Histopatolojik Görüntülerde Doğru Mitoz Tespiti için Geliştirilmiş Renk Normalleştirme Yöntemi

Enhanced Stain Normalization Method for Accurate Mitosis Detection in Histopathological Images

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***Öz*—H&E (Hematoksilen ve Eozin) boyalı görüntülerdeki mitoz, tümörün agresifliğini değerlendirmek ve doğru tanı ve tedavi için kapsamlı ve güvenilir bilgi sağlamak için önemli bir prognostik belirteçtir. Dozaj oranındaki değişkenlik ve H&E boyalarındaki farklı solma oranları histopatolojik analizde zorluklara yol açmaktadır. Boyama sürecinin standartlaştırılması ve boyamayı etkileyen faktörlerin anlaşılması leke stabilitesi, tanıda tutarlılık ve doğruluk için kritik öneme sahiptir. Bu makale, histopatolojik görüntülerde mitozu yüksek doğrulukla tespit etmek için DDPM tabanlı (Denoising Diffusion Probabilistic Models) difüzyon modeli ile geliştirilmiş bir renk normalleştirme yöntemi önermektedir. DDPM tabanlı difüzyon modelindeki zorluklardan biri, DDPM tabanlı difüzyon modellerinin yüksek çeşitlilik doğası nedeniyle modelin hematoksilen ile eozini karıştırabileceği yanlış transferdir. Bu sorunu çözmek için CD-SNMF (Color Deconvolution-Sparse Non-Negative Matrix Factorization) kullanan bir renk ayırma yöntemi önerilmiştir. Önerilen yöntemin, CCMCT (Canine Mast Cell Tumors) ve MIDOG21 (Mitosis Domain Generalization Challenge 2021) veri setleri görüntülerindeki mitozları iyi bir performansla tespit ettiği kanıtlanmıştır.**

Anahtar Sözcükler — Histopatoloji görüntüleri, H&E renk normalizasyonu, Mitoz, DDPM tabanlı difüzyon modeli, CD-SNMF.

***Abstract*—Mitosis on H&E-stained (Hematoxylin and Eosin) images is an important prognostic marker for evaluating the tumor's aggressiveness and providing comprehensive and reliable information for accurate diagnosis and treatment. The variability in dosage rate and different fading rates in H&E stains lead to challenges in histopathological analysis. Standardizing the staining process and understanding the factors that influence stain stability is critical for consistency and accuracy in diagnosis. This paper proposes an improved stain normalization method with DDPM-based (Denoising Diffusion Probabilistic Models) diffusion model to detect mitosis with high accuracy in histopathological images. One of the challenges in the DDPM-based diffusion model is incorrect transfer, where the model may confuse hematoxylin with eosin due to the high diversity nature of DDPM-based diffusion models. A stain separation method using CD-SNMF (Color Deconvolution-Sparse Non- Negative Matrix Factorization) is proposed to address this issue. This method normalizes the mitosis in images in CCMCT (Canine Mast Cell Tumors) and MIDOG21 (Mitosis Domain Generalization Challenge 2021) datasets by this stain normalization pathway with decent performance.**

Keywords — Histopathology images, H&E stain normalization, Mitosis, DDPM-based diffusion model, CD-SNMF.

I. INTRODUCTION

Histopathology images are crucial for diagnosing diseases, particularly cancer, by examining tissue samples stained with specific dyes to reveal cellular details. These images allow pathologists to analyze tissue morphology and identify cancer type and stage, which is vital for treatment planning and prognosis [1]. Mitosis, a key indicator of tumor aggressiveness, is often assessed in these images to evaluate malignancy and tumor grade. Advances in digital pathology and image analysis have improved the precision of mitosis detection, enhancing diagnostic accuracy and patient outcomes [2].

Despite being the gold standard in medical pathology the H&E staining technique lacks a standardized dosage ratio between H&E stains [3]. Additionally, the stains fade at different rates, leading to variability in H&E-stained images. Therefore, stain normalization is crucial for the deep learning (DL) analysis of digital pathology images. Various techniques, including traditional methods and autoencoders, have been employed to normalize histopathologic image staining. Conventional stain normalization methods, such as those by Macenko and Vahadane, often lead to loss of tissue structure and texture in reference images. While manual hematoxylin staining techniques are widely used and effective for histopathological analysis, they have limitations, as H&E

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staining does not reveal all tissue features and may require additional special stains. Recent advancements in digital pathology, including whole-slide imaging (WSI), offer practical applications in surgical and diagnostic pathology, as well as education. However, WSI's large size poses challenges and deep learning-based normalization methods for image patches face issues like overfitting and contrast variability between patches.

Color Deconvolution (CD) identifies the stain components in the image based on their characteristic absorption spectra. This step is critical for accurate stain separation, particularly in histopathology where stains like hematoxylin and eosin are commonly used. Sparse Nonnegative Matrix Factorization (SNMF) [4] stains are identified and applied to decompose the stained components into their pure spectral profiles. This method leverages the sparsity constraint to ensure that each stain component remains as pure as possible, reducing cross-talk between stains and improving accuracy in stain quantification. Combining the specificity of color deconvolution with the precision of SNMF enhances stain separation and normalization, thereby improving the reliability of quantitative analysis in medical imaging and pathology.

Diffusion models have become the latest leading group of deep generative models, surpassing the long-standing dominance of generative adversarial networks (GANs) in the complex field of image synthesis. They have also demonstrated potential in numerous areas, including computer vision, natural language processing, temporal data modeling, multi-modal modeling, robust machine learning, and interdisciplinary applications such as computational chemistry and medical image reconstruction. Furthermore, diffusion models are increasingly being utilized for color normalization tasks. By leveraging their ability to model the distribution of pixel intensities, these models can effectively adjust the color balance in images, ensuring consistent color representation across different datasets. This capability is particularly beneficial in fields like medical imaging, where accurate color representation is crucial for diagnosis and analysis [5].

Despite the strong generative capabilities of the DDPM, it can occasionally result in incorrect color transfers during image synthesis. To address this challenge, a CD-SNMF approach is implemented, which is widely used in digital pathology and medical imaging for stain separation and normalization. This technique effectively restricts the generative capacity of the DDPM by accurately decomposing hematoxylin and eosin stains, thus preventing erroneous color transfers during normalization. Consequently, a stain normalization approach is developed that integrates the DDPM model with the stain separation capabilities of CD-SNMF. This combined methodology enhances the model's performance in maintaining color fidelity and improving the overall quality of generated images, particularly in applications requiring precise color representation, such as medical imaging. The primary contributions of our study are:

- The primary objective is to develop an advanced stain normalization technique that integrates the DDPM with CD-SNMF. This method aims to improve the consistency and accuracy of color representation in histopathological images, ensuring that hematoxylin and eosin stains are accurately decomposed and normalized.
- Aim to enhance the detection and quantification of mitotic figures in histopathological images by utilizing the improved stain normalization approach. This involves assessing the performance of our proposed method in identifying and analyzing mitotic activity, which is crucial for accurate cancer diagnosis and prognosis.

The paper is structured as follows. Section II reviews pertinent literature. Section III describes the proposed stain normalization method. Section IV presents the results and discussion. Lastly, Section V concludes the paper and addresses the future research directions.

II. Related Works

Many studies have tried using diffusion models for stain normalization in H&E images. A summary of some existing works are presented as follows:

Khan et al. [6] developed a Specific Color Deconvolution (SCD) algorithm that uses a classification model to identify pixels of the same stain and estimate a staining vector based on these pixels. This vector is then used for non-linear color alignment with a template image. The algorithm also incorporates nuclei structure knowledge to improve stability in pixel classification. Moghadam et al. [7] used diffusion probabilistic models to generate high-quality synthetic histopathology images of brain cancer. They enhanced these models with prioritized morphology weighting and color normalization, achieving better results than GAN. Their first experiment on the TCGA dataset reported a recall of 0,8528 and a precision of 0,2573. Shrivastava et al. [8] introduced NASDM, a nuclei-aware semantic tissue generation framework utilizing conditional diffusion modeling. This approach generates high-quality, realistic histopathology images with accurate nuclei localization. NASDM demonstrates superior performance in generating colon tissue samples, surpassing existing methods on the Lizard dataset, and is effective at magnifications of 10× and 20×.

Harb et al. [9] proposed a coarse-to-fine sampling scheme to address the challenge of generating high-resolution whole slide images (WSIs). Their method begins with a low-resolution image and progressively enhances its resolution by sequentially adding fine details using a diffusion model. The model is trained on WSIs from the TCGA-BRCA dataset. Yellapragada et al. [10] introduced PathLDM, a text-conditioned Latent Diffusion Model for generating high-quality histopathology images by integrating pathology text reports. They achieved a state-of-the-art Fr´echet Inception Distance (FID) score of 7,64 on the TCGA-BRCA dataset, outperforming the closest competitor with an FID score of 0.301. Xu et al. [11] introduced ViT-DAE, a model combining Vision Transformers and diffusion autoencoders for high-quality histopathology image synthesis. It outperforms recent GAN-based and vanilla DAE methods. The model uses self-supervised learning with the DINO framework and was tested on the TCGA-CRC-DX, NCT-CRC-HE-100K, and PCam datasets. Zeng and Xu [12] introduced LDGL, a semi-supervised method for breast tissue recognition that integrates CNNs with graph convolution. By applying consistency loss to unlabeled data and employing a novel pseudo-labeling strategy, LDGL achieved an accuracy of 0,9505, precision of 0,9527, recall of 0,9505, and an F1-score of 0,95 using only 20% labeled data.

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In summary, this study addresses several gaps identified in the referenced works by enhancing the applicability, efficiency, and generalizability of histopathology image analysis methods. By extending existing approaches to handle diverse staining protocols, improving computational efficiency, and integrating various data modalities, the research aims to push the boundaries of current methods and address their limitations in practice.

III. Roposed Stain Normalization Method

In this section, firstly the existing datasets are briefly described and then the proposed method is presented.

A. Datasets

The study utilizes mitosis datasets MIDOG21 and CCMCT. MIDOG21 is a large-scale dataset designed for mitosis detection in breast cancer. It contains WSI of breast cancer tissues scanned at 40x magnification. The dataset is divided into a training set and a test set, with no overlapping cases between them. The training dataset comprises 200 WSIs, with an equitable distribution of 50 WSIs sourced from each of the four scanners utilized [13]. The CCMCT consists of 32 WSIs from canine cutaneous mast cell tumors. These images encompass various severities, including low-grade and high-grade cases. The CCMCT dataset provides complete annotations for entire slides, unlike prior datasets that only focused on smaller regions. This allows researchers to develop and test algorithms for mitosis detection on a more comprehensive scale [14].

B. Proposed Method

Firstly, the Initial Stain Matrix Estimation with CD-SNMF, and then the DDPM Diffusion Model are described, next, the proposed stain normalization method is presented and, finally, evaluation metrics are described.

Stain normalization without stain separation typically involves directly adjusting the color properties of the image to match a target standard. The hematoxylin and eosin components from H&E stained images are separated to minimize the model's excessive variability. For this aim the CD SNMF is used. It aims to decompose a matrix into two nonnegative matrices, typically representing the stain matrix and the concentration matrix. Then DDPM is trained. Additionally, Reinhard [15] and Macenko [16] are popular stain normalization techniques, and for comparison purposes, they have been applied directly to the images.

1) Initial Stain Matrix Estimation with CD-SNMF: SNMF is a variant of NMF that imposes sparsity on the factors, which is useful for decomposing images into a small number of basis components and their corresponding activations [17]. It helps in identifying the stain vectors in histopathological images. Color deconvolution uses color profiles of stains like hematoxylin or diaminobenzidine to digitally separate stains from a color image. This step can help to isolate components like nuclei or positive staining structures which can improve quantitation or other image analysis tasks like segmentation. The CD is applied to the problems with non-negative constraints of SNMF. CD-SNMF is used to separate stains in H&E images. The stain matrix (W) represents the basis stains that are mixed to form the observed image. Each column of the stain matrix corresponds to a stain or color channel. It is typically non-negative and sparse, meaning each stain's concentration is non-negative and contributes to forming the observed image. The activation matrix (H) indicates how much of each stain is present at each pixel in the image. Each column in the activation matrix corresponds to a pixel in the image, and each row corresponds to a stain. It is non-negative, indicating the amount of each stain at each pixel location. For normalizing stains, after training the DDPM model on *datasets,* a target stain matrix is generated. For each source image to be normalized, its stain matrix is first extracted.

2) DDPM Diffusion Model: A denoising diffusion probabilistic model (DDPM) [18] utilizes two Markov chains: a forward chain that introduces noise to the data, and a reverse chain that reconstructs the data from the noise. The forward chain is usually designed to convert any data distribution into a simple prior distribution, like a standard Gaussian. The reverse chain, parameterized by deep neural networks, learns to reverse the process of the forward chain. New data points are generated by first sampling a random vector from the prior distribution and then using ancestral sampling through the reverse Markov chain.

3) Proposed Stain Normalization: The experiments are conducted using two histopathological MIDOG21 and CCMCT datasets. 512 × 512 patches from the original images of datasets are created. Each image is converted from BGR to RGB color space to ensure accurate color representation for subsequent processing steps. Before applying SNMF, color deconvolution is performed. This process involves the separation of the hematoxylin and eosin stains from the image based on a predefined deconvolution matrix. The matrix, specific to H&E staining, is used to convert the image into optical density (OD) values. The image is first normalized to a float32 format and then converted to OD. The OD values are then processed using the inverse of the deconvolution matrix to isolate the H&E components. To further refine the stain separation, CD-SNMF is employed. CD-SNMF is a dimensionality reduction technique that decomposes the image into nonnegative components, which helps in identifying and isolating different stain patterns. CD-SNMF by flattening the image into a matrix of pixel values, is used to extract and visualize separate stain components to allow for a deeper understanding of the staining characteristics in the image.

To address the challenges of stain normalization and enhance image quality, the DDPM is utilized. This model operates through a forward and a reverse process. During the forward process, noise is systematically introduced to an image over multiple time step. Initially, the image is clear, but as noise is added incrementally, the image transitions towards a state of complete noise. This process, modeled as a Markov chain, effectively turns the original image into a noisy distribution. The reverse process, which is learned through deep neural networks, aims to reverse this noise addition. The model is trained to predict and subtract the noise at each step, allowing it to reconstruct the original image from the noisy version by progressively removing the noise. In the context of color normalization, the DDPM is trained on datasets of images with known color characteristics. This training enables the model to understand and handle various color properties effectively. During training, the DDPM learns to reconstruct images.

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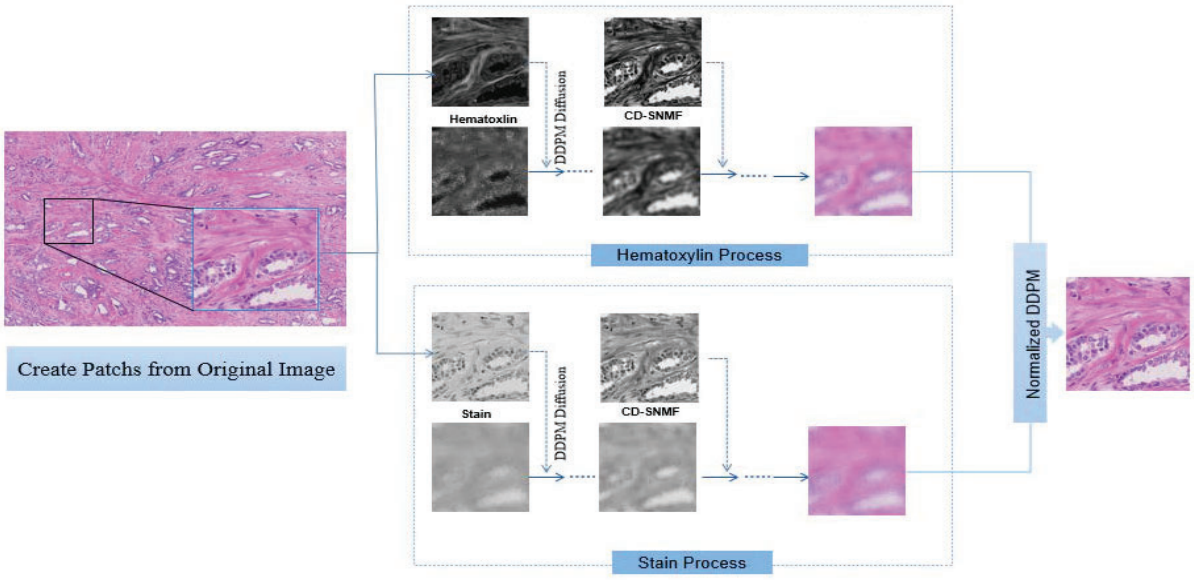


Fig. 1. Flow of the proposed stain normalization method.

while preserving or modifying specific color features. Once trained, the model generates a target stain matrix that captures the desired color characteristics. For each new source image, the DDPM extracts its stain matrix, which represents the relative concentrations of different stains or colors. This extracted matrix is then used to normalize the source image, aligning its color properties with the target characteristics. Through this process, the DDPM facilitates the effective transfer and normalization of color information, improving the overall image quality and consistency. Figure. 1 represents the flow of the proposed stain normalization method.

4) Performance Evaluation Metrics: PSNR, MSE, and SSIM offer a comprehensive view of image quality by combining error quantification and perceptual similarity. Their selection enables clarity, reliability, and relevance in image quality assessment. Thus, while other metrics exist, these three provide a well-rounded foundation for evaluating and comparing image processing techniques.

a) Peak signal-to-noise ratio (PSNR) is the ratio between the maximum possible power of an image and the power of corrupting noise that affects the quality of its representation. It measures the similarity between the original and normalized images. PSNR is defined as follows:

$$PSNR = 10.log_{10}\left(\frac{MAX^2}{MSE}\right) \quad (1)$$

where MAX is the maximum possible pixel value of the image.

b) Mean Squared Error (MSE) is the Mean Squared Error between the original and the reconstructed image, defined as:

$$MSE = \frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}(I(i,j) - k(i,j))^2 \quad (2)$$

where I (i, j) is the pixel value at position (i, j) in the original image, K (i, j) is the pixel value at position (i, j) in the reconstructed image, and m and n are the dimensions of the images.

c) **Structural Similarity Index (SSIM)** is the structural similarity between the original and normalized images. The SSIM is calculated using the formula:

$$SSIM(x,y) = \frac{(2_{\mu_x\mu_y} + c_1)(2_{\sigma_{xy}} + c_2)}{(\mu_x^2 + \mu_y^2 + c_1)(\mu_x^2 + \mu_y^2 + c_2)} \quad (3)$$

where "mu sub x" and "mu sub y" pixel values in image x and y. "sigma squared sub x" and "sigma squared sub y" variance of pixel values in image x and y. "sigma sub xy" variance of pixel values in image x and y. "c sub 1" and " c sub 2" constants stabilize the division and prevent division by zero, typically small values.

IV. RESULTS AND DISCUSSION

This section presents the results and graphical plots for stain normalization using DDPM diffusion on mitosis datasets.

A. Used Platform

The experiments were implemented using a PC with an NVIDIA RTX 4000 GPU, Intel(R) Xeon(R) W-2245 CPU@3.90GHz, and 64GB System RAM with Python programming language via the Google Colab platform.

B. *Experiment Results*

Stain normalization was performed on MIDOG21 and CCMCT datasets using stain separation. These are trained with CD-SNMF and DDPM models. In addition, these datasets are trained in the Reinhard and Macenko method using a conventional method. Results of stain normalizations on MIDOG21 and CCMCT datasets are proposed in Tables I and II.

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TABLE I .STAIN NORMALIZATION RESULTS ON MIDOG21

Stain Normalization Technique	Metrics		
	SSIM ↑	***PSNR*** ↑	***MSE*** ↓
Macenko	0.95	0.184	0.34
Reinhard	0.806	0.147	0.53
Proposed Method	0.943	0.195	0.287

TABLE II STAIN NORMALIZATION RESULTS ON CCMCT

Stain Normalization Technique	Metrics		
	SSIM ↑	***PSNR*** ↑	***MSE*** ↓
Macenko	0.944	0.17	0.353
Reinhard	0.788	0.125	0.60
Proposed Method	0.938	0.186	0.29

In Table I, the proposed method achieves competitive results with an SSIM of 0.943, PSNR of 0.195, and MSE of 0.287, indicating good preservation of image quality and similarity to the target reference. The Macenko method also performs well with a high SSIM of 0.95, albeit with slightly lower PSNR and higher MSE than the proposed method. Reinhard's method shows lower SSIM and PSNR, and a higher MSE, suggesting less effective normalization on this dataset.

Table II (CCMCT dataset) demonstrates that the proposed method performs well with an SSIM of 0.938, PSNR of 0.186, and MSE of 0.29. Macenko's method also shows strong results with an SSIM of 0.944, though with a slightly higher MSE compared to the proposed method. Reinhard's method again performs less effectively with lower SSIM and PSNR, and a higher MSE.

The plots in Figure. 2 compare the performance of three

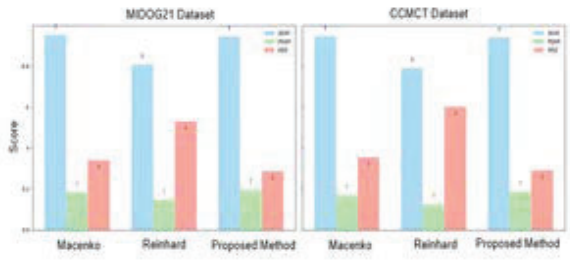


Fig. 2. Plot representation of results on datasets

stain normalization methods of Macenko, Reinhard, and the proposed method on the MIDOG21 and CCMCT datasets using SSIM, PSNR, and MSE metrics. Each subplot shows three groups of bars, each representing an appropriate method. SSIM and PSNR values are desirable when higher (indicated by upward arrows), while MSE values are better when lower (indicated by downward arrows). The proposed method consistently shows superior performance, with the highest SSIM and competitive PSNR and MSE values, indicating excellent structural similarity and minimal distortion and error in the normalized images. Figure. 3 represents the proposed stain normalization method outperforms Macenko and Reinhard regarding visual quality, structure preservation, and consistency. This suggests that it could be more effective for clinical applications where accurate and reliable stain normalization is critical.

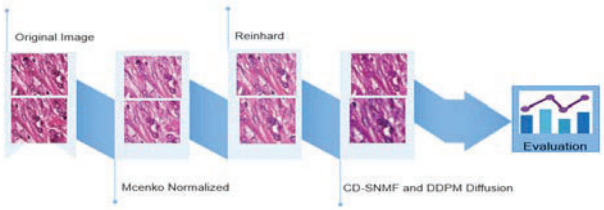


Fig. 3. Results of stain normalization

C. *Comparison of the Obtained Results*

Table III evaluates various stain normalization methods using SSIM, PSNR, and MSE metrics.

TABLE III STAIN NORMALIZATION RESULTS ON CCMCT

Stain Normalization Methods in Literature	Metrics		
	SSIM ↑	***PSNR*** ↑	***MSE*** ↓
Score-based diffusion [19]	-	0.1979	0.2866
StainDiffuser [20]	0.612	0.1908	-
Cycle-consistent GAN [21]	0.335	0.111	0.509
Isotropic Model (HSV) [22]	0.116	0.5902	0.105
Proposed Method	0.943	0.195	0.287

The proposed method stands out with the highest SSIM score of 0.943, demonstrating excellent structural preservation, and competitive PSNR (0.195) and MSE (0.287) values. In contrast, while the isotropic model (HSV) excels in PSNR and MSE, it has low SSIM, indicating poor structural similarity. The Cycle consistent GAN performs the worst, with the lowest PSNR and highest MSE, suggesting significant noise and artifacts that distort tissue appearance. Overall, the proposed method offers strong structural integrity and balanced performance, making it highly suitable for real-world applications and effective cross-dataset evaluation.

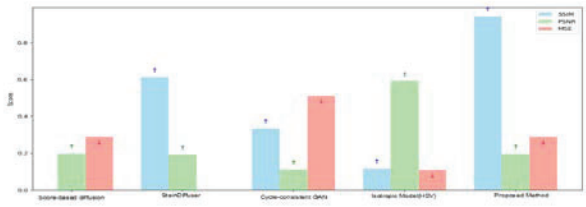


Fig. 4. Comparison of stain normalization methods

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Figure. 4 displays the performance of various methods based on SSIM, PSNR, and MSE metrics. The proposed method achieved the highest SSIM score of 0.943, indicating superior preservation of image quality and structure. While the proposed stain normalization method shows strong results in these metrics, its clinical adoption will require thorough validation to ensure effectiveness across diverse clinical settings and patient populations. Challenges to address include computational efficiency, integration into clinical workflows, standardization, and cost management. Successfully overcoming these obstacles is crucial for widespread implementation and use in clinical practice.

V. CONCLUSION

This study proposes a novel approach to enhancing H&E-stained histopathology images using CD-SNMF and DDPM diffusion models. CD-SNMF decomposes images into individual stains, isolating hematoxylin to better identify cell nuclei and mitosis, which improves analysis clarity. The study also compared the proposed stain normalization method with Reinhard and Macenko techniques. The DDPM model demonstrated superior image translation capabilities, achieving the best results on the MIDOG21 and CCMCT mitosis datasets, and enhancing mitosis detection and classification by minimizing color misapplication. Limitations include dependency on the quality of stain separation and the absence of a definitive quantitative metric for evaluating stain Normalization performance. We used SSIM, PSNR, and MSE metrics. Our approach impacts clinical practice by enhancing the clarity and accuracy of histopathology images. This leads to more precise diagnoses and better assessment of cellular features like mitosis. Improved image quality aids in reliable cancer detection and supports pathologists with more accurate, informed decisions, ultimately improving patient outcomes. Future work will focus on improving mitosis segmentation with KAN models, developing better evaluation metrics for Stain normalization, and incorporating Explainable AI to enhance model interpretability.

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