where a larger bin size is required, a second artifact appears along the edges of the features, and there can be smoothing of image features.

Conclusions and recommendations

Three methods have been evaluated for correcting ToF-SIMS images for dead-time effects: pixel binning, image segmentation and a binomial statistical approach. In cases where there are no fully saturated pixels, it is preferable to correct for dead time directly pixel by pixel. Since this is not possible when there are fully saturated pixels, an alternative must be used. All three of the methods investigated in this paper work satisfactorily when there are very few fully saturated data points. The statistical approach is very attractive because of the simplicity of implementation, but unfortunately it works poorly whenever there are a large number of fully saturated pixels. The binning approach is also relatively easy to implement, but is only recommended when the bin size required is much smaller than the image features. The segmentation approach provides the most accurate answers under all conditions investigated but is difficult to implement, as it requires an accurate image segmentation algorithm.

It is recommended that images be collected using a combination of number of pulses and percent saturation that does not fall far below the line shown in Fig. 2, such that there are few fully saturated pixels. In these cases, Keenan's statistical correction is recommended. Since it is sometimes impractical to operate in this range, particularly when doing 3-D images or when a large dynamic range is required for detecting all species of interest, the binning and segmentation approaches are then recommended. Binning will be adequate when the feature size is much larger than the required bin, but for smaller features image segmentation is required to eliminate the dead-time artifacts.

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Figure 1.

The MAF factor 2 output, for a negative ion image of HeLa cells, shows an artifact of detector dead time. The Inv. Loadings show a chemically nonsensical anti-correlation between the PO_3^- peak and the other phosphate peaks.

Figure 2.

This graph shows the relationship between the average percent detector saturation and the number of pulses per pixel required to eliminate having fully saturated pixels. In the region below the line, there is greater than 50% probability of having at least one fully saturated pixel, which would prevent use of the standard Poisson correction formula.

Figure 3.
Example pair of topographic (right) and chemical (left) patterns used to generate the synthetic data.

Figure 4.

Recovered peak ratios for images with 90% saturation. Results from the binning method are dependent on feature size so values are shown for 4 pixel (blue), 32 pixel (green) and 128 pixel (red) features. The results for the statistical method (cyan) and segmentation method (circles) are independent of feature size. The true ratio is shown in black.

Figure 5. MAF results for 90% saturation images with each correction approach. A dead-time artifact is clearly visible in MAF 3 for both the uncorrected data and the data corrected using the statistical approach but is absent using the other correction methods.