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INVITED REVIEW

Analysis of 3D elemental distribution in nanomaterials: Towards higher throughput and dose efficiency

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Abstract

Many advanced nanomaterials rely on carefully designed morphology and elemental distribution to achieve their functionalities. Among the few experimental techniques that can directly visualise the 3D elemental distribution on the nanoscale are approaches based on electron tomography in combination with energy-dispersive X-ray spectroscopy (EDXS) and electron energy loss spectroscopy (EELS). Unfortunately, these highly informative methods are severely limited by the fundamentally low signal-to-noise ratio, which makes long experimental times and high electron irradiation doses necessary to obtain reliable 3D reconstructions. Addressing these limitations has been the major research question for the development of these techniques in recent years. This short review outlines the latest progress on the methods to reduce experimental time and electron irradiation dose requirements for 3D elemental distribution analysis and gives an outlook on the development of this field in the near future.

KEYWORDS
electron microscopy, elemental analysis, tomography

1 | INTRODUCTION

With the ongoing advance of nanotechnology, there is an ever-growing interest towards nanostructures with increasing complexity: both in terms of morphology as well as the number of different compositions combined in a single material. Establishing the structure-property relationship for such materials requires advanced characterisation methods that would be able to assess the (3D) distribution of chemical elements on very small spatial scales, reaching an atomic level of detail. One of the few experimental methods that can directly visualise complex nanostructures is electron tomography, which uses transmission electron microscopy (TEM) images acquired from different directions to mathematically reconstruct the 3D structure of the imaged object. In materials science, electron tomography is typically performed using high-angle annular dark-field scanning TEM (HAADF-STEM), which minimises unwanted crystal orientation-dependent contrast in the images and enables correct reconstruction of the studied object's morphology. An additional advantage of the HAADF-STEM imaging is that it allows for recording additional signals generated by the electron probe scanned across the sample. Of special interest for materials science are energy-dispersive X-ray spectroscopy (EDXS) and electron energy loss spectroscopy (EELS) signals, which can be used to retrieve the distribution of chemical elements in the studied objects with a very high spatial resolution.[1] Notably, these techniques can be combined with the principle of tomography to assess elemental distribution in 3D. However, although EDXS and EELS tomography provide exceptionally rich information about the structure of nanomaterials – in theory allowing for identifying every atom in a given nanostructure – they are severely limited by the fundamentally low probabilities of generating characteristic X-rays and inelastic electron

scattering events. This leads to poor signal-to-noise ratio of the respective techniques, resulting in high electron irradiation doses and long experimental times required for obtaining 3D reconstructions with acceptable quality. This reason makes EDXS and EELS tomography applicable only to materials that are relatively stable against electron irradiation, such as noble metals. Moreover, experimental time limitations make these techniques unsuitable for studying dynamic processes and for high throughput applications, for example statistical analysis of the sample or quality control in industrial settings. Extending 3D elemental analysis to more electron beam sensitive materials and reducing the experimental time requirements have therefore been the main research questions in the field for the last decade. This mini-review outlines the recent progress on addressing this challenge brought by exploring new approaches for visualising elemental distribution and by improving data analysis methodology to retrieve higher quality 3D reconstructions from limited data.

2 | RECENT TRENDS AND DEVELOPMENTS

2.1 | Quantitative HAADF-STEM tomography

One of the recent lines of development in 3D elemental distribution analysis represents approaches based on HAADF-STEM imaging. In the first approximation, the HAADF-STEM signal depends on the atomic number of chemical elements in the illuminated area of the sample, which results in a so-called Z-contrast. This property is routinely used in materials science applications of TEM to differentiate components of heterogeneous materials and locate different elements in atomic resolution images of crystals. HAADF-STEM imaging offers a drastically better signal-to-noise ratio in comparison to EDXS and EELS, which makes it very attractive for high-throughput and low electron dose applications. However, quantitative analysis that would be able to retrieve the 3D distribution of the constituting chemical elements based on HAADF-STEM signal is a non-trivial task, which had not been explored in the literature until recently. This problem has been carefully analysed by van den Bos et al. who showed that because of electron diffraction effects, the HAADF-STEM signal generated by each column of atoms in a crystalline nanostructure depends both on the number and relative depth coordinates of atoms corresponding to different chemical elements.[2] In principle, this opens exciting perspectives for elemental distribution analysis, since even a single atomic resolution HAADF-STEM image can be sufficient to retrieve the 3D locations of atoms in a nanostructure. In practice, however, such analysis is complicated by the immense search space for the possible atomic configurations, where many configurations correspond to nearly identical HAADF-STEM intensities. To constrain the search space, prior knowledge about the studied object can be employed: for example, van den Bos et al. investigated the tips of Au-Ag nanorods that are known to have spherical core-shell morphology. In combination with a newly proposed 'atomic lensing' model that allowed to efficiently simulate HAADF-STEM intensities produced by atomic columns with different configurations, the authors could retrieve the number and position of Au atoms in the core, effectively reconstructing the full 3D structure for the tips of nanorods from HAADF-STEM images acquired from two directions. Furthermore, numerical experiments demonstrated that for very thin crystals (about 15 atoms thick or less for Au-Ag system) the precision of the method should be sufficient to retrieve 3D reconstruction from even a single image.

Following an alternative approach, Yang et al. assumed a simplified linear relationship between the HAADF-STEM intensity and the number of atoms corresponding to each constituting element illuminated by the electron beam.[3] With this, the 3D structure of the studied objects – Fe-Pt nanoparticles – was reconstructed from a full tilt series of 68 images acquired using a wide angular range. The position of each atom in the 3D reconstruction was determined using a Gaussian peak fitting and the individual peaks were assigned to either Fe or Pt depending on their intensity. Using numerical experiments based on physically accurate simulated HAADF-STEM images, the authors demonstrated that their approach leads to a good accuracy both in terms of the determined atom positions and their classification. The proposed method therefore provides an ultimate picture of the atomic structure of the studied object, making it invaluable for answering a range of materials science questions. However, since tens of high quality HAADF-STEM images are required for obtaining the atomically resolved 3D reconstructions, the technique still has a significant experimental time and electron dose cost.

The experimental time and electron dose requirements for retrieving the 3D elemental distribution using HAADF-STEM tomography were significantly improved in an approach reported by Skorikov et al., who focused on obtaining lower resolution reconstructions using the techniques of accelerated tilt series acquisition involving a rapid rotation of the sample holder in the microscope.[4] In absence of atomically resolved data, a continuous model for the relationship between the HAADF-STEM intensity and elemental composition was used. Hereby, the intensity of each voxel in the 3D reconstruction was assumed to be linearly proportional to the concentration of each chemical

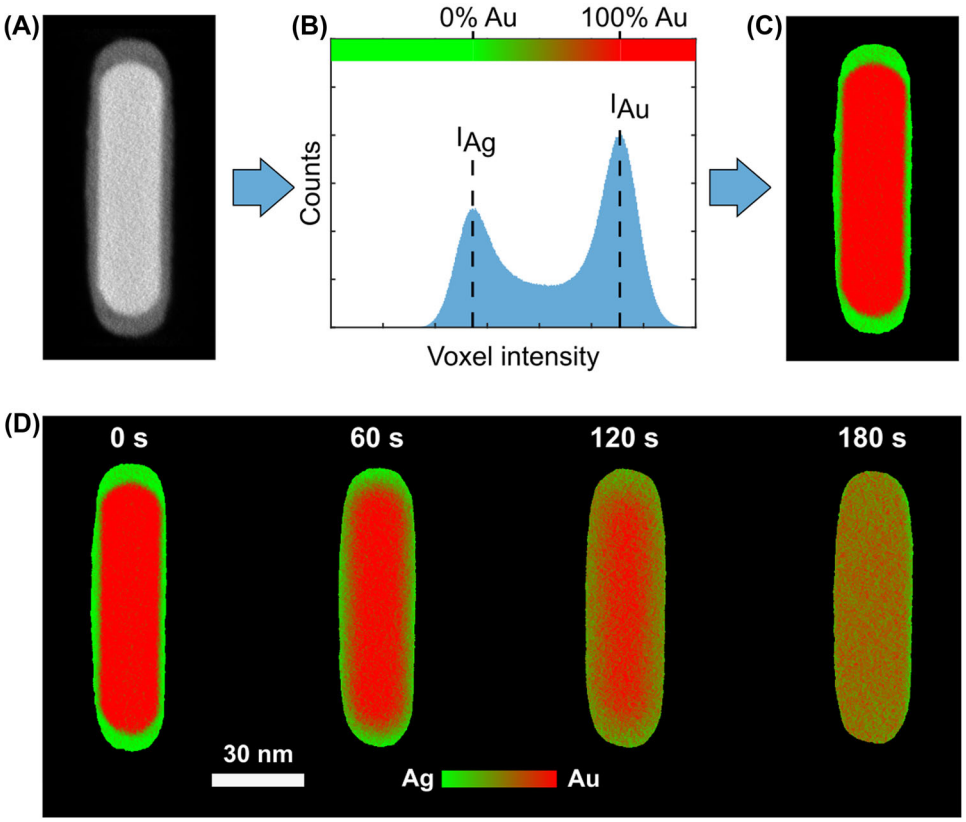

FIGURE 1 Analysis of 3D elemental distribution based on HAADF-STEM tomography. (A) Slice through a HAADF-STEM 3D reconstruction of a Au-Ag nanorod. (B) Concentrations of Au and Ag in each voxel are calculated based on the assumption that HAADF-STEM intensity is linearly proportional to the concentration of the constituting chemical elements. (C) Slice through the calculated 3D elemental distribution. (D) Slices through the 3D elemental distributions in the Au-Ag nanorod at different stages of heat-induced alloying, which were captured in situ in the electron microscope using the described method. Adapted with permission from 4. Copyright 2019 American Chemical Society

element within this voxel. When only two chemical elements can be present in any given voxel, this relationship is unambiguous, and therefore can be inverted to calculate the concentration of the respective elements at each point of the 3D reconstruction (Figure 1A–C). In combination with the accelerated tilt series acquisition technique, the proposed approach allows for retrieving the 3D elemental distribution in a nanostructure in only about 10 minutes of acquisition time, enabling studies of dynamical behaviour of heterogeneous nanomaterials (Figure 1D) and their high-throughput analysis.

One major drawback of all HAADF-STEM based methods for elemental distributions analysis remains the fact that the contrast between different elements strongly depends on the ratio between their atomic numbers. This means that it is fundamentally challenging to resolve elements with similar atomic numbers, for example Au and Pt that are commonly combined in advanced catalytic materials. In such cases, spectroscopic methods such as EDXS or EELS are indispensable.

2.2 | Multimodal tomography

A promising idea towards combining the superior ability of EDXS and EELS to resolve different chemical elements and the better signal-to-noise ratio of HAADF-STEM imaging lies in mathematically searching for a 3D reconstruction that would optimally match several imaging modalities simultaneously. One of the first applications of this concept to elemental distribution analysis was reported by Zhong et al., who used the fact that HAADF-STEM image of a thin object must equal a weighted sum of EDXS signals from each constituent element.[5] This allowed the authors to reconstruct 3D distributions of each chemical element that simultaneously fit both EDXS maps and HAADF-STEM images in the experimental tilt series. The relative importance of fitting either imaging modality was controlled by a weighting parameter, which was chosen based on the difference in noise level between the EDXS maps and HAADF-STEM images. Using simulated data for a core-shell structure, the authors demonstrated the

superior performance of the proposed method in comparison to reconstructing the 3D distribution of each chemical element separately. Furthermore, the improved signal-to-noise ratio of 3D reconstructions provided by the multimodal approach was qualitatively demonstrated on experimental data for core-shell and partially alloyed Au-Ag nanoparticles.

A different approach to connecting the HAADF-STEM and EDXS signals in the 3D reconstruction of elemental distribution consists in using an algorithm that promotes common features in the reconstructions obtained using the different modalities. To achieve this goal, Zhong et al. proposed to minimise total nuclear variation (TNV) of all reconstructed signals as an additional constraint in the reconstruction algorithm.[6] TNV forces the 3D reconstructions obtained from different signals to have common edges and intensity gradients – in this manner, these features can be transferred from the high signal-to-noise ratio HAADF-STEM reconstruction to the reconstructions of individual chemical elements obtained from EDXS signal to improve their fidelity. An additional advantage of minimising TNV is that it suppresses noise in the reconstructions by promoting piecewise-constant 3D reconstructions. This approach was further expanded by Huber et al., who replaced TNV with total generalised variation (TGV), which applies the idea of common edges to the higher order derivatives.[7] This allows for smooth reconstructions, making TGV applicable to materials exhibiting gradual variations in the distribution of constituting chemical elements. The authors tested the proposed approach on both simulated data and experimental measurements for an Al-based alloy with inclusions of Yb and Si (Figure 2), where it was shown to significantly improve the accuracy and signal-to-noise ratio of 3D reconstructions in comparison to the more conventional approaches that do not utilise the correlation between different imaging modalities or do not promote reconstruction smoothness.

The described developments in the methodology for multimodal reconstruction show that coupling HAADF-STEM with EDXS or EELS can be used to obtain 3D reconstructions that complement the strengths of the respective imaging modalities. In the future, the significantly higher signal-to-noise ratios resulting from this combination can therefore be instrumental in reducing the experimental time and electron dose required for visualising the features of interest in relevant heterogeneous nanomaterials.

2.3 | Deep learning-based approaches

One of the most promising directions for approaching the low signal-to-noise ratio problem of EDXS and EELS tomography has been brought by the advancements in the methodology of processing the experimental data. This has been underlined by the emergence of learning-based approaches for denoising and 3D reconstruction, which attempt to mathematically extract the typical features of relevant objects from a sufficiently large set of experimental or simulated data and use them as prior knowledge to improve the quality of data analysis for new experimental measurements. This contrasts with the more conventional data processing methods that rely on explicit modelling of underlying data features based on expectations about, for example, smoothness of the studied objects or the properties of experimental noise. In comparison to the classical methods, the learned approaches allow for flexibly incorporating more complex prior information about the studied objects, for example their shape, and avoid having to manually implement and tune algorithms that would optimise the result for a given quality of interest. Because of these properties, the learning-based methods – especially based on deep artificial neural networks – are having a transformative impact on data processing workflows in various scientific fields, including electron microscopy.

The strengths of the deep learning-based data denoising have recently been applied to EDXS tomography of nanoparticles by Skorikov et al.[8] In their work, the authors generated an extensive set of 3D shapes that are typically encountered in nanoparticles, for example, cubes, spheres, rods, bipyramids and platelets with randomised size, aspect ratio, rotation and smoothness. The dataset includes solid and core-shell structures with both sharp and smooth interfaces, which allows for representing the relevant variability in the typical geometric features observed in nanoparticles. The provided dataset can therefore be used for implementation and quantitative analysis of various data-driven approaches for (3D) analysis of nanoparticles, and hence has been published by the authors in open access. In the context of EDXS tomography, the authors used this dataset to simulate a large number of elemental maps and corrupted them with heavy Poisson noise characteristic of EDXS measurements obtained with low exposure times and electron doses. Next, a deep artificial neural network was trained to recover the original clean elemental maps from the simulated noisy measurements, and the denoised maps were used in combination with a classical reconstruction algorithm to obtain 3D reconstructions of elemental distribution. Using a set of simulated data that had not been exposed to the neural network during training, the authors quantitatively demonstrated that the proposed deep learning-based approach produces more accurate results both in terms of denoised elemental maps and reconstructed 3D distributions when compared to the conventional data denoising approaches used in processing EDXS data, such as Gaussian denoising and total variation minimisation. Furthermore, an analysis of

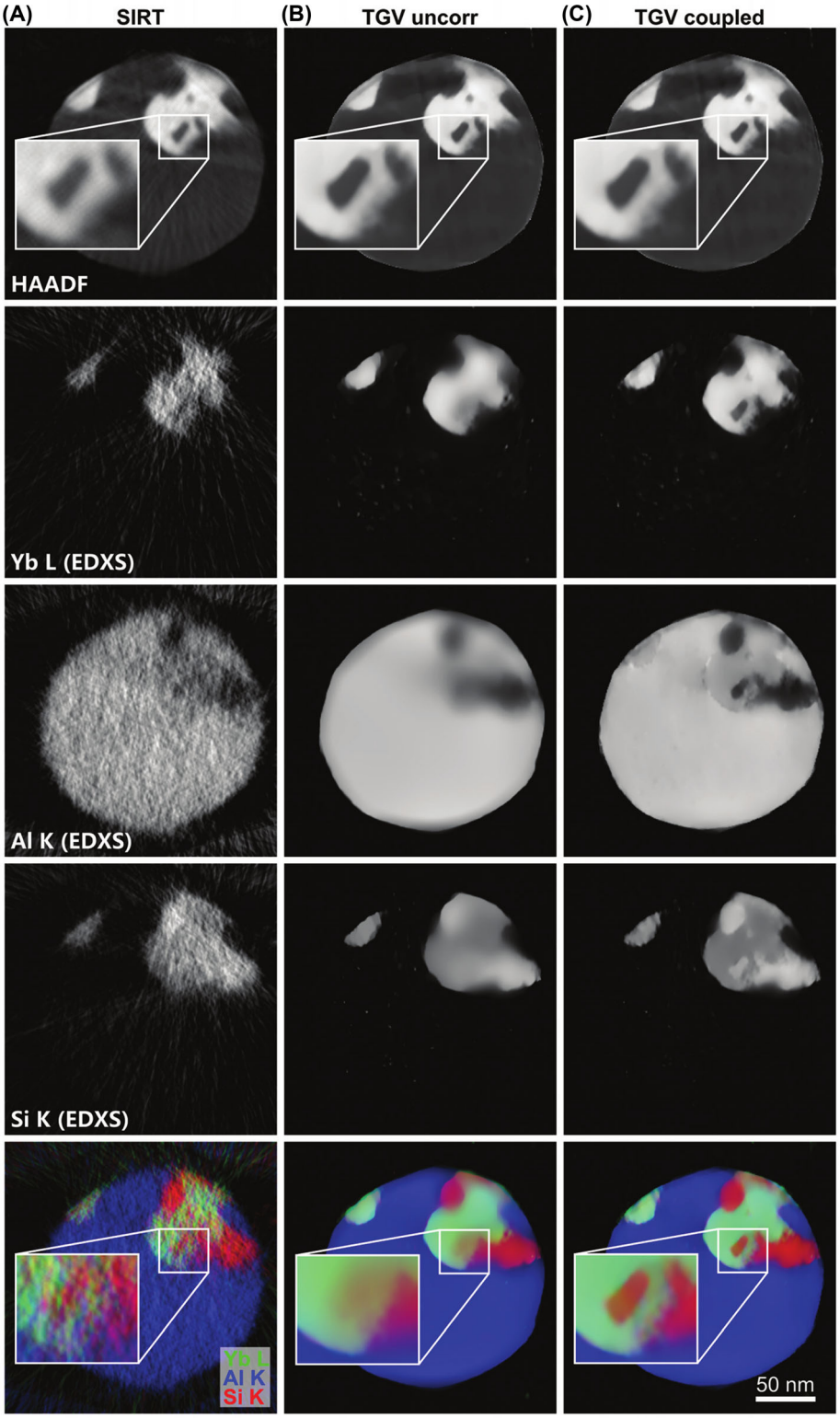

FIGURE 2 Multimodal 3D reconstruction method based on total generalised variation (TGV) minimisation applied to a specimen of Al-based alloy with inclusions of Yb and Si. (A) Slices through 3D reconstructions obtained from HAADF-STEM and EDXS signals for different elements that were calculated using simultaneous iterative reconstruction technique (SIRT) – a conventional reconstruction algorithm. (B) Slices through the reconstructions using the TGV minimisation approach that does not employ correlation between HAADF-STEM and EDX signals. Reconstruction smoothness is improved but details in the elemental distributions are insufficiently resolved. (C) Slices through the reconstructions using TGV minimisation with multimodal coupling between HAADF-STEM and EDXS signals. The additional information from HAADF-STEM helps to resolve finer details in the elemental distributions. Reprinted with permission form 6. Copyright 2019 Royal Society of Chemistry

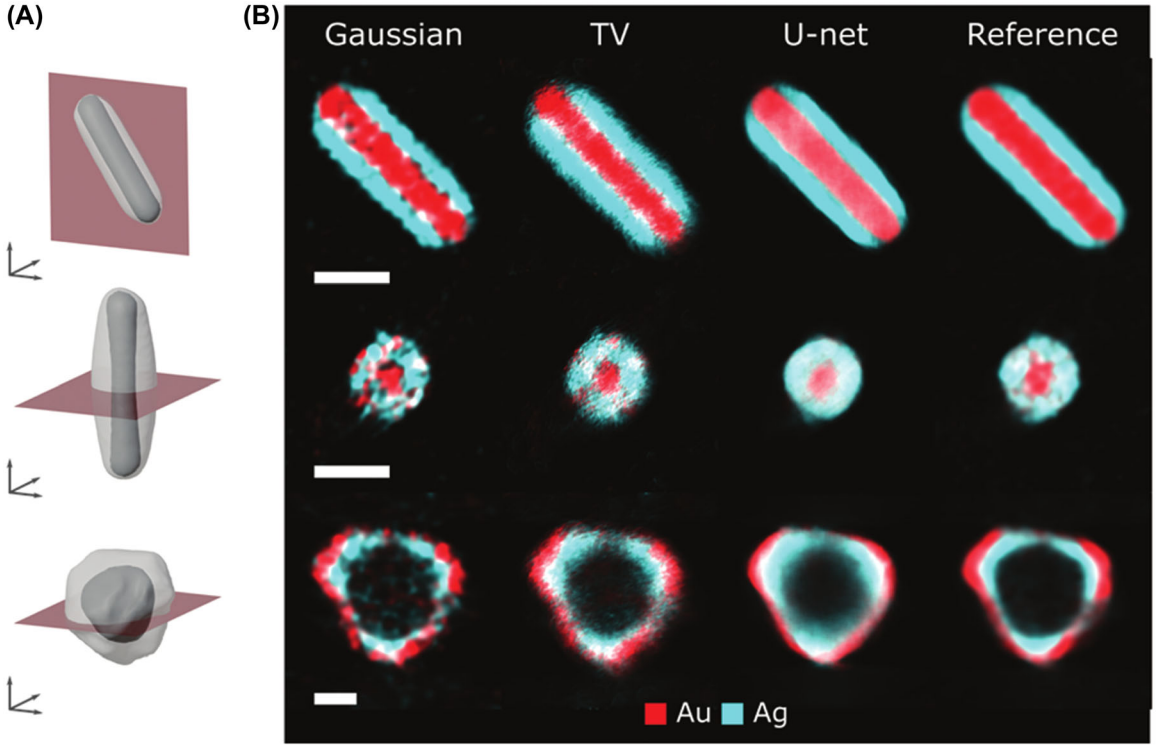

FIGURE 3 Deep learning-based denoising for improving 3D elemental distribution reconstructions from noisy data. (A) 3D visualisations of bimetallic nanoparticles used for testing the proposed method and the orientation of the depicted slices. (B) Slices through 3D reconstructions based on low exposure EDXS data denoised using conventional methods – Gaussian filtering and total variation (TV) minimisation – in comparison to the proposed deep learning-based method (U-net). The latter shows smoother distributions and a better correspondence to the reference reconstructions, which were obtained from EDXS data with about an order of magnitude longer exposure. Scale bars represent 30 nm. Reprinted with permission from 7. Copyright 2021 Royal Society of Chemistry

experimental data for Au-Ag nanoparticles with different shapes showed that the developed method allows for reconstructing 3D elemental distribution with sufficiently high quality while using EDXS measurements obtained with experimental times and electron doses that are more than an order of magnitude lower than the conventionally used values (Figure 3).

An alternative approach to training a deep learning method for EDXS tomography was proposed by Han et al. and further developed in the subsequent work by Cha et al.[9,10]. They used unsupervised learning, where instead of using pairs of noisy and clean elemental maps the neural network is trained purely on noisy experimental measurements in a manner that attempts to extract consistent features from the underlying data. The advantage of this approach is that it eliminates the need for simulating the training data, which is especially relevant for complex objects of interest that can be too challenging to representatively reproduce in a simulation. The authors applied the deep neural network-powered unsupervised learning both for denoising individual elemental maps and for synthesising projection images of nanoparticles corresponding to tilt angles not captured in the experiment. The developed approach was applied to several core-shell InP/ZnSe quantum dots, which are prone to electron beam-induced damage and therefore can withstand only moderate electron dose and exposure times during the experiment. A qualitative analysis indicated that the proposed combination of learning-based approaches resulted in a higher fidelity and fewer artefacts in the reconstructed 3D elemental distributions in comparison to various classical algorithms for denoising and tomographic reconstruction. The authors showed that the achieved qualitative improvement is instrumental for answering several relevant questions about the materials of interest, for example whether the shell of the nanoparticles completely covers the core. This study therefore illustrates that the advanced learning-based data processing methods may be the key ingredient for a successful application of EDXS tomography to beam sensitive materials.

3 | OUTLOOK

In the near future, it can be expected that the methodology for the 3D analysis of elemental distribution will continue

its development towards using lower electron irradiation doses and experimental times. On the experimental side, this will be driven by improvements in detector technology. For EDXS, the emergence and commercial availability of very large detectors covering solid angles of more than 4 sr (in comparison to about 0.7 sr typical for the detectors commonly used for EDXS tomography so far) will bring the much-needed increase in the signal collection efficiency, which directly translates into electron dose and/or experimental time reduction.[11] In EELS, the recent adoption of single-electron counting detectors will be instrumental in extracting useful information from very low exposure measurements, where the signal would typically be buried in the read-out noise of traditional CCD-based detectors.[12]

On the data analysis side, one of the most promising directions consists in the further development of deep learning-based approaches, as evidenced by their transformative effect in many other scientific fields. By developing more comprehensive and openly available datasets for training and analysing the respective methods, various advanced neural network architectures and training regimes proposed for image denoising and 3D reconstruction tasks can be explored for application in EDXS and EELS tomography. Moreover, the ideas on employing the HAADF-STEM signal in a multimodal manner to improve the quality of 3D elemental distribution analysis can be incorporated in the deep learning-based framework. Finally, learning-based approaches can be applied in the spectral domain at the stage of extracting elemental maps. Especially for EELS, where the spectral signatures of chemical elements are complex and difficult to model explicitly, learning-based approaches can make a difference in the practical applicability of this technique. In turn, addressing this problem could give a new impetus to the improvement of the methodology for EELS tomography, which received only limited attention in recent years.

The combination of advancements in instrumentation and data processing methodology has a potential to bring a wide adoption to 3D elemental distribution analysis. The main milestone for the field will be transitioning from occasional experiments on beam stable materials to a wider range of nanostructures as well as enabling dynamic and large-scale studies, where assessing elemental distribution in 3D could bring an invaluable piece of information for answering the relevant materials science questions.

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REFERENCES

1. Collins, S. M., & Midgley, P. A. (2017). Progress and opportunities in EELS and EDS tomography. *Ultramicroscopy*, *180*, 133–141.
2. Van den Bos, K. H. W., De Backer, A., Martinez, G. T., Winckelmans, N., Bals, S., Nellist, P. D., & Van Aert, S. (2016). Unscrambling mixed elements using high angle annular dark field scanning transmission electron microscopy. *Physical Review Letters*, *116*, 246101.
3. Yang, Y., Chen, C. C., Scott, M. C., Ophus, C., Xu, R., Pryor, A., Wu, L., Sun, F., Theis, W., Zhou, J., Eisenbach, M., Kent, P. R. C., Sabirianov, R. F., Zeng, H., Ercius, P., & Miao, J. (2017). Deciphering chemical order/disorder and material properties at the single-atom level. *Nature*, *542*, 75–79.
4. Skorikov, A., Albrecht, W., Bladt, E., Xie, X., Van Der Hoeven, J. E. S., Van Blaaderen, A., Van Aert, S., & Bals, S. (2019). Quantitative 3D characterization of elemental diffusion dynamics in individual ag@au nanoparticles with different shapes. *ACS Nano*, *13*, 13421–13429.
5. Zhong, Z., Goris, B., Schoenmakers, R., Bals, S., & Batenburg, K. J. (2017). A bimodal tomographic reconstruction technique combining EDS-STEM and HAADF-STEM. *Ultramicroscopy*, *174*, 35–45.
6. Zhong, Z., Palenstijn, W. J., Adler, J., & Batenburg, K. J. (2018). Tomographic reconstruction regularized by total nuclear variation joined with HAADF-STEM tomography. *Ultramicroscopy*, *191*, 34–43.
7. Huber, R., Haberfehlner, G., Holler, M., Kothleitner, G., & Bredies, K. (2019). Total generalized variation regularization for multi-modal electron tomography. *Nanoscale*, *11*, 5617–5632.
8. Skorikov, A., Heyvaert, W., Albecht, W., Pelt, D. M., & Bals, S. (2021). Deep learning-based denoising for improved dose efficiency in EDX tomography of nanoparticles. *Nanoscale*, *13*, 12242–12249.
9. Han, Y., Jang, J., Cha, E., Lee, J., Chung, H., Jeong, M., Kim, T. G., Chae, B. G., Kim, H. G., Jun, S., Hwang, S., Lee, E., & Ye, J. C. (2021). Deep learning STEM-EDX tomography of nanocrystals. *Nature Machine Intelligence*, *3*, 267–274.
10. Cha, E., Chung, H., Jang, J., Lee, J., Lee, E., & Ye, J. C. (2022). Low-dose sparse-view HAADF-STEM-EDX tomography of nanocrystals using unsupervised deep learning. *ACS Nano*, *16*(7), 10314–10326.
11. Zaluzec, N. J. (2021). Quantitative assessment and measurement of X-Ray detector performance and solid angle in the analytical electron microscope. *Microscopy and Microanalysis*, *2021*, 1–13.
12. Maigné, A., & Wolf, M. (2018). Low-dose electron energy-loss spectroscopy using electron counting direct detectors. *Microscopy*, *67*, i86–i97.

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