STAIN REMOVAL THROUGH COLOR NORMALIZATION OF HAEMATOXYLIN AND EOSIN IMAGES: A REVIEW

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ABSTRACT- Histopathology images are used for the diagnosis and examination of cancer cells. Preparing and scanning histopathology slides consist of numerous steps of which staining are an important process. But these staining procedures cause multitude problems as there may be variations in the slides due to multiple reasons. Color variations in histopathology images can occur due to inconsistent staining of biopsy tissue, color responses of different scanners or difference in raw materials and manufacturing techniques used by stain. These factors hamper the generalization of automatic image analysis method. Hence there is a need for standardizing the image before analysis by performing stain normalization which is achieved by removing the stains for visual enhancement. Color normalization techniques play a vital in the developing computerized decision support system. In this paper, a detailed study and performance evaluation of various color normalization techniques such as Histogram Specification, Macenko Method, Reinhard Method on histopathology images are presented. In these normalization procedures the mean color of the target image is transferred onto the source image. Quality performance of different stain normalization techniques is evaluated based on Entropy and Structure Similarity Index Measure (SSIM). In this work, we record the time complexity of the color normalization algorithms. The normalization techniques are tested on histopathological images from UCSB dataset and Mitosis Atypia 2014 dataset. This article reviews and summarizes the color normalization techniques on histopathological images for visual improvement.

Keywords: Color Normalization, Color transfer, Histopathology Images, Stain removal, Visual enhancement

1. INTRODUCTION

Breast Cancer is a very common type of cancer among people which causes thousands of lives. In a survey [23] during 2018,266,120 new cases of invasive breast cancer were diagnosed in women in the U.S, along with 63,960 new cases of non-invasive breast cancer. About 2550 new cases of invasive breast cancer were diagnosed in men. With advancement in technology, there is an increase in the number of diagnostic tools that help detect cancer. Laboratory tests, Biopsy and Imaging tests such as X-ray, PET/CT, MRI, etc are some of the common diagnostic tools. A biopsy is a procedure in which the doctor removes a sample of tissue and then examines to see if cancer is present. Imaging procedures create pictures of areas inside the human body that helps the doctor see whether a tumor is present whereas in most cases, doctors need to do a biopsy to make a diagnosis of cancer.

Histopathology is a branch that deals with the pictorial examination of tissues to study cancerous disease under microscope. It allows the study of function of cells and tissues and helps pathologists to gain maximum clinical information from the sample which is very much required in the treatment process. The main objective of histopathology analysis is to provide better diagnosis of cancer and
also other diseases. Digital Histopathology is an emerging field where in color normalization techniques, segmentation procedures, feature extraction and classification methods are exploited for the purpose of understanding and diagnosing.

The tissue under the microscope is usually transparent and hence there is a necessity to make the slides visible which is achieved by staining. The main purpose of staining procedure is to highlight the important features of the tissues. Histologists usually use Haematoxylin and Eosin (H&E) and Immune Histo Chemistry (IHC) staining. Haematoxylin is a dark blue or violet positive dye whereas Eosin is pink and negatively charged. Figure 1(a)-(d) shows the different stain variations in histopathology images due to numerous factors.

![](image1)

Fig.1 (a)-(d) Stain variation in histopathology images. These images are collected from Mitosis Aytypia2014 and UCSB dataset.

The most important task in the normalization techniques is altering the image for better visual where in the color of one image is transferred to another i.e. the color of the target image is transferred onto the source image. If the image is processed without preprocessing, this might result in incorrect diagnosis. So, to decrease the variations, the RGB images are converted into grayscale images. But the problem with grayscale conversion is that most of the information is lost and hence we go for normalization techniques. Color normalization is a process where mean color transformation from one image to another image is performed. There are various normalization algorithms such as Histogram Specification, Reinhard Method, Macenko Method, Stain Color Descriptor (SCD), Complete Color Normalization, Structure Preserving Color Normalization (SPCN) and many other methods. System architecture of color normalization is presented in Figure 2.

![](image2)

Fig.2: Color normalization process

This article reviews some of the most accepted color normalization techniques for the breast cancer from a histopathology image.
The paper is organized as follows. In section II, we present the related work to color normalization methods. In Section III, the materials and methods. Different parameter used for performance evaluation explained in Section IV. Section V discusses and compares different algorithms used for color normalization techniques. Finally Section VI describes conclusion and future work.

2. RELATED WORK

Reinhard et al.,[3] proposed a technique which is based on color transfer between a standard image and color varied image using mean and variance of both the images. In this method, source image is altered to the target image. Here, color distribution of source image to that of the target image by linear transform in perceptual color space. Better results achieved by adding the scaling factor to the Reinhard normalization algorithm. Contrast of the source image is approximately same as that of the target image. In this technique the image is transformed to lαβ space in which stains cannot be properly separated.

Macenko et al.,[4] presented an algorithm to find particular stain vectors for each image based on the colors that are present in the image. In this method, there is a specific stain vector corresponding to each of the two stains in image and this is a fully automatic method that is suitable for analyzing multiple slides rapidly because of having very few parameters and no optimizations required. This method is performed on twelve different slides with considerable variation. For each stain, calculate the intensity histograms for all pixels that have a majority of that particular stain and estimate 99th percentile of these intensity values for robust approximation. It gives better results for less stained images. It doesn’t have negative co-efficient in color appearance matrix.

Ruifrok et al.,[5] proposed a technique that maps the color distribution of a stained image to a well stained target image. It demonstrates the inherent variability in original data, and it preserves the information of original source image. Several image analysis algorithms require parameters for defining the expected color distribution and fails if these parameters are incorrect. In this method, it uses a linear transformation in LAB color space to match the means and standard deviations of each color channel in the two images in that color space. Separation of stains is performed in a histology image, such that color proportions of H & E stains in each location can be estimated. Prior information (single stained slide) is needed for the purpose of color appearance matrix estimation. The original color that was before staining cannot be got back if some non linear mixing is done.

Lee et al.,[6] has put forth an idea that identifies causes of color by using an illuminant normalization module and a spectral normalization module. To take advantage of color information, variation caused by operational inconsistency in histopathology slides should be removed beforehand. In Illuminant normalization module, intensities of an image are generated under illuminant with standard SPD. Image intensities in blank areas need to be estimated for illuminant normalization. In spectral normalization module, spectral matching is performed by using Beer-Lambert Law which describes an optical phenomenon that light is absorbed by materials. Reduce the solution space of NMF by employing SW statistics which converts the image to saturated image or color appearance matrix is becoming diagonal. Saturated weight (SW) statistics is not a natural process because it depends on the dominant color.

Vahadane et al.,[7] presented a method used for color normalization is the image is decomposed into stain density map that are sparse and non-negative. Then, the stain density maps are combined on the basis of stain color of a pathologist preferred target image. Thus, altering only its color and preserving the structure. In SNMF, solution space is totally reduced. Structure of the source image is preserved. The computation complexity for reducing the solution space is higher. The solution provided for optimization problem may lead to estimation of local minima rather than global minima.
3. MATERIALS AND METHODS

DATA SET

A. UCSB

The UCSB breast cancer cell dataset [22] can be used for cell segmentation in both benign and malignant cell images. The dataset consists of 26 cancerous cell images and 32 normal cases obtained from ten H&E stained breast cancer biopsies. All images are scanned in the same laboratory, with resolution of 896 X 768.

B. MITOS-ATYPIA-14:

It is a publically available dataset which can be accessed from the Pathology Informatics web source: https://mitos-atypia-14.grand-challenge.org/dataset/. A total of 1302 images are available in this dataset which are stained with haemotoxylin and eosin. The slides are scanned by two scanners namely (1) Aperio Scanscope XT and (2) Hamamatsu Nanozoomer 2.0 HT. Out of 1302 images, 651 slides were scanned by Aperio Scanscope XT and another 651 slides were scanned by Hamamatsu Nanozoomer 2.0 HT. There are several frames at 10X, 20X and 40X magnification for each slide.

This section provides the description of the color normalization techniques. There are three types of major color normalization methods which have been discussed in this paper namely,

A. Histogram Specification
B. Macenko Method
C. Reinhard Method

A detailed description about the methods is given below.

A. HISTOGRAM SPECIFICATION

Histogram Specification[2] is one of Global Color Normalization method and is done by separating color and intensity information in space and also it is treated as an optimization problem. In this algorithm, the histogram of the source image is mapped with the histogram of the target image in a way such that the brightness and color of the source image will be very much like the target image. But this method is a kind of unnatural process, as the histogram of source image is forcefully stretched until it is approximately equal to that of the histogram of the target and hence it might bring some complications in the processed image. The main advantage is that the brightness and the color statistics of the source image are more like that of the target image. There are a few limitations which include that not all information is preserved in this process and not applicable if both the source and target images are dissimilar.

Algorithm: Histogram Specification (Source Image, Target Image)

1. Read source image and the target image
2. Resize both the images and consider the intensity of both the images as a discrete random variable.
3. The histogram \( p_x \) of the input image is first equalized, 

\[
y = f(x) = \int_0^x p_x(u)du 
\]

4. The desired histogram \( p_z \) of the target image is then equalized,

\[
y = g(z) = \int_0^z p_z(u)du 
\]
\[ y' = g(z) = \int_0^z p_z(u)du \quad \text{---- (2)} \]

5. The inverse of the above transform is given as,

\[ z = g^{-1}(y') \quad \text{---- (3)} \]

6. The two intermediate images \( y \) and \( y' \) have the same equalized histogram. Hence they can be considered as same images i.e., \( y = y' \), and the overall transform for the desired image \( z \) can be found as,

\[ z = g^{-1}(y') = g^{-1}(y) = g^{-1}(f(x)) \quad \text{---- (4)} \]

7. Mapping is done between the new gray level and the initially present pixel values which is achieved by mapping the intensity of the source to that of the target with initial pixel values.

**B. MACENKO METHOD**

In this method [4], based on the colors that are present an algorithm to find stain vectors for each image is presented. A pixel with Optical Density (OD) value 0 represents that there was no light absorbed. Such pixels were removed for stability reasons. An adaptive mechanism was employed and threshold value of \( \beta = 0.15 \) was found to provide best results. In order to find the endpoints that correspond to the stain vectors, the geodesic direction (shortest path between two unit-norm color vectors) is found and then the OD transformed pixels are projected onto it. The first step is to calculate the plane that these vectors form. This is done by forming a plane corresponding to two largest singular values of decomposition. Then the OD transformed pixels are projected onto this plane. Then the angle with respect to the first SVD direction is calculated. With respect to stain separation process, the stain vector corresponding to the minimum vector represents Haematoxylin stain and the stain vector corresponding to that of the maximum vector represents Eosin stain.

**Algorithm: Macenko Method (Input Image, \( \beta \), Reference Image)**

1. Optical Density of RGB image \( I \) is calculated \( OD = -\log(I) \) ---- (5)
2. Data with Optical Density intensity less than \( \beta \) is removed. By default \( \beta = 0.15 \)
3. Singular Value Decomposition on the Optical Density tuples is calculated.

\[ \text{CoVar}(x, y) = \sum (X_i - \mu(X_i)(Y_i - \mu(Y_i))) / n - 1; \text{Where } i = 1 \text{ to } n \quad \text{---- (6)} \]

\[ A * V = \lambda * V \quad \text{---- (7)} \]

Any value of \( \lambda \) for which this equation has a solution is known as an eigenvalue of the matrix A, where A is the OD matrix and V is the vector

\[ V = \text{eigen(Co var(A))} \quad \text{---- (8)} \]

4. Project on the plane spanned by the eigen vectors corresponding to the two largest eigen values. \( A * V \) (sliced with largest eigen values)
5. Calculate angle of each point with respect to the Singular Value Decomposition direction
6. Find robust extremes (\( \alpha \) th and (100–\( \alpha \) ) th percentiles) of angle. By default alpha=1
\[ i = \left( \frac{p}{100} \right) n \], Where \( i \) = position; \( n \) = number of input elements. ---- (9)

\[ \text{minimumangle} = \text{percentile(\text{angle, alpha})} \] ----(10)

\[ \text{maximumangle} = \text{percentile(\text{angle, 100-alpha})} \] ----(11)

7. The minimum and maximum vectors are found and projected back to OD space.

\[ \text{vectorMin} = V* [\cos(\text{minimumangle}), \sin(\text{minimumangle})] \]

\[ \text{vectorMax} = V* [\cos(\text{maximumangle}), \sin(\text{maximumangle})] \] ----(12)

8. Make the vector corresponding to haematoxylin first and the one corresponding to eosin second.

\[
\text{if vectorMin}(1) > \text{vectorMax}(1) \\
\text{HE} = [\text{vectorMin} \text{vectorMax}](\text{Haematoxylin})
\]

\[
\text{else} \\
\text{HE} = [\text{vectorMax} \text{vectorMin}](\text{Eosin}).
\]

9. Determine concentrations of the individual stains.

\[ C = \text{HE} \text{Y.} \] ---- (13)

\( \text{Y} \) is the matrix columns represent RGB channel, Rows represent OD intensity.

10. Recreate the image using reference mixing matrix

\[ I_{\text{norm}} = I_0 * \exp (-\text{HRef*}C) \] --- (14)

\( \text{HRef} \) = reference H&E OD matrix

\( I_0 \) = Transmitted Light Intensity.

\( I_{\text{norm}} \) = Normalized image.

C. REINHARD METHOD

This approach \[3,24\] maps the color distribution of an under stained image or an over stained image to that of a well stained target image. This is achieved by use of linear transformation in \( l\alpha\beta \) color space so as to match the mean and standard deviations of each color channel in both the images. Reinhard et al preferred another global color normalization method in which the mean color of the target image is transferred onto to the source image. This method ensures that the intensity variations of the source image is preserved. Also the processed image will be very much like the target image. The main advantage is that the structure of source image is preserved and the contrast of the processed image is same as that of the contrast of target image. But in \( l\alpha\beta \) color space the stains are not properly separated.

Algorithm: Reinhard Method(Source Image, Target Image)

1. Read the source and the target image.

2. Convert the RGB image to \( l\alpha\beta \) color space. The \( l\alpha\beta \) color space is itself a transform of LMS cone space.

   a. While this conversion, do first convert the RGB image into an independent XYZ space.

   b. Next, do convert the image in XYZ space into LMS cone space. In LMS cone space the data is in the form of skew which is removed by converting the data into logarithmic space.
3. Initialize the number of channel \( i = 0 \) and the number of channel in RGB image as \( c = 3 \).

4. If \( i < c \), do the following,

\[
\ell_2 = \frac{1}{\ell_2 + \ell_1} + (\ell - \text{mean}(\ell)) \cdot \frac{\text{std}(\ell)}{\text{std}(\ell)} \quad \text{(15)}
\]

\[
\alpha_2 = \frac{1}{\alpha_2 + \alpha_1} + (\alpha - \text{mean}(\alpha)) \cdot \frac{\text{std}(\alpha)}{\text{std}(\alpha)} \quad \text{(16)}
\]

\[
\beta_2 = \frac{1}{\beta_2 + \beta_1} + (\beta - \text{mean}(\beta)) \cdot \frac{\text{std}(\beta)}{\text{std}(\beta)} \quad \text{(17)}
\]

where,

\( \ell_2, \ell_1, \ell \) are the processed image, target image and source image respectively in \( \ell \) space

\( \alpha_2, \alpha_1, \alpha \) are the processed image, target image and source image respectively in \( \alpha \) space

\( \beta_2, \beta_1, \beta \) are the processed image, target image and source image respectively in \( \beta \) space

5. To display convert \( \ell \alpha \beta \) color space to RGB image.

4. PERFORMANCE EVALUATION

The performance analysis of normalization methods can be evaluated using image quality metrics. The metrics such as Structural similarity index metric (SSIM) (Wang and Bovik et al., 2004), and Entropy are used to analyze the histopathology images. The descriptions about these quality metrics are given in the further subsections.

A. Structural similarity index metric (SSIM)

Structure similarity index metric (SSIM) is a method for measuring similarity between the images. The SSIM index can be viewed as a quality measure of one of the images being compared provided the other image is regarded as of perfect quality. SSIM is consisting of the three factors such as luminance, structural and contrast.

\[
SSIM(x, y) = \frac{2\mu_x\mu_y + c_1}{\mu_x^2 + \mu_y^2 + c_1} \cdot \frac{2\sigma_{xy} + c_2}{\sigma_x^2 + \sigma_y^2 + c_2} \quad \text{(18)}
\]

where,

\( \mu_x, \mu_y \) is the mean values of \( x \) and \( y \)

\( \sigma_x, \sigma_y \) is the standard deviation of \( x \) and \( y \)

The numerical value of SSIM lies between 0 to 1. The value closer to 1, better is the color normalization method.

B. Entropy (E)

The image enhancement is based on information content of an image. Larger entropy value the image has, the higher information contained in the output image. The entropy for the whole image can be defined by,
\[ E(x, y) = \sum_{i=0}^{255} p_i \log_2 p_i \]  

(19)

where,

\[ p_i \] is the probability of intensity I at pixel in enhanced image.

5. RESULTS AND DISCUSSIONS

This part discusses the results of the each algorithm of the stain normalization methods performed in histopathology images. Figure 3 shows the results of the three normalization methods.

| TARGET IMAGE | SOURCE IMAGE 1 | SOURCE IMAGE 2 | SOURCE IMAGE 3 |
|--------------|---------------|---------------|---------------|
| HISTOGRAM SPECIFICATION | (Gurcan et al., 2009) | | |
| MACENKO METHOD | (Macenko et al., 2009) | | |
| REINHARD METHOD | (Reinhard et al., 2001) | | |
Fig. 3: Comparison of some of the color normalization techniques. The target and the source image are selected from the Mitosis Atypia2014 and UCSB dataset. Image in the first column represent the normalized image for test 1. The normalized image of the second column represents to test 2 and so on.

![Graph showing entropy values for various color normalization methods]

Fig. 4: Entropy values obtained for original image and normalized image for color normalization methods.

Figure 4 shows the entropy value obtained for original image and the normalized image for color normalization methods. It shows Reinhard method outperforms other two normalization methods.

![Graph showing SSIM values for various color normalization methods]

Fig. 5: Structure Similarity Index Metric (SSIM) values for color normalization methods.
Figure 5 shows the Structure Similarity Index Metric (SSIM) values obtained for these methods. It is found that SSIM value for Reinhard Method is 0.93 which is closer to 1 and it is a better color normalization method compared to other two methods.

![Graph showing time complexity analysis for color normalization methods.](image)

**Fig.6: Time complexity analysis graph for color normalization methods.**

Figure 6 shows time complexity value obtained for color normalization algorithms estimated for sample of 150 stain images taken from Mitosis Atypia2014 contest dataset and UCSB dataset. Here, execution time is less for Reinhard method when compared to other two methods.

### 6. CONCLUSION AND FUTURE WORK

A study and implementation about various color normalization algorithm was presented in this paper. Experimentally, it is evident that histogram specification is not applicable if the histogram or the statistics of both the source and the target image do not match. Reinhard method preserves the source intensity variation but it relies too much on the target image. In Macenko method, if the number of stains is more, then it produced inconsistent results and the resulting image deviates too much from the target image. Thus quantitatively and qualitatively, Reinhard method provided better results in comparison to all the other methods presented in this paper. Time complexity of the algorithms is done to show which algorithms performs faster and produces good normalization results. In future, deep learning based color normalization techniques can be developed to learn the amount of staining present in the huge voluminous data and to perform the color normalization process. Deep learning based model does not require the target image for color normalization process. Effective choice of color normalization technique will helpful for detecting cancerous and non cancerous cells.
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8. CONFLICT OF INTERESTS
The authors declare that there is no conflict of interests regarding the publications of this paper.

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