

Modified Reinhard Algorithm for Color Normalization of Colorectal Cancer Histopathology Images

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Abstract— In recent trends, Computer Assisted Diagnosis (CAD) enables the pathologists to diagnose cancer disease from histopathology images very efficiently. Color normalization is a pre-processing step prior to cancer classification task which can reduce the computational complexity of the classifier. However, existing color normalization methods are fraught with the problems of data loss and huge computational complexity. The purpose of employing this color normalization method is to reduce the color variation among a set of histopathology images so that in the next step, the classifier can efficiently extract the prominent features for cancer grading. This color variation is generally occurred due to using different scanners, stain concentration variability and poor tissue sectioning, while preparing the histopathology slides. In this paper, a modified Reinhard algorithm is proposed for color normalization of Hematoxylin and Eosin (H&E) stained colorectal cancer histopathology images. The limitations of Reinhard algorithm are alleviated by the proposed algorithm. Moreover, a statistical analysis is provided to prove that proposed algorithm does not cause any data loss and subsequently, it satisfies all four hypotheses of color normalization. Furthermore, the performance of the proposed algorithm is compared with other existing color normalization methods both qualitatively and quantitatively.

Keywords— Color Normalization, Computer Assisted Diagnosis, H&E stained histopathology images, colorectal cancer, image processing, contrast enhancement, correlation coefficient

I. INTRODUCTION

Histopathology [1] can be defined as examination of suspected tissues under the microscope in order to study the cancer diseases in efficient way. In comparison to the radiology images, which are easily obtained through CT scans, MRI, X-rays and PET, and, the cytopathology images that involves direct scanning of organs, histopathology images are obtained through scanning and collection of the information from the tissue level. First, the suspected tissue is collected by biopsy needle aspiration [2]. Thereafter, many steps are employed in the pipeline of preparing histopathology datasets like fixation, embedding, sectioning, staining [2] and eventually they are converted into digital images. This digital image is given input to a CAD system and they are called as source images throughout this paper. The manual cancer detection by pathologists is fraught with the problems of inter-observer variability. Moreover, the manual detection is very much tedious process and very much dependent on human psychology and pathologists' experience in the relevant field. With the advent of Computer Assisted Diagnosis (CAD) [1],

those difficulties and challenges by the manual cancer detection can be easily alleviated. Color variation in histopathology images may occur due to employing different scanners, variation of stain concentration and manual tissue sectioning. Moreover, any fault in the pipeline of the histopathology slides' preparation may cause color variation [2] in the source histopathology images. Color normalization is very necessary pre-processing step prior to classification task, because small variation of color may decrease the accuracy of cancer detection which is not desirable. The main objective of color normalization in histopathology images is to reduce color variation among a set of source images to a huge extent. A reference image is chosen from the dataset (this reference image must be preferred by pathologists) just to transfer desirable color from reference image to source image and after doing this color normalization we call the final image as color normalized image.

This has been observed that Hematoxylin stain is closely bounded to the nuclei (blue color) and Eosin stain is limited to only the cytoplasm (Redish purple color). Ruifrok and D.A. Johnston [3] first observed that H&E color spectrum overlaps significantly. Therefore, many researchers (including Ruifrok et al [3]) have employed stain separation methods to separate Hematoxylin only channels and Eosin only channels. We have observed that this stain separation is only required if there is color artifact present in the image and they are affecting the important parts like nuclei, lymphocytes, stroma etc in H&E-stained histopathology images. However, we did not observe any such artifacts present in our employed colorectal cancer dataset, thus, we did not employ any such stain separation method prior to color normalization method. Moreover, in RGB space there is a huge correlation among R, G and B channels. Thus, first we need to transform the histopathology color images from RGB space to *lab* space [4] so that there will not be any color mixing while doing color transformation.

In this manuscript, we have employed the color normalization for colorectal cancer histopathology images. This dataset is readily available in internet [5]. Colorectal cancer is also being termed as colon cancer or rectal cancer, is a type of cancer where the colon or the rectum portion of the human body is affected. In this paper, we have proposed a modified Reinhard method which is a global color normalization method. Moreover, a global statistical analysis is provided in order to prove that our method satisfies all four hypotheses of color normalization. This kind of global statistical analysis is feasible for only histopathology images because histopathology images have a unique texture property [6] that it does not have a large region where intensity value is

homogenous. In other words, autocorrelation co-efficient [6] among pixels in histopathology images is comparatively higher than the autocorrelation coefficient of natural images. For this particular texture property, we believe that global color transformation is actually preferable over any local transformation, for histopathology images.

Reinhard method [5] and histogram specification are the global color normalization methods where the same color (background color) is transferred to all the pixels in the source histopathology images globally. Color transformation in such methods, should be done in *lab* space such that during color transformation there will not be any color mixing [6]. Here l denotes luminance intensity and ab denotes color information; l , a and b channels are separated or kind of uncorrelated by Principal Component Analysis (PCA) [7]. In Histogram Specification (HS), the color and luminance statistics are transferred from reference image to source image globally until the color normalized image histogram will be similar with the histogram of reference image. In Reinhard method, background color (and luminance) of the color normalized image is replaced with the same of reference image. A depth explanation of Reinhard method can be found in [4]. A novel unsupervised color normalization method is recently proposed by S. Roy et al [6], for H&E-stained histopathology images. Their method overcomes the limitations of Reinhard method by incorporating fuzzy function in color transformation. Additionally, they also have resolved the problem of preserving white luminance portions which is associated with fatty tissues and mostly observed in breast cancer dataset. All the color transformations in their method are implemented in *lab* space.

A. Rabinovich et al [7] have employed unsupervised learning methods, for example, Independent Component Analysis (ICA) and Non-Negative Matrix Factorization (NMF) [7], in order to separate the stains. ICA method [8] is based on the fact that each stain acts independently, however, their method is not practically feasible. On the other hand, NMF method is having a major problem that it has many solutions. A. Vahadane et al [9] have recently proposed a structure preserving method which incorporates sparseness into optimization equation of NMF, which enables them to reduce the solution space of NMF. However, in Sparse NMF (SNMF) [9], the computational complexity is considerably increased. Many researchers [10, 11] further employed Neural Network in order to separate stains from H&E stained histopathology images. A review of color normalization methods can be further studied from [12].

II. HYPOTHESES OF COLOR NORMALIZATION

Color normalization method of histopathology images must satisfy the following hypotheses, according to S. Roy et al [6]. We had further added one more hypothesis of background luminance preservation of source images.

1. Any loss of data from histopathology images is not acceptable during color transformation, i.e. correlation co-efficient [6] between source image and color normalized image must be closed to 1. Why correlation co-efficient is chosen as desired metric of data loss is already explained in depth in [6].

2. Mean color (background color) difference [6] between reference image and color normalized image must be closed to 0.
3. Contrast of the color normalized image must be greater than equal to contrast of the source image [6], during color normalization.

$$C_{norm} \geq C_{source} \quad (1)$$

4. Background luminance between color normalized image and source image must be closed to 0. We have added this hypothesis, because we observed that performance of some color normalization methods (e.g. Reinhard method) is too much dependent on the statistics of the target image. However, the performance evaluation of color normalization should be independent on reference image, we are choosing.

$$\mu_{source}(l) \approx \mu_{norm}(l) \quad (2)$$

III. METHODOLOGY

A. Limitations of Reinhard Method

Conventional Reinhard algorithm and its statistical analysis is already explained in depth in [6]. Unlike other methods, Reinhard algorithm preserves all the essential source information in the final color normalized image. Correlation co-efficient between source and color normalized image by Reinhard method is found to be exactly equal to 1 in [6]. Moreover, this has been observed that Reinhard method satisfies hypotheses 1 and 2 of color normalization, however, it does not satisfy the hypotheses 3 and 4, which are explained below.

- I. The source image background luminance is not exactly preserved in the color normalized image by Reinhard method [6]. Rather it is dependent on reference image. If reference image is chosen dark, it directly affects the performance of color normalization by Reinhard method.
- II. Reinhard method sometimes produce a poor contrast color normalized image if the reference image contrast is lesser than that of source image [6].

B. Modified Reinhard Method or Proposed Method

We propose a modified Reinhard algorithm which overcomes the limitations of Reinhard algorithm. The various steps of our proposed algorithm are explained below.

Step1. Transform the source image A and reference image B from RGB to *lab* space [4].

Step2. Calculate ‘ q ’ for each source images separately. ‘ q ’ is a defined below in equation (3).

$$q = \frac{\sigma_{global}(l_r) - \sigma_{global}(l_s)}{\sigma_{global}(l_r)} \quad (3)$$

Step3. Following transformations is done in *lab* space. if $q > 0$

$$l_n = \mu_{global}(l_s) + [l_s - \mu_{global}(l_s)] \cdot (1 + q) \quad (4)$$

else

$$l_n = \mu_{global}(l_s) + [l_s - \mu_{global}(l_s)] \cdot (1 + 0.05) \quad (5)$$

$$\alpha_n = \mu_{global}(\alpha_r) + [\alpha_s - \mu_{global}(\alpha_s)] \quad (6)$$

$$\beta_n = \mu_{global}(\beta_r) + [\beta_s - \mu_{global}(\beta_s)] \quad (7)$$

Here l_n, α_n, β_n are intensity of color normalized image in *lab* space, l_r, α_r, β_r are intensity of reference image in *lab* space and l_s, α_s, β_s are intensity of source histopathology image, μ_{global} indicates overall (global) mean of the image.

Step 4. Transform the color normalized image C from *lab* space to RGB space.

In our proposed algorithm, ‘ q ’ is a parameter which is dependent on overall contrast difference between reference image and source image. In equation (4), this parameter ‘ q ’ is further incorporated in order to do contrast enhancement by the amount of ‘ q ’. This is mathematically proved in the next section that ‘ q ’ is just the amount of contrast enhancement done in the color normalized image. If ‘ q ’ is negative, that means contrast of the reference image is lesser than the contrast of source image. At that case, when contrast enhancement is not so necessary, proposed method has done a little bit contrast enhancement (i.e. 0.05 or 5%), shown in equation (5). This will ensure that the contrast of the color normalized image will be always greater than that of source image. Therefore, proposed modified Reinhard algorithm always satisfy the third hypothesis which was not true for conventional Reinhard algorithm. In equation (6) and in equation (7), the background color of source image is just replaced by background color of reference image in order to transfer background color from reference image to final color normalized image. The proposed method is further explained in depth in the next section IV.

S. Roy et al [6] have also employed similar kind of Fuzzy based Modified Reinhard (FMR) method for color normalization of histopathology images. However, their method doesn’t always satisfy the second hypothesis. Because they have computed the no of pixels associated with the white luminance and thereafter those computations are incorporated in the color space equations, in order to reduce the fade color effect [6]. In our employed colorectal dataset [5], mostly we did not observe any such fade color effect [6], while doing color normalization, thus, we did not incorporate the notion of fade color effect reduction in our proposed color normalization method. This actually helps us to reduce the computational complexity a little bit compared to [6] and of course our proposed method always satisfies the second hypothesis which was not true in case of FMR method [6].

IV. STATISTICAL ANALYSIS OF PROPOSED MODIFIED REINHARD METHOD

In this section, a statistical analysis is provided in order to evaluate our proposed method. A similar analysis is already done in [6].

From the theory of statistics [13], we know that

$$\sigma^2(aY + b) = a^2 \sigma^2(Y) \quad (8)$$

Where Y is random variable, a and b are real constants.

By taking global variance in equation (8), and by substituting value from equation (4), we get

$$\sigma_{global}^2(l_n) = \sigma_{global}^2(l_s) \cdot (1 + q)^2 \quad (9)$$

$$\text{or, } \sigma_{global}(l_n) = \sigma_{global}(l_s) \cdot (1 + q) \quad (10)$$

By taking the global mean in equation (4), we get

$$\mu_{global}(l_n) = \mu_{global}(l_s) + \mu_{global}(l_s) \cdot q - \mu_{global}(l_s) \cdot q = \mu_{global}(l_s) \quad (11)$$

From equation (11), we can say that mean luminance of color normalized image is equal to the mean luminance of source

image. Therefore, background luminance has been well preserved in color normalized image by our proposed algorithm. Hence, our proposed method satisfies the fourth hypothesis which was not true for Reinhard method.

Contrast [14] of image is given by following equation (12).

$$C = \sigma / \mu, \quad (12)$$

where ‘ σ ’ is the standard deviation of intensity values, μ is the local mean of intensity.

From equation (10) and (11), we can substitute the values in equation (12) and getting the contrast of the color normalized image C_2 given in the following equation (13).

$$C_2 = \frac{\sigma_{global}(l_n)}{\mu_{global}(l_n)} = \frac{\sigma_{global}(l_s)}{\mu_{global}(l_s)} \cdot (1 + q) \quad (13)$$

Equation (13) reveals that contrast of the color normalized image is $(1+q)$ times the contrast of source image. Since ‘ q ’ is a real positive constant, equation (13) proves that the contrast of the color normalized image is always greater than equal to contrast of source image. Hence our proposed modified Reinhard method satisfies the third hypothesis. The same was not true for Reinhard method [6].

Hence, our proposed method alleviates all the flaws of Reinhard method, to the best of our knowledge.

Now, in *ab* space, taking global mean in equation (6), we get

$$\mu_{global}(\alpha_n) = \mu_{global}(\mu_{global}(\alpha_r)) + [\mu_{global}(\alpha_s) - \mu_{global}(\mu_{global}(\alpha_s))] \quad (14)$$

$$\text{or, } \mu_{global}(\alpha_n) = \mu_{global}(\alpha_r) \quad (15)$$

$$\text{Similarly, } \mu_{global}(\beta_n) = \mu_{global}(\beta_r) \quad (16)$$

Equation (15) and (16) indicates that mean color of the color normalized image is exactly equal to the mean color of reference image. Hence, second hypothesis has been satisfied by our proposed algorithm. The same is also proved for Reinhard method in [6]. However, the same was not true for FMR method [6].

Covariance between color normalized image and source image in *l* space is given by the following equation (17).

$$\sigma_{l_n l_s} = \frac{1}{N^2} \sum_{i=1}^N \sum_{j=1}^N (l_{ni} - \mu_{global}(l_{ni})) \cdot (l_{sj} - \mu_{global}(l_{sj})) \quad (17)$$

where $N \times N$ is the entire image size in *l* space.

Replacing the value from equation (11) and (4), in equation (17) we get,

$$\sigma_{l_n l_s} = \frac{1}{N^2} \sum_{i=1}^N \sum_{j=1}^N (l_{si} - \mu_{global}(l_{si}))^2 \cdot (1 + q) \quad (18)$$

$$\text{or, } \sigma_{l_n l_s} = \sigma_{global}^2(l_s) \cdot (1 + q) \quad (19)$$

Correlation coefficient between source image and color normalized image in *l* space is given by

$$r = \frac{\sigma_{l_n l_s}}{\sigma_{global}(l_s) \cdot \sigma_{global}(l_n)} \quad (20)$$

Putting the value from equations (19) and (10) into equation (20) we can get,

$$r = 1 \quad (21)$$

Hence, this is proved that correlation coefficient [6] between source image and color normalized image in *l* space is always equal to 1, by proposed modified Reinhard method. Similarly, in *ab* space, the same can be proved. This indicates that all the important source information is exactly preserved

in the color normalized image, by our proposed method. Hence, the first hypothesis has been satisfied by our proposed Modified Reinhard method. Similar proof is also available for Reinhard method and for FMR method in [6].

V. RESULTS AND ANALYSIS

Our proposed method satisfies all the hypotheses which was mathematically proved in section IV. Experimental results of proposed algorithm is compared with other state-of-the-art methods such as histogram specification, Color Deconvolution by A. M. Khan [5], structure preserving color normalization [9], Fuzzy based Modified Reinhard method by S.Roy et al [6] and Reinhard algorithm [4]. The hardware which was incorporated to implement all these methods is Intel® Core™ i5 PC with 2.2 GHz CPU and 8 GB RAM. The software which was employed for these implementations is MATLAB 2019. For experimentation, colorectal cancer histopathology images are utilized which are readily available in internet [5]. The visual results of various color normalization methods are shown in Fig.1. The performances of several color normalization methods are measured by the quality metrics Pearson Correlation Co-efficient (PCC) [6], $AMCE_a$ and $AMCE_b$ [6]. According to S. Roy et al [6], PCC is measuring the structural similarity between two images. In other words, it can measure whether any data loss is there or not between source image and color normalized image. $AMCE_a$ and $AMCE_b$ [6] represent the mean color difference between reference image and color normalized image in 'a' space and 'b' space respectively. Many researchers [5, 9] employed a very complicated method for color normalization which is consuming higher computational complexity. Thus, computational complexity is an important quality metric in order to evaluate the performance of color normalization algorithms and it's recorded for various color normalization methods in TABLE-I.

The following must be true for evaluating the performance of color normalization methods, inspired from the hypotheses mentioned in the section-II.

- The mean value of PCC [6] should be closed to 1.
- The mean value of AMCE [6] both in 'a' and 'b' space should not deviate much from zero.
- Additionally, we have also introduced a new metric Absolute Mean Luminance Error (AMLE) which is associated with the fourth hypothesis. The mean value of AMLE must be closed to 0.

Mathematical formula for AMLE is given below which is computed in l space.

$$AMLE = \left| \frac{1}{W} \sum_{i=1}^W \mu(l_{in}) - \frac{1}{W} \sum_{i=1}^W \mu(l_{is}) \right| \quad (22)$$

where l_{in} is the local content at i^{th} window of color normalized image in l space, l_{is} is local content at i^{th} window of source image in l space, μ indicates local mean and W is the total no of windows.

All these aforementioned quality metrics are evaluated for 100 no of colorectal cancer histopathology images. The mean values of those quality metrics along with CPU time is presented in TABLE-I.

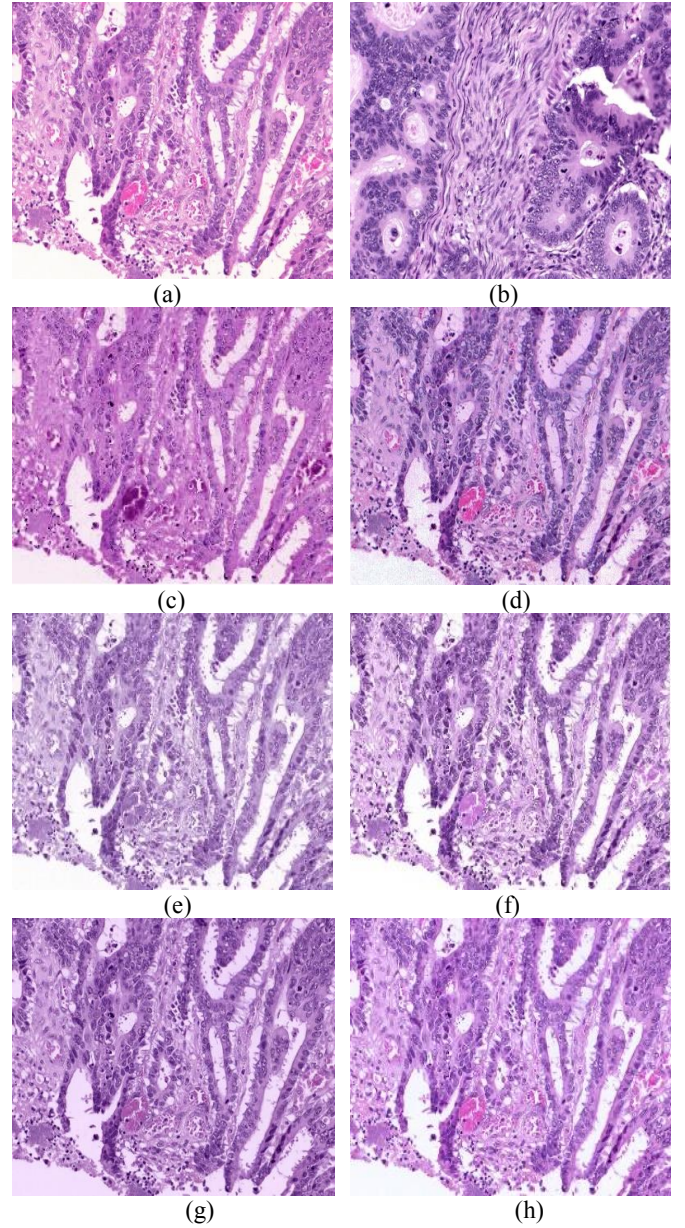


Fig. 1. (a) Source image of colon cancer histopathology image, (b) Target image, (c) Color Deconvolution by A.Khan [5], (d) Histogram Specification, (e) Structure preserving color normalization [9], (f) FMR by S.Roy et al [6], (g) Reinhard algorithm [4], (h) Proposed Modified Reinhard method

Clearly from Fig.1, it can be observed that Histogram Specification (HS) and Reinhard method [4] do not always preserve the background luminance of source image, during color normalization. Moreover, it can be observed from TABLE-I that, mean value of PCC of both the HS and Reinhard method are very closed to 1, which indicates that most of the source information is preserved in their color normalized image. Thus, HS method and Reinhard method satisfy the first hypothesis, however, they are unable to satisfy third and fourth hypothesis. The AMLE value for both of the methods are significantly higher. Color Deconvolution method, proposed by A.M. Khan et al. [5], have mean value of PCC 0.864, shown in TABLE-I. This reveals that by their method there is approximately 13.6% data loss, while doing color normalization. Thus, their method does not satisfy the

first hypothesis. Subsequently, this can also be visualized from Fig.1c.

Vahadane et al [9] tried to preserve the structure of the source image in the color normalized image by their method, shown in Fig.1e. However, they did not preserve all the color variation of source image for example they did not preserve the pink spot in Fig1e. Although their method has done a

TABLE- I
QUALITY METRICS FOR COLOR NORMALIZATION OF COLORECTAL CANCER
HISTOPATHOLOGY IMAGES (MEAN VALUE OF 100 IMAGES)

Color Normalization Method	PCC	$AMCE_a$	$AMCE_b$	AMLE	Proc Time (sec)
HS	0.9835	0.04	0.06	21.82	1.25
Reinhard [4]	0.9976	3.5×10^{-14}	1.0×10^{-14}	20.53	1.2
Color Deconvolution [5]	0.8640	1.17	2.32	14.65	93
FMR [6]	0.9988	2.26	3.27	1.3×10^{-6}	2.1
SPCN [9]	0.9910	1.08	2.35	4.89	119
Proposed method	0.9999	1.5×10^{-14}	1.2×10^{-13}	1.2×10^{-7}	1.1

decent job in terms of preserving all the essential data of source image, the computational complexity by their method is significantly higher which can be observed in TABLE-I. FMR method by S.Roy et al [6] have almost preserved all the essential source information in their processed image, the mean value of PCC by their method is 0.9988 which is very closed to 1. However, the only limitation by their method is that they got AMCE value deviated from 0, thus, their method does not satisfy the second hypothesis.

In TABLE-I, this is observed that proposed Modified Reinhard method has the best mean values of quality metrics, compared to any other state-of-the-art methods. This can also be visualized from the Fig.1 that our proposed method has got the best visual result, compared to other existing methods. Subsequently, this can be observed that mean PCC value by proposed method is closest to 1 (0.9999), shown in TABLE-I, which supports the result of our statistical analysis. This reveals that proposed Modified Reinhard method preserves every little information of source image in the final color normalized image. Moreover, by our proposed method, mean value of AMCE value both in 'a' and 'b' space are found very much closed to zero, which is desirable. This was not true for FMR [6] method. Subsequently, from Fig.1, this can be observed that our proposed method preserves the white luminance portion of the source image, which was not true for Reinhard method [4]. Moreover, Fig.1h shows that our proposed method can preserve all the color variation (even the reddish-pink spot) of source image, unlike other existing color normalization methods. Also, the computational complexity by our proposed method is the least compared to existing methods, which can be noticed from TABLE-I.

VI. CONCLUSION

A modified Reinhard algorithm was proposed for color normalization of histopathology images. The limitations of conventional Reinhard method were first addressed and then those were alleviated in our proposed method. Moreover, because of transferring the color globally, the computational complexity of proposed color normalization method was significantly lesser than other recent existing methods. This is quite amazing that without much computation, our proposed algorithm achieved desirable result for color normalization. We believe that color normalization is just a pre-processing technique which should be employed prior to classifier, thus, according to our understanding, employing neural network or other complicated method just for color normalization is not so feasible. Furthermore, it was mathematically proved that our proposed method satisfied all the four hypotheses of color normalization. The experimental results also supported this mathematical proof. The qualitative and quantitative results shown that our proposed Modified Reinhard method is outperforming other state-of-the-art methods.

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