REVIEW

Machine Learning and Deep Learning Applications in Magnetic Particle Imaging

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In recent years, magnetic particle imaging (MPI) has emerged as a promising imaging technique depicting high sensitivity and spatial resolution. It originated in the early 2000s where it proposed a new approach to challenge the low spatial resolution achieved by using relaxometry in order to measure the magnetic fields. MPI presents 2D and 3D images with high temporal resolution, non-ionizing radiation, and optimal visual contrast due to its lack of background tissue signal. Traditionally, the images were reconstructed by the conversion of signal from the induced voltage by generating system matrix and X-space based methods. Because image reconstruction and analyses play an integral role in obtaining precise information from MPI signals, newer artificial intelligence-based methods are continuously being researched and developed upon. In this work, we summarize and review the significance and employment of machine learning and deep learning models for applications with MPI and the potential they hold for the future.

Level of Evidence: 5

Technical Efficacy: Stage 1

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In modern clinical settings, biomedical imaging plays a huge supporting role, enabling the physicians to visualize and provide precise diagnostics for a wide range of diseases and conditions. Biomedical imaging encompasses various modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, and more, generating invaluable data for medical diagnoses. Biomedical imaging has seen remarkable improvements throughout the years. With a vast plethora of available imaging modalities, like X-rays, CT, MRI, PET, and ultrasound, comes a large amount of corresponding imaging data. Image reconstruction plays a crucial role in biomedical imaging through tomographic methods by transforming raw data into visual representations. It enables the generation of detailed and accurate images, facilitating the diagnosis of medical conditions. This process enhances the effectiveness of various imaging techniques, such as CT scans and MRI, in healthcare applications.[1] Traditional methods of image processing can suffer from noise, artifacts, or low resolution due to various reasons. Fast and accurate handling of this data has necessitated the use of artificial intelligence (AI) in medical image reconstruction, processing, and analysis. AI has shown significant promise in image reconstruction and analysis and can be used to enhance the quality and interpretability of these images.[2] AI based techniques have improved the imaging process in several ways. It can help reduce noise, enhance the spatial resolution, real-time quality control, contrast enhancement, reduction of construction time, dose reduction (eg, ionizing radiations in CT and PET), and artifact reduction (implants, dental fillings, pacemakers, motion artifacts from patients) to name a few. AI techniques for medical image reconstruction largely rely on training the models on large datasets of both clean and noisy images. These trained models can then be applied to process

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newly acquired images, resulting in improved image quality and diagnostic accuracy. However, it is essential to validate and carefully integrate AI solutions in a clinical setting to ensure their safety and efficacy.

Magnetic particle imaging (MPI) is an emerging, noninvasive, radiation-free, preclinical imaging technique first reported almost 20 years ago.[3,4] MPI has shown great promise in recent years and has experienced numerous advancements.[5] This article elaborates on the different AI based image reconstruction and analysis approaches targeted towards MPI. Unlike traditional imaging methods like X-ray, MRI, or CT, MPI relies on this unique non-linear magnetic response of superparamagnetic nanoparticles to generate images. The most commonly used nanomaterial for this imaging modality is the superparamagnetic iron oxide nanoparticles (SPIONs). The working principle of MPI is based on Maxwell configuration, which involves the use of magnetic field-free points (FFPs) to generate images. In this setup, two opposing electromagnets create a field-free region/point where the SPIONs experience minimal magnetic forces. An oscillating magnetic field gradient is then applied, causing the SPIONs to align with the field thereby generating a signal detectable by the receiving coils. At this moment, SPIONs have the ability to produce a signal due to their unsaturated state. The system captures signals from multiple FFPs, enabling the reconstruction of high-resolution images based on the spatial distribution of SPIONs.[6] There are no signals that are produced in the receiver coil outside of FFR due to magnetically saturated SPIONs.[7,8] The intensity of the signal depends on the concentration of nanoparticles at each location, making it possible to differentiate tissues based on their nanoparticle content. This quantitative correlation of MPI signal intensity and nanoparticle concentration is a characteristic unique to MPI.[9,10] After the receiver coil picks up the MPI signal, the next step includes the image reconstruction. This can be achieved by using the harmonic-space MPI and X-space MPI.[11–13] Although full sized human scanners have not been available yet, researchers have been making persistent efforts to scale-up this imaging modality.[14,15] As MPI scanners have acquired recognition throughout the years, more extensive research has been conducted in attempts of improving the imaging performance and broaden the scope of its applications.[16] So far, MPI has been used for cell tracking, vascular imaging, neurodegenerative disorders, lung imaging, and cancer detection and treatment.[17–25]

MPI Image Generation: System Matrix-Based and X Space-Based

System matrix-based image reconstruction is a technique involving the use of a matrix, which represents the mathematical relationship between the acquired raw data and the desired image. The matrix incorporates information about the imaging system's geometry, characteristics, and the physical processes involved. By applying this matrix to the raw data, image reconstruction algorithms can generate a detailed image, providing a clear representation of the imaged object or tissue. The system matrix is a critical component in the image reconstruction process for MPI, which contains Fourier components that correspond to the MPI response of every point source location.[26,27] The system matrix relates the spatial distribution of SPIONs within the imaging region to the measurements acquired by MPI detectors. Therefore, precharacterization of SPIONs becomes essential for accurately reconstructing the SPIONs distribution from the acquired data. It also establishes the relationship between the SPIONs distribution and the acquired MPI signal. It describes how the spatial positions of SPIONs affect the measurements obtained by MPI detectors (Fig. 1).[12] The dimensions of the system matrix correspond to the number of detectors and the number of spatial positions (voxels) within the imaging region. In practical terms, this matrix is typically quite large and sparse, given that there are many voxels and detectors involved in MPI imaging.[28] Building the system matrix is a computationally intensive process as it requires the placement of the nanoparticle probe to different spatial positions in the field of view the magnetic field which is then used to populate the matrix based on the detector measurements for each spatial position.[29] The output of the reconstruction process is a high-resolution 2D or 3D image that represents the spatial distribution of SPIONs within the imaged region. Accurate reconstruction relies on calibration of the system matrix, which includes accounting for the system's geometry, sensitivity, and the properties of the SPIONs. A major drawback of system matrix-based image reconstruction is its computational complexity and memory requirements. Constructing and manipulating the system matrix can be resource-intensive, especially for large and high-resolution datasets. This complexity may lead to increased processing times and demands on computational resources, limiting its the real-time applicability. Additionally, inaccuracies in the modeling of the system matrix can introduce artifacts or errors in the reconstructed images, affecting the overall reliability of the reconstruction process.

In contrast, there also exists a concept of hybrid system matrix. Hybrid system matrix-based image reconstruction combines elements of system matrix-based reconstruction with other methodologies (like magnetic particle spectrometer) to improve imaging accuracy. It typically involves integrating information from multiple imaging modalities or employing hybrid imaging systems. By incorporating data from various sources or using hybrid systems that capture complementary information, this approach aims to enhance the reconstruction process.[30] This fusion of techniques can lead to more detailed and comprehensive images, particularly in scenarios where the strengths of different imaging modalities can be leveraged for a more robust reconstruction.

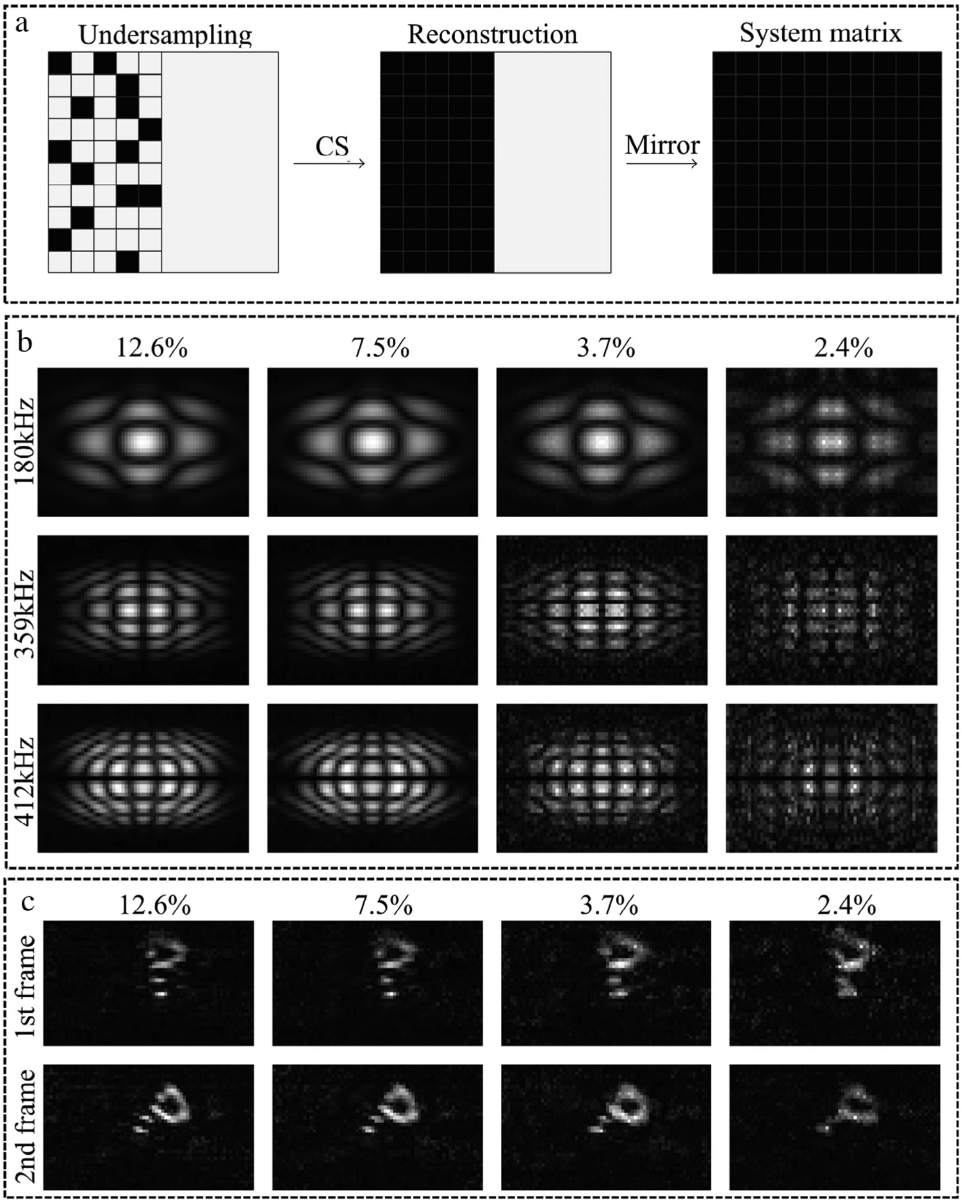

FIGURE 1: (a) The principle of the CS-symmetry method: the first half of the SM is recovered based on the CS method. Then, the complete SM is recovered based on mirror symmetry (alternatively, by changing the order of the two steps, symmetry-CS is permissible). (b) The SM components at different frequencies recovered with the symmetry-CS method at different sampling rates. (c) Reconstructed phantom results of the recovered SM at different sampling rates based on the symmetry-CS method, reproduced with permission from Springer Nature.[12]

X-space-based MPI image reconstruction is a fundamental approach that leverages the spatial encoding principles of MPI and the mathematical relationships between nanoparticle distribution and detected signal. In MPI, the concept of "X-space" is an important framework for image reconstruction. It is a mathematical representation used to describe the spatial distribution of SPIONs and their response to the MPI measurement process. It typically refers to a three-dimensional Cartesian grid that covers the entire imaging volume. The system model in X-space relates the measured MPI signal to the nanoparticle distribution within the imaging region. It describes how the spatial positions of nanoparticles affect the measurements obtained by the MPI detectors. Unlike system matrix-based approach, X-space allows the generation of a native MPI image without requiring precharacterization of nanoparticles.[31] MPI utilizes spatial encoding, such as magnetic field gradients, to encode the position of nanoparticles within the imaging volume. This spatial encoding is described in X-space, where each voxel (volume element) in the grid represents a potential position for tracer particles.[32] Langevin equation provides a directly proportional relationship of the field required to saturate a single magnetic nanoparticle with the nanoparticle's volume. MPI detectors capture the signals emitted by the SPIONs, often referred to as the "k-space data," which serve as the input data for the image reconstruction process. The data is typically transformed from the time domain to the frequency (k-space) domain before reconstruction. X-space method holds advantages over harmonic space due to its proven linearity and shift invariance (LSI).[31] LSI systems ensure that there is a linear relationship between the pixel intensity in the image and the quality of the tracer at those pixels. This allows for better accuracy and can be more reliable. Overall, MPI X-space relies on three hypotheses: 1) The uniqueness of FFP, which refers to the region where the static magnetic field is zero. Here, it is assumed that the position of the FFP is unique at all times, 2) Adiabatic Langevin model. It is assumed that the magnetic particles align adiabatically with the applied magnetic field, and 3) Recovery from loss of low-frequency information. The issue of low-frequency signal loss is not new to X-space MPI since the system matrix experiences it as well; however, it is recoverable through resilient signal signaling techniques.[11,31,33] Ongoing research aims to further improve reconstruction techniques and optimize the use of regularization for better image quality and accuracy.

AI Methods in Biomedical Imaging

Various AI methods are increasingly being used to generate biomedical images, improving the speed, quality, and efficiency of the imaging processes.[34–37] These methods are particularly valuable for applications such as denoising, reconstruction, image augmentation, and even generating synthetic images for training AI models. AI can also be used to enhance the spatial resolution of medical images, such as upscaling low-resolution MRI or CT scans to higher resolution.[38–43] AI can reduce noise and artifacts in medical images, making them clearer and more diagnostically valuable. AI-based denoising methods are particularly beneficial in noisy imaging modalities like ultrasound.[44–46] In recent years, the advent of machine learning (ML), particularly its subset deep learning (DL), has significantly transformed the field of biomedical imaging.[47,48] One of the critical challenges in MPI is image reconstruction. Incorporating ML and DL techniques into MPI, has the potential to substantially enhance image resolution, accelerate data processing, and improve diagnostic accuracy.[49] These advanced algorithms have demonstrated remarkable capabilities in image analysis, interpretation, and decision support. Various DL architectures, such as convolutional neural networks (CNNs),[48,50,51] can be used for image-to-image translation tasks in the biomedical field. Conditional generative adversarial networks,[52,53] U-Net architectures,[54] and similar models can convert images from one domain to another, for example, converting 2D scans into 3D volumes. AI can generate augmented versions of real images for training DL models. Techniques like rotation, scaling, translation, and color variation can be applied to increase dataset size and model robustness.

With all the promises and encouraging results, it also has some drawbacks. AI-driven image reconstruction in biomedical imaging faces challenges such as heavy reliance on extensive, diverse datasets, potentially compromising performance for underrepresented cases. Lack of interpretability in DL models raises concerns about understanding critical decisions. Demanding computational resources hinder real-time applications and difficulties in generalization across modalities and patient demographics may limit broad applicability. Ethical and legal considerations regarding privacy and data security also pose challenges for responsible AI integration in clinical settings.

Conventional Machine Learning (CML) Approaches in Biomedical Imaging

CML is a subset of AI that focuses on the development of algorithms that learn patterns and make predictions or decisions based on data. As CML algorithms can be trained to recognize patterns, they are revolutionizing biomedical imaging by enhancing image reconstruction processes, segmenting regions of interest, and analyzing images. This further aids in disease diagnosis, and even predicts patient outcomes.[55–57] In this context, image reconstruction involves converting raw data, often acquired from imaging modalities like MRI,[58,59] CT,[60] or ultrasound,[61,62] into high-quality, diagnostically valuable images. These techniques have proven to be quite effective in this domain and are increasingly employed to learn the complex mappings between the acquired data and the desired reconstructed images. Their capability to handle large and high-dimensional datasets make them suitable for processing the vast amount of data generated by the imaging modalities. One significant advantage of CML-based image reconstruction is its ability to improve image quality while reducing acquisition times and radiation exposure, which is crucial for patient safety. It can effectively denoise images, correct artifacts, and enhance resolution, providing healthcare professionals with clearer and more informative images for diagnosis and treatment planning. Furthermore, CML allows for adaptive and patient-specific reconstruction, optimizing the process for each clinical scenario. These models can classify medical images into categories, such as healthy or diseased, based on patterns and features extracted from the images. CML algorithms can accurately delineate regions of interest within images, such as tumor boundaries, facilitating treatment planning and assessment.[63,64] CML models have been applied to detect diseases from various imaging modalities. For example, they can detect lung nodules in chest scans,[65,66] neurodegenerative disorders,[49] or abnormalities in mammograms.[67]

CML APPROACHES IN MPI. CML is helping MPI make significant strides by transforming its image reconstruction and analysis processes. These models are particularly adept at learning the intricate relationships between raw MPI measurements and the spatial distribution of nanoparticles.[68,69] They cannot only contribute to artifact reduction, improve image quality and spatial resolution, and expedite reconstruction times but also play a crucial role in segmenting MPI images and quantifying nanoparticle distribution within tissues (Fig. 2).[70] Accurate segmentation allows for precise measurements and analysis of nanoparticle concentrations, which can aid in disease characterization and treatment planning. While this approach employs unsupervised ML for segmentation and subsequent iron quantification, it achieved excellent performance of *K-means*++ based model on segmentation and quantification analysis of MPI data.

The results demonstrated that the *K-means*++ algorithm exhibited a high degree of specificity in segmenting true signals, showing little susceptibility to signal bleeding or noise. This held true even in the presence of spatially complex signal patterns. The algorithm's accuracy, when compared to assessments by an imaging specialist, was reinforced by a high degree of inter-rater reliability across all *in vitro*, *in vivo*, and *ex vivo* models. In some instances, the algorithm exhibited fewer instances of salt noise and false positives in its region of interest (ROI) predictions, potentially enabling more accurate prediction of iron content compared to that of an imaging specialist.[70]

A method that combined deblurring and region scalable fitting (DeRSF) was proposed to determine the imaging tracer distribution. Then, a uniform erosion and scaling criterion was established based on simulation experiments to correct the segmentation results, which was further validated on phantom imaging. MPI tracer at gradient concentrations were imaged to establish the calibration curve between the MPI signal and iron mass for iron quantification in phantom and *in vivo* imaging. Three alternative MPI segmentation methods including grayscale morphological reconstruction, *k-means* clustering, and *k-means* + RSF were compared with the DeRSF method. The segmentation results of four different

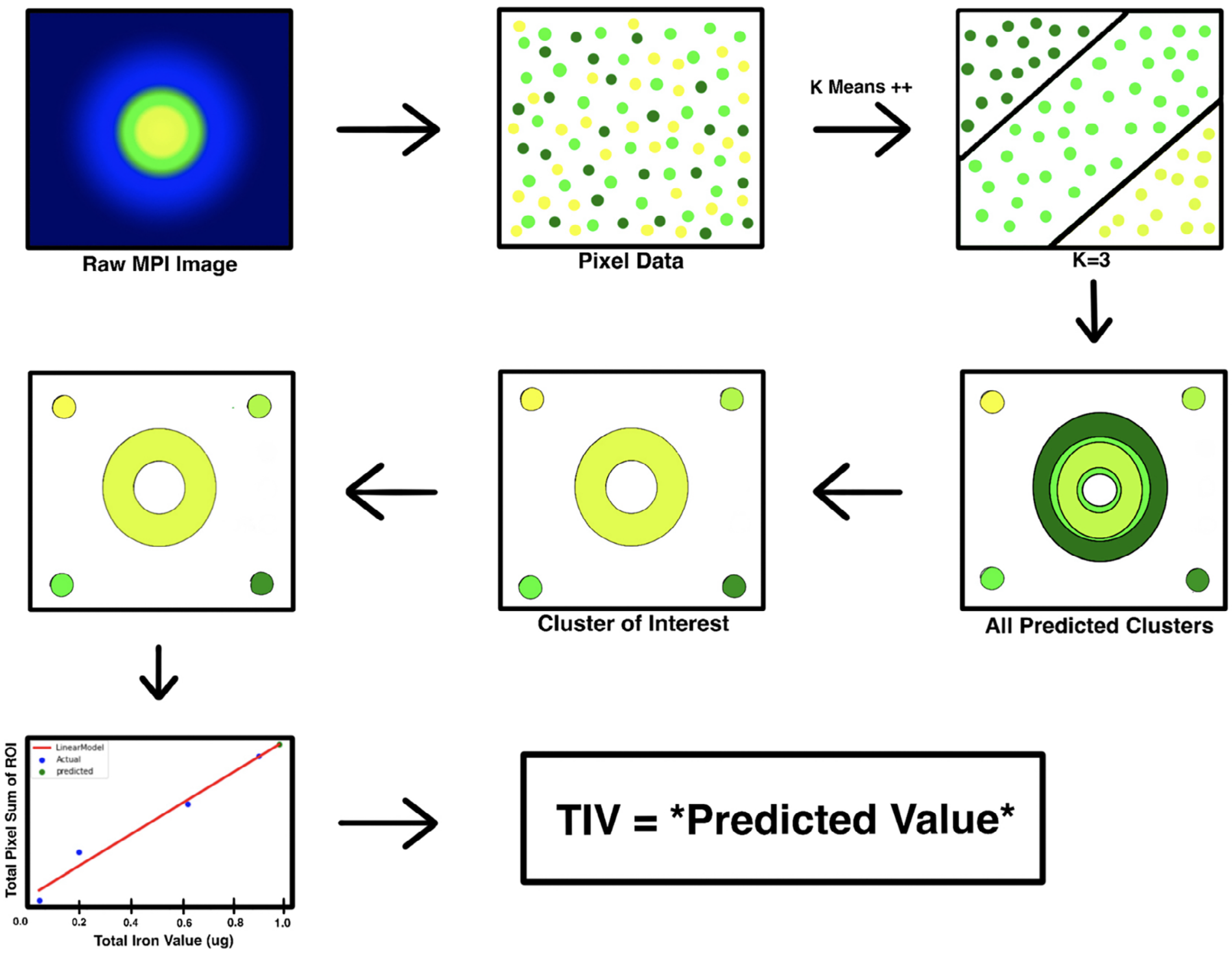

FIGURE 2: Overview of the *K-means*++ algorithm and standard curve for total iron value (TIV) prediction. Raw image of MPI is loaded into the algorithm, and a *k* value is chosen in order to cluster the data points for segmentation. The cluster of interest is then selected from the predicted clusters. A standard curve is then generated based on the total pixel sum value and corresponding total iron value of the four reference markers. This standard curve is used to estimate the unknown TIV of the segmented ROI of interest, reproduced with permission from Springer.[70]

algorithms and the ground truth images, demonstrating that the DeRSF segmented results were closer to the ground truth images. The quantitative evaluation also showed that the DeRSF had the highest dice coefficient.[71] Moreover, CML algorithms can aid in real-time reconstruction, making it instrumental in scenarios where rapid image generation is crucial.[72] These CML algorithms can also address challenges unique to MPI, such as compensating for system-specific characteristics, improving signal-to-noise ratio, avoiding ringing artifacts in MPI and providing reconstructions with sharpened edges.[72] In addition, CML can be applied to integrate MPI data with data from other imaging modalities (eg, CT, or PET).[73–77] This further enables multimodal imaging, providing complementary information for more comprehensive diagnostics.

While CML has made significant contributions to biomedical imaging, it is not without challenges and limitations. High-quality labeled data is essential for training CML models. Gathering large, diverse, and well-annotated datasets can be time-consuming and costly. Many CML models are challenging to understand about their decision-making processes. In critical medical applications, interpretability is crucial. Ensuring that CML models generalize well to diverse patient populations and imaging modalities is a complex task.

DL Approaches in Biomedical Imaging

DL is a subset of ML that leverages deep neural networks to automatically learn hierarchical features from raw data. It is well-suited for complex tasks with large datasets but often requires more computational resources and lacks the interpretability of traditional ML algorithms. The choice of DL techniques depends on the specific problem, available data, and computational resources. DL techniques are making substantial advances in the realm of biomedical imaging by revolutionizing image reconstruction processes.[78,79] Its ability to automatically learn features from data using deep neural networks is key to its prominent use. DL techniques, particularly CNNs, are proving to be exceptionally effective in enhancing image reconstruction in this context, enabling the diagnosis of diseases from medical images with high accuracy. DL algorithms can decipher complex patterns and relationships in medical image data, offering remarkable advantages in terms of denoising, artifact correction, and resolution enhancement. This integration of DL within biomedical imaging is poised to transform medical diagnostics, providing healthcare professionals with sharper, more informative images that drive better clinical decision-making and improved patient outcomes.[80] These networks are designed to learn from large datasets, enabling them to grasp intricate details and features within the acquired data. One of its most remarkable aspects for biomedical image reconstruction is its capacity to expedite imaging procedures while maintaining, or even enhancing, the quality of images. These results in a reduced burden on patients, shorter scan times, and decreased radiation exposure in the case of modalities like MRI and CT. DL models, such as U-Net and Mask region-based convolutional neural network (R-CNN), are widely used for precise image segmentation, allowing for the identification and measurement of specific structures or abnormalities. On the other hand, models like generative adversarial networks (GANs) can generate synthetic medical images, which can be used for data augmentation or simulating different scenarios.[53,81] Due to their adaptability, the DL models can also tailor reconstruction to specific clinical requirements and the unique anatomical characteristics of individual patients. This personalized approach boosts diagnostic accuracy and enables more targeted and effective treatments. As technology continues to advance, the impact of DL on biomedical imaging is only expected to grow. DL models are extensively used for medical image analysis in radiology, pathology, and dermatology. It can identify and classify anomalies in X-rays, MRIs,[82–84] CT scans,[41,85] PET,[86–88] and histopathology slides,[89–91] aiding in the detection of lung anomalies, tumors, fractures, skin diseases, and cell tracking.[92–99]

DL APPROACHES IN MPI. In context of MPI, DL plays a crucial role in enhancing the image reconstruction process, offering several advantages. Traditional reconstruction methods often face challenges in extracting clear and accurate images from the raw MPI data, which can be noisy and contain artifacts. DL models, on the other hand, excel at learning intricate patterns and relationships within this data, enabling them to generate high-quality images with greater speed and precision.[100–102] DL for MPI image reconstruction aids in denoising images, reducing artifacts, and enhancing spatial resolution.[103–105] In MPI, DL algorithms, particularly CNNs, are employed to tackle the complex task of image reconstruction due to their ability to automatically learn hierarchical features from data.[50,51,106] While the primary application of CNNs in MPI may be image reconstruction, they can also be used for other tasks such as image enhancement, artifact reduction, and feature extraction.[107] They can learn to map raw MPI data to high-quality images by capturing complex patterns and relationships in the data.[108,109] CNN-based reconstruction methods are data-driven and can enhance the quality of MPI images, especially in the presence of noise and artifacts. It enables the production of clearer and more diagnostically valuable images for medical professionals, which is crucial in various clinical applications, including cancer imaging, vascular mapping, and cell tracking.[70,110,111] Another area emerging to supplement MPI image analysis is the GANs. GANs are a type of DL model composed of a generator and a discriminator, and they are used for various tasks in MPI, including image reconstruction, and denoising. GANs can generate synthetic medical images, aiding in data augmentation and anomaly detection. They can be used to enhance the

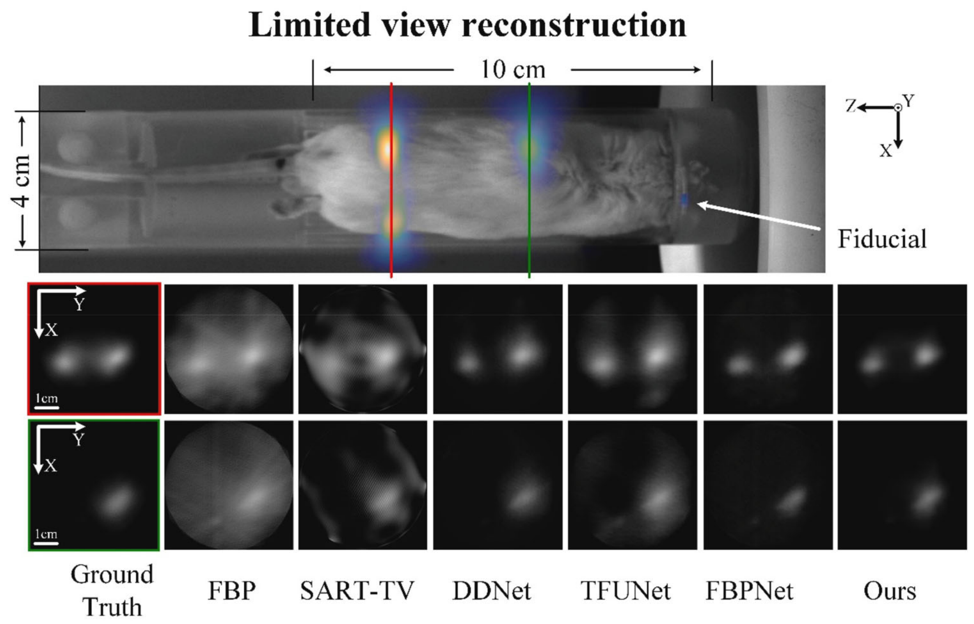

FIGURE 3: Comparison of limited view reconstruction results using *in vivo* mouse data, reproduced with permission from Elsevier.[113]

image reconstruction process in MPI too. By training a GAN on a dataset of MPI measurements and corresponding high-quality images, the generator network can learn to produce more accurate and high-resolution images from the raw MPI data. This is particularly useful for improving image quality and reducing noise and artifacts.[112] This is important in cases where MPI images are affected by noise, making it easier to interpret the results. They can also be used for quantitative analysis of MPI images by learning to estimate nanoparticle concentration and distribution in a ROI, aiding in image analyses.[71] In addition, a projection generative network was employed to obtain sparse-view projections for the reconstruction, aiming to enhance the temporal resolution of 3D imaging in projection MPI.[54] The researchers utilized simulated data for algorithm training and validation, while actual phantom and mice data were employed to assess the accuracy of the network. This approach is grounded in pretrained models for related tasks, which proves advantageous in cases where labeled data for MPI is limited. It also contributes to enhancing the model's performance with less specific training data. However, the selection of an appropriate sparse representation and robust handling of noise pose challenges. Projection MPI has the potential to greatly enhance the temporal resolution of 3D imaging when compared to traditional point-by-point scanning methods. However, the requirement for a dense view of projections in tomographic reconstruction poses limitations on optimizing temporal resolution. In the context of CT, addressing this challenge involves utilizing limited view projections (sparse view or limited angle) during reconstruction. This can be achieved by completing the limited view sinogram and employing image post-processing techniques to mitigate streaking artifacts resulting from insufficient projections. Despite significant progress made by DL algorithms in both categories, which have benefited from large-scale CT datasets, the implementation of similar methods in MPI faces hurdles due to limited data availability. To overcome this limitation, a cross-domain knowledge transfer learning strategy aims to transfer the prior knowledge of limited views learned by a CT model to MPI was proposed.[113] This novel approach helps alleviate network requirements for authentic MPI data. Additionally, the size of the imaging target influences the extent of streaking artifacts arising from inadequate projections. In response, a parallel-cascaded multi-scale attention module has been developed. This module enables the network to dynamically recognize streaking artifacts across different scales. The effectiveness of the proposed method was assessed using phantoms and *in vivo* animal models, demonstrating its superior performance compared to several alternative limited view methods (Fig. 3).[113] It is promising that these proposed methods could eliminate streaking artifacts caused by an insufficient number of projections for MPI.[113]

Overall, the application of DL in MPI is a dynamically evolving field, and the development of DL architectures and training strategies tailored to MPI is an area of ongoing research.

Despite their successes, DL models come with their own set of challenges. First, they typically require large and diverse datasets which can be scarce in medical imaging due to privacy concerns. Second, DL may not generalize well to new and diverse data across different imaging systems, patient populations, and nanoparticle types, and it can be sensitive to variations in image quality or acquisition protocols. Last, training these models demand substantial computational resources, which can be a barrier for widespread adoption in healthcare systems with limited infrastructure.

Conclusions and Future Directions

ML and DL models have revolutionized the field of biomedical imaging, empowering healthcare professionals with advanced tools for diagnosis, treatment planning, and patient care. As technology continues to advance and datasets grow, the potential for AI-driven healthcare solutions becomes even more promising. The integration of CML and DL techniques in MPI image reconstruction and analyses have the potential to significantly enhance the diagnostic capabilities and research potential of this cutting-edge imaging modality. These advanced algorithms can enhance image reconstruction, segmentation, and quantification, enabling better disease diagnosis and treatment planning. As the field of MPI continues to evolve and datasets grow, the amalgamation of AI-based approaches will play a vital role in advancing patient healthcare and improving decision-making. We believe in near future, these new AI tools can also facilitate remote diagnosis and monitoring, enhancing healthcare accessibility in underserved areas. However, it is essential to address challenges related to data availability, model interpretability, integration with clinical workflow, ethical considerations, and regulatory to fully harness the potential of AI in MPI. With continued research, collaboration, and responsible implementation, these technologies have the potential to reshape the future of biomedical imaging and personalized medicine.

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