An efficient TOF-SIMS image analysis with spatial correlation and alternating non-negativity-constrained least squares

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ABSTRACT

Motivation: Advances in analytical instrumentation towards acquiring high resolution images of mass spectrometry constantly demand efficient approaches for data analysis. This is particularly true of time-of-flight secondary ion mass spectrometry (TOF-SIMS) imaging where recent advances enable acquisition of high resolution data in multiple dimensions. In many applications the distribution of different species from a sampled surface is spatially continuous in nature and a model which incorporates the spatial correlation across the surface would be preferable to estimations at discrete spatial locations. A key challenge here is the capability to analyse the high resolution multidimensional data to extract relevant information reliably and efficiently.

Results: We propose a framework based on alternating non-negativity-constrained least squares which accounts for the spatial correlation across the sample surface. The proposed method also decouples the computational complexity of the estimation procedure from the image resolution, which significantly reduces the processing time. We evaluate the performance of the algorithm with biochemical image data sets generated from mixture of metabolites.

Supplementary information: Supplementary materials are available at Bioinformatics online.

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1 INTRODUCTION

Imaging mass spectrometry (IMS) is an increasingly popular approach in characterisation of biological samples Alexandrov and Kobarg (2011); Alexandrov and Bartels (2013). It is a powerful tool to image surface structure with a mass spectrum measured at each pixel. One IMS technique is Time-of-flight secondary ion mass spectrometry (TOF-SIMS) with applications in areas as varied as hair care Kempson and Skinner (2005), medical implants Vionnery et al. (2002) and drug delivery systems Belu et al. (2000). It is primarily applied in monitoring the distribution of targeted chemical species, but can also be employed for imaging surfaces in non-targeted analyses. When surface compositions are not well defined, in particular in the analysis of biological systems, the presence of negative peaks in the spectrum computed using PCA or MAF makes it more difficult to interpret the resulting factorisation. MCR optimised by alternating least squares (MCR-ALS) Esteban et al. (2000); Garrido et al. (2008), overcomes this problem by imposing a non-negativity constraint in an iterative optimisation process Lawson and Hanson (1974); Park (2007). However, these methods can be computationally expensive when applied to large three-way data sets. The fast combinatorial non-negativity-constrained least squares (FC-NNLS) algorithm Van Bentham and Keenan (2004) is specifically designed to handle such data sets, allowing for significant gains in the speed and computational demands of the optimisation process in ALS applications.

Despite a substantial performance increase in FC-NNLS, the estimation of loadings and scores when decomposing large ToF-SIMS data in an MCR-ALS algorithm can still be problematic. One limitation is that the complexity of the scores estimation is coupled with the number of image pixels. Therefore, an increase in the image resolution of the sample surface leads to increases in the uncertainty and computational demands of the scores and loadings.

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estimates. This is becoming increasingly important as sophisticated TOF-SIMS images with higher spatial resolution are becoming more widespread Hanrieder et al. (2013); Kubicke et al. (2014). Even for a currently typical ToF-SIMS data set with 128 × 128 pixels and a spectral mass-range up to 1000 Da, the implementation of ALS algorithm with three spectral basis functions contains the estimation of 128 × 128 × 3 values in the scores estimation step. This emphasises the benefit of decoupling the number of pixels in images and the number of parameters. In addition the progress towards acquisition of image data in voxels as opposed to pixels confers further demand on the analysis time and efficiency of data processing Fletcher et al. (2007); Fletcher and Vickerman (2012).

Additionally, in cases where the spatial distribution of compounds in an image is continuous such as chemical samples or samples from a biological cell or a cellular environment, the characteristics at proximate/distant regions on the surface are expected to be highly/weakly correlated. This requires the inclusion of the spatial correlation across the surface in the estimation of scores and loadings from TOF-SIMS data.

We propose an approach to MCR-ALS that incorporates a continuous-over-space formulation which accounts for spatial correlation across the sample surface. Additionally, the algorithm does not couple the complexity of the estimation procedure to the resolution of TOF-SIMS images, resulting in a significant reduction in the processing time. We exploit the method of a basis function decomposition of scores images which simplifies the estimation of individual pixel values into a set of weights. These weights scale the continuous basis functions and lie in a significantly lower dimensional space. We set out to examine the algorithm with biochemically relevant model image data sets that were generated from simple mixture of metabolites, as an example.

2 METHODS

2.1 Datasets description

Three metabolites, tyrosine, phenylalanine and citric acid (all from Sigma Aldrich, UK) were used in the study. The metabolites were spotted on hexamethyldisilazane (HMDs) (Sigma Aldrich, UK) coated silicon wafers (Compart Technology, UK), prepared as detailed elsewhere Salim et al. (2012). A focused spot of the sample (individual metabolites or metabolite mixture) was obtained, each spot containing about 125 pmoles of the metabolite.

ToF-SIMS negative ion spectra and images were obtained using a SIMS V instrument (ION-TOF Inc., Germany). 50 keV Bi$^{+}$ was used as the primary ion source for the high current, bunched mode spectral acquisition, with a target current of 0.11 pA and 500 nm$^2$ field of view. The images collected contained 128 × 128 pixels. The vacuum in the analytical chamber was held at 10$^{-9}$ mbar. Primary ion dose was kept below the static limit of 500 pA and 500 pA per pixel. The TOF-SIMS measurement is factored into a p × m matrix, W($\cdot$), and a v × m loadings matrix, B($\cdot$), comprising of m spectral basis vectors.

2.2 MCR model

The spatio-spectral TOF-SIMS data matrix can be described by the bilinear MCR model

$$Y(f, s) = W(s)B^T(f) + E(f, s),$$

where f denotes the mass-to-charge ratio and s is the spatial location in the two dimensional physical surface. The superscript T denotes the transpose operator. Each TOF-SIMS image with the dimension of l pixels by l$^2$ pixels is reshaped to form a column of the p × v data matrix, Y($\cdot$), where p = l × l$^2$. The TOF-SIMS measurement is factored into a p × m matrix scores, W($\cdot$), and a v × m loadings matrix, B($\cdot$), comprising of m spectral basis vectors.

2.3 Estimation algorithm

A solution to the MCR model given in Equation (1) can be obtained by minimising the following cost function

$$J(W, B) = \|Y - WB^T\|^2_F,$$

where $\| \cdot \|$ denotes the Frobenius norm. This optimisation problem can be solved using the ALS algorithm Paatero and Tapper (1994). When initialised, at each iteration the estimated scores are used to update the loadings. The resulting estimates of the loadings are then used when estimating new scores for the next iteration. The procedure stops when the convergence is achieved. The ALS algorithm is often combined with a non-negativity-constrained least squares to provide chemically meaningful solutions. In this case the cost function (3) becomes

$$J(W, B) = \|Y - WB^T\|^2_F \text{ s.t. } W, B > 0$$

where $W, B > 0$ indicates that all the elements of W and B are non-negative. Here we use the FC-NNLS algorithm with ALS Van Bentham and Keenan (2004) which efficiently solves the non-negativity-constrained least squares problem.

The knowledge of the system’s rank or the number of spectral basis vectors, m, is required prior to the ALS algorithm. Here we use PCA and the screene test criterion as a guide to determine the number of spectral basis vectors. There are more sophisticated techniques that incorporate smoothing methods or subspace comparisons, in order to reduce the effect of measurement noise in the system’s rank identification Jiang et al. (2004).

The stopping rule adopted is based on observing the Frobenius norms of the successive estimates of W matrices in Equation (4), i.e.,

$$\|W_k\|_F - \|W_{k-1}\|_F < \rho,$$

where $\rho$ is a threshold value.

2.4 Model decomposition

To facilitate the estimation procedure we use a decomposition using a finite set of continuous basis functions to represent scores images. The proposed model accounts for the spatial correlation across the sample surface. This is preferable to estimations at discrete spatial locations where the distribution of species in the surface is continuous in nature. The decomposition is described by

$$w_i(s_p) \approx \sum_{j=1}^{n} \alpha_{ij}\phi_j(s_p)$$

where $\alpha_{ij}$ are the mixing coefficients.
where $\phi(\cdot)$ are known basis functions scaled by unknown weights, $\alpha_{ji}$, and $n$ is the number of basis functions used to perform the decomposition. The basis functions used here are two dimensional Gaussian functions given by

$$\phi(s) = \exp\left(-\frac{(s - \mu_s)\cdot(s - \mu_s)}{2\sigma_s^2}\right),$$  

(7)

where $\sigma_s$ and $\mu_s$ are the basis function width and centre respectively. These are standard basis functions often used to approximate continuous fields from sampled observations Park and Sandberg (1991). They satisfy all the required conditions for reconstruction functions Scerri et al. (2009) and have advantageous characteristics: (i) semi-compact support; (ii) dimensionally factorizable, allowing efficient computation in higher dimension; (iii) a closed form Fourier transform which is also Gaussian Sanner and Slotine (1992). The latter facilitates the determination of the width of the basis functions using spatial frequency analysis described in the following section.

Substituting Equation (6) into Equation (2) we obtain a continuous approximation which can be evaluated at $f = f_s$ and $s = s_p$ as

$$Y(f_s, s_p) = \sum_{i=1}^{m} \sum_{j=1}^{n} \alpha_{ji} \phi_j(s_p) \delta_i(f_s) + E(f_s, s_p).$$

(8)

This formulation accounts for spatial correlation across the sample surface via sum of weighted Gaussian basis functions. This can be written in a compact form

$$Y = \Phi AB^T + E,$$

(9)

where $A$ is an unknown $n \times m$ weight matrix and $\Phi$ is a constant $p \times n$ matrix given by

$$\Phi = \begin{bmatrix} \phi_1(s_1) & \phi_2(s_1) & \phi_3(s_1) & \cdots & \phi_n(s_1) \\ \phi_1(s_2) & \phi_2(s_2) & \phi_3(s_2) & \cdots & \phi_n(s_2) \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \phi_1(s_p) & \phi_2(s_p) & \phi_3(s_p) & \cdots & \phi_n(s_p) \end{bmatrix}_{p \times n}.$$  

(10)

This representation allows for a more efficient implementation of the ALS algorithm. The complexity of the scores estimation step in the optimisation problem given in Equation (4) is directly linked to the resolution of TOF-SIMS images, limiting the applicability of the ALS algorithm to big data sets. However, in Equation (9) the scores matrix is decomposed into two parts: an unknown weight matrix $A_{n \times m}$, and a constant matrix $\Phi_{p \times n}$ depending only on basis functions. Therefore, the estimation problem of the scores matrix is simplified to the estimation of a matrix of weights with a significantly lower dimension. Similarly, the decomposition also simplifies the estimation of loadings matrix. This leads to decreases in uncertainty in the scores and loadings estimates and also improvement in the convergence property of the algorithm. An example of the decomposition of a score image using an equally spaced grid of 9 x 9 basis functions is shown in Figure 1.

Using the basis function representation, the cost function for the estimation of loadings, $B$, becomes

$$J(A, B) = \|Y - AB^T\|_F^2 \text{ s.t. } B > 0,$$

(11)

where

$$\hat{Y} = \Phi^1 Y,$$

(12)

$$\Phi^1 = \left(\Phi^T\Phi\right)^{-1}\Phi^T$$

(13)

and $A$ is fixed. The cost function for estimating the weight matrix, $A$, is given by

$$J(A, B) = \|Y^T - B A^T\|_F^2 \text{ s.t. } A > 0,$$

(14)

where $B$ is fixed. The matrix, $\hat{Y}$, can be calculated once and stored prior to the commencement of the algorithm. Here the Frobenius norms of the successive estimates of $A$ can be monitored to stop the algorithm.

Fig. 1. Example of a basis decomposition. A 128 pixels by 128 pixels TOF-SIMS image decomposed by a 9 x 9 grid of basis functions (shown by blue circles). The centre of each basis function is shown by a green cross.

It should be noted that basis decomposition technique results into smoother estimates of scores images which might blur sharp boundaries and details. However, if high resolution scores images are required an extra step can be added to the estimation algorithm. The final estimate of $B$, obtained from the iterative optimisation of Equations (11) and (14) can be used in a single run of the FC-NNLS algorithm to minimise

$$J(W, B) = \|Y - WB^T\|_F^2 \text{ s.t. } W > 0,$$

(15)

and $B$ is fixed. This way a detailed estimate of the scores images are obtained while the loadings are still calculated from the reduced continuous representation of scores images. The complete estimation framework is given in Algorithm 1. The minimisation of Equations (11), (14) and (15) can be implemented using the Matlab m-file fcnnls provided by Van Benthem and Keenan (2004). Note, FC-NNLS uses the solution of the overwriting method Gallagher et al. (2004) to initialise the algorithm.

2.5 Spatial frequency analysis

The spatial frequency response of the ion image can be used to specify the width and spacing of the basis functions. The spatial cutoff frequency of the image, $\nu_c$, can be found by calculating its power spectral density (PSD). This can be then used to determine the distance between basis functions such that Shannon’s sampling theorem is satisfied

$$\Delta_0 \leq \frac{1}{2\nu_c},$$

(16)

where $\nu \in \mathbb{R} \geq 1$ is an oversampling parameter Sanner and Slotine (1992). The width of the basis functions is also governed by the spatial cutoff frequency of scores images. For an attenuation of 3 dB at $\nu_c$ the width of Gaussians basis functions should be set to Freestone et al. (2011)

$$\sigma_\nu = \frac{1}{\pi\nu_c} \sqrt{\ln 2 \over 2},$$

(17)

The number of basis functions can then be specified by dividing the spatial region of interest into $\Delta_0$ intervals. From reciprocal role of $\nu_c$ in Equations (16) and (17) it follows that a high cutoff frequency results into a representation which comprises a large number of basis functions with narrow widths. This results into a computationally more complex estimation procedure as a higher number of weights is required to be estimated. Therefore, a compromise should be made between the accuracy and the computational demands of the estimation algorithm. The number of basis functions can be reduced by limiting the spatial bandwidth of the approximated images to a lower value.

3 RESULTS

The proposed algorithm was first implemented on “pure” species to extract discriminatory information from the estimated scores and loadings. The extracted information were then used to perform
Algorithm 1 Scores and loadings estimation

1. Decomposition:
   - determine \( m \) using PCA.
   - define basis function centres \( \mu_j \) using Equation (16).
   - define basis function widths \( \sigma \) using Equation (17).
   - construct \( Y \) using Equations (10), (12) and (13).
2. Initialisation:
   - initialise the weight matrix, \( A_k \), as a random dense matrix.
3. scores and loadings estimation:
   - define stopping condition threshold \( \rho \).
   - set \( k = 1 \).
   - while \( \| A_k - A_{k-1} \|_F > \rho \)
     - update the loadings, \( B_{k-1} \), using FC-NNLS and Equation (11).
     - update the weight matrix, \( A_k \), using FC-NNLS and Equation (14).
     - set \( k = k + 1 \).
   - end while
   - update the loadings, \( B_k \), using FC-NNLS and Equation (11).
4. Estimation of high resolution scores matrices:
   - calculate \( W \) from Equation (15) and the final estimate of \( B \).

Peak assignment in the computed spectra of TC and TPC mixtures. During this process the spectral information was summarised into three major peaks that can differentiate different species. This information was also used to examine replicate measurements of each data set to further evaluate the performance of the algorithm. The total ion images for each data set are depicted in Supplementary Figure S1. TOF-SIMS images were mapped onto \([-1 1]\) in both \( x \) and \( y \) directions and therefore the spatial aspects of the model can be considered arbitrary. Cross-section of the spatial frequency response along the \( x \)-axis for TPC mixture is shown in Figure 2. From this figure, it can be seen that to capture the full spatial bandwidth, \( \nu_c \) should be set to a high value (\( \approx 5.5 \), shown by blue dashed line), resulting into a high number of basis functions (a grid of \( 44 \times 44 \) with \( \rho = 2 \)).

Alternatively, the configuration can be chosen to represent the reconstructed images up to a specified bandwidth to limit the number of basis functions and hence computational demand of the estimation algorithm. We set the cutoff frequency to \( \nu_c = 0.85 \), giving approximately 10 dB attenuation from the maximum power spectrum. This is shown by a red circle in Figure 2. In order to account for the slow roll-off in the frequency response of Gaussian basis functions the oversampling parameter of \( \rho = 2 \) was chosen. Using these values in Equations (16) and (17) yielded the distance between adjacent basis functions’ centres \( \Delta_\phi = 0.3 \) and the width of basis functions \( \sigma_\phi = 0.22 \). Given the spatial domain of interest a grid of \( 9 \times 9 \) equally spaced basis functions can be used to satisfy Shannon’s sampling criterion. With this arrangement the number of unknown parameters was reduced from \( m \times 16384 \) to \( m \times 81 \).

The pre-processing stage involved normalising the data to the total ion counts. This followed by Poisson-scaling Keenan and Kotula (2004) for the system’s rank analysis.

An initial guess of the number of spectral basis vectors, \( m \), for each Poisson-scaled data set was obtained using PCA and the scree test. The scree plot for the first few principal components are shown in Figure 3. The results suggested three spectral basis vectors for each of T, P and C elements and two and three spectral basis vectors for TC and TPC mixtures respectively.

The proposed algorithm was then applied on TOF-SIMS data sets to estimate loadings and the corresponding scores images. In the estimation procedure we set \( m = 3 \) for all pure and mixed species despite the suggested rank of two for TC compound in the PCA analysis. The results for scores and loadings estimation for T, P and C components are shown in Figure 4. The \( m/z \) number for dominant peaks are illustrated in the loadings plots where the inset figures show the corresponding ion images in the TOF-SIMS data set. Figure 4d shows large peaks (sorted in order of decreasing magnitudes) at \( m/z = 180.06, 121.02 \) and 71.01 for the first factor of component T. For component P, the first factor comprises of large peaks at \( m/z = 164.05, 71.01 \) and 26.01 (Figure 4f). For component C, significant peaks for the first factor are located at \( m/z = 87.02, 41.01, 111.02 \) and 191.02 (Figure 4p). As can be seen, the \([M – H]^–\) signals for each of the metabolite predominates, but fragment ion contributions also exist.

Peaks at \( m/z = 26.01 \), \( m/z = 27.98 \) and \( m/z = 136.93 \) are common between second factors and the third factors of all components. Therefore, these \( m/z \) values do not contain discriminatory information and can be considered noise in the system. In fact the corresponding scores images of the second and third factors show noisy structures. Also the peak at \( m/z = 71.01 \) presents in the first factors of T (Figure 4d) and P (Figure 4i) and cannot be used to distinguish these species. From this analysis the characteristic peak for component P can be identified as \( m/z = 164.05 \) which would be the deprotonated metabolite ion \([M – H]^–\).
Fig. 4. Scores and loadings estimates using ALS with non-negativity constraint for individual components. (a-f) scores and loadings for component T; (g-l) scores and loadings for component P; (m-r) scores and loadings for component C.
The result of the algorithm for TC mixture is illustrated in Figure 5. Similar to the previous example we associate the peak at m/z = 136.93 in Figure 5f to the existence of the noise in the system. The peak at m/z = 180.06 of the first factor in component T can be also identified in Figure 5d with its corresponding scores image illustrated in Figure 5a. The same observation can be made for the component C, where three peaks of the first factor, i.e., m/z = 41.01, 87.02 and 191.02 can be identified (see Figure 5e). The algorithm performed well in this case where both T and C species were successfully identified. The analysis suggested m/z = 180.06 and m/z = 191.02 as characteristic peaks for T and C respectively.

The results for the scores and loadings estimates for TPC mixture is depicted in Figure 6. The algorithm is able to identify all the species, T (m/z = 180.06), P (m/z = 164.05) and C (m/z = 191.02) as it is shown in Figure 6d to Figure 6f. Again the fragment ions at m/z = 41.01 and m/z = 87.02 are also present in the spectrum shown in Figure 6e. The algorithm is unable to separate the distribution of T (m/z = 180.06) and P (m/z = 164.05) as it is shown in Figure 6a. We attribute this to the peak at m/z = 71.01 which is common between T and P species, making it difficult to separate the two types. However, the algorithm can almost isolate the distribution of C component from the mixture. Note a small peak at m/z = 191.02 still exists in Figure 6d.

From the above analysis, the important peaks required to identify T, P and C components are m/z = 180.06, 164.05 and 191.02 respectively. There are also strong peaks at m/z = 121.02 and
It is shown in Figure 8. approximately 100 times faster when the reduced model is used as different number of spectral basis vectors. The computation time is (FC-NNLS) and the reduced model (Algorithm 1 with n=81) using pixel densities to compare the computation time for the full model when the reduced model is used.

The extracted information was also used to perform similar analysis on replicate images of T, P, C, TC and TPC to further examine the performance of the algorithm on discerning different species. In this case we used the correct number of spectral basis vectors, i.e., m = 1 for T, P and C data sets and m = 2 for TC data set are also provided in Supplementary Figure S.2, showing successful identification of different components in each case.

The authors thank Dr. Claire Hurley for help with the TOF-SIMS measurement. The novel and key developments of the paper include a continuous-over-space formulation which accounts for the spatial correlation across the sample surface and, decoupling the computational complexity of the estimation procedure from the number of pixels in the ion images. This results in a significant reduction in the processing time that will translate favourably when high resolution images are analysed and in the analyses of 3D images, where voxels of information require processing.

To demonstrate the new methodology the proposed algorithm was evaluated using image data from simple mixture of metabolites. Although the algorithm performed well, validating the framework on more complex test data sets is still required. Such data sets can include multiple components with similar mass spectrum but different intensities, patterned samples or images with higher pixel densities.

### ACKNOWLEDGEMENT

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<td>1.85 x 10^-3</td>
</tr>
<tr>
<td>P</td>
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<td>1.96 x 10^-3</td>
</tr>
<tr>
<td>C</td>
<td>1.70 x 10^-3</td>
<td>1.77 x 10^-3</td>
</tr>
<tr>
<td>TC</td>
<td>1.36 x 10^-3</td>
<td>1.44 x 10^-3</td>
</tr>
<tr>
<td>TPC</td>
<td>1.30 x 10^-3</td>
<td>1.38 x 10^-3</td>
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Fig. 7. Convergence of the estimation algorithm. The change in the Frobenius norm of the error, E (see Equations (1) and (9)). The full and reduced models are shown by dotted and dashed lines respectively.

Fig. 8. Computation time in seconds for one step of the algorithm. (a) full model; (b) reduced model using Algorithm 1 (n=81). In each case 1000 random images of the size $l \times l$ pixels are used.

### 4 DISCUSSION

This paper has presented a novel framework for solving the alternating non-negativity-constrained least squares using TOF-SIMS measurement. The novel and key developments of the paper include a continuous-over-space formulation which accounts for the spatial correlation across the sample surface and, decoupling the computational complexity of the estimation procedure from the number of pixels in the ion images. This results in a significant reduction in the processing time that will translate favourably when high resolution images are analysed and in the analyses of 3D images, where voxels of information require processing.

### Table 1. Model error for different experiments.

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reduced and full models were used is also shown in Figure 7. Note that for 128 pixels by 128 pixels images and m = 3, each iteration of the algorithm takes 65.3 ms for the full model. This is 7.8 ms when the reduced model is used.

We also generated images using random numbers with different pixel densities to compare the computation time for the full model (FC-NNLS) and the reduced model (Algorithm 1 with n=81) using different number of spectral basis vectors. The computation time is approximately 100 times faster when the reduced model is used as it is shown in Figure 8.