Original Article

Referenceless image quality evaluation for whole slide imaging

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Abstract

Objective: The image quality in whole slide imaging (WSI) is one of the most important issues for the practical use of WSI scanners. In this paper, we proposed an image quality evaluation method for scanned slide images in which no reference image is required. **Methods:** While most of the conventional methods for no-reference evaluation only deal with one image degradation at a time, the proposed method is capable of assessing both blur and noise by using an evaluation index which is calculated using the sharpness and noise information of the images in a given training data set by linear regression analysis. The linear regression coefficients can be determined in two ways depending on the purpose of the evaluation. For objective quality evaluation, the coefficients are determined using a reference image with mean square error as the objective value in the analysis. On the other hand, for subjective quality evaluation, the subjective scores given by human observers are used as the objective values in the analysis. The predictive linear regression models for the objective and subjective image quality evaluations, which were constructed using training images, were then used on test data wherein the calculated objective values are construed as the evaluation indices. **Results:** The results of our experiments confirmed the effectiveness of the proposed image quality evaluation method in both objective and subjective image quality measurements. Finally, we demonstrated the application of the proposed evaluation method to the WSI image quality assessment and automatic rescanning in the WSI scanner.

Key words: Digital pathology, image quality evaluation, linear regression analysis, visualization, whole slide imaging

INTRODUCTION

The technology of whole slide imaging (WSI) system is a key to the innovation of digital pathology,[1-3] such as workflow management, image analysis,[4,5] conferencing, and education. However, there still remain a number of issues: improvement of image quality, acquisition, and display of the accurate imagecolor, and standardization of image format. As it is practically important for WSI scanners to provide images of good quality, image quality evaluations of scanned slide is needed to manage the image quality of the WSI scanner. In this paper, an image quality evaluation method suitable for WSI is presented.

Currently, image quality assessments are usually performed subjectively by an individual. However, this approach is

not efficient because it takes a long time for a person to perform the evaluation, and, on top of this, there are the variability of human perceptions and observers' fatigue. For the objective image quality assessment, mean square error (MSE), peak signal-to-noise ratio (PSNR) or other objective measures[6-8] are used. These image quality assessments need a reference image, which is the undegraded version of the image under evaluation. In the application to the WSI scanner, however, it is not possible to obtain an ideal reference image, and the quality evaluation must be performed without using a reference image. Thus, no-reference image quality evaluation methods are most suitable for WSI applications. Methods for no-reference (or blind) image quality assessment have been developed,[9-14] but most of them are based on the evaluation of either sharpness or noise.[9-13] Since the main factors that affect the image quality in the WSI scanner are the focusing error and the noise, it is ideal to derive an image quality evaluation index incorporating both blur and noise. Choi *et al.*, proposed a no-reference image quality assessment method using both blur and noise measurements.[14] In their method, quantitative values for blur and noise were calculated, and the evaluation index was determined by applying linear regression analysis to the linear combination of four factors related to noise and blur. Similar to the method in reference 14, we present a no-reference image quality evaluation method which considers both blur and noise. The conventional methods to evaluate blur and noise are employed, and the image quality evaluation index is predicted by the linear combination of two degradation factors - blur and noise. In our proposed method, the weights for these factors are determined by regression analysis using a training data set which is selected in accordance with the intended purpose of the image quality evaluation, i.e., image analysis or clinical usage. In this case, the scale of the image quality metric is uniquely determined based on users' intents, making it easy to manage the image quality evaluation.

In our experiment, both objective and subjective measurements were used as the target of predictions wherein the validity of the proposed algorithm is confirmed. We also demonstrate the application of the proposed evaluation method to the image quality management in the WSI scanner. The proposed method is applied to the WSI of a mouse embryo slide. The mouse embryo slide image contains all tissue organs and as such the evaluation results from the mouse embryo images can be utilized for image quality management. Furthermore, we show the capability of the proposed image quality evaluation method to enhance the efficiency of WSI scanning.

METHODS

The proposed image quality evaluation method is based on the information of the image's sharpness and noise measurements. The quality evaluation indices are then calculated from the linear combination of both measurements. Although image compression is also known to have an effect on image quality, in this work the effect of image compression is not considered.

Sharpness Evaluation

Many papers have reported on methods to quantify the blur in the image based on sharpness evaluation. Most of them detect the edges in the image and defines the evaluation index based on the spread of each edge.[10,11] In these detection methods the edges in the image are detected by differential filters such as the Sobel filter. In our work, we refer to Canny's edge detection[15] and applied the Sobel filter to both horizontal and vertical directions to make the results more robust from image rotations. Since the scanned slide image is usually a color image, such as RGB color, it is converted into a gray-scale image before processing; the gray-scale image is the Y component in CIE XYZ color space.[16] The gray-level image is first processed with a two-dimensional Gaussian filter (3×3 pixels, $\sigma=0.5$), followed by the application of Sobel filter where the gradients of the horizontal direction G_x and vertical direction G_y are calculated at each pixel. The intensity and the direction of the edge are computed as

$$|G| = \sqrt{G_x^2 + G_y^2} \tag{1}$$

$$\theta = \arctan\left(\frac{|G_y|}{|G_x|}\right) \tag{2}$$

where θ is the direction sampled at $\frac{\pi}{4}$ as shown in Figure 1. The local maximum gradient is detected for each edge's direction. The pixels whose gradient are larger than the threshold value are regarded as the edge pixel. The pixel width between local maximum and local minimum is measured at all edge pixels as shown in Figure 2 and their average value is defined as the measure for sharpness.

Here, the width of edge w is modified as follows:

$$w_C = \begin{cases} w & \text{if edge direction is horizontal or vertical} \\ \sqrt{2}w & \text{otherwise} \end{cases} \tag{3}$$

and the sharpness evaluation measure s for the image which has N edges is represented as

$$s = \frac{1}{N}\sum_{i=1}^{N} w_C(i) \tag{4}$$

where $w_C(i)$ is the edge's spread of ith edge. If the measured sharpness s is large, it is considered to be a blurry image. Otherwise, the image is regarded as sharp.
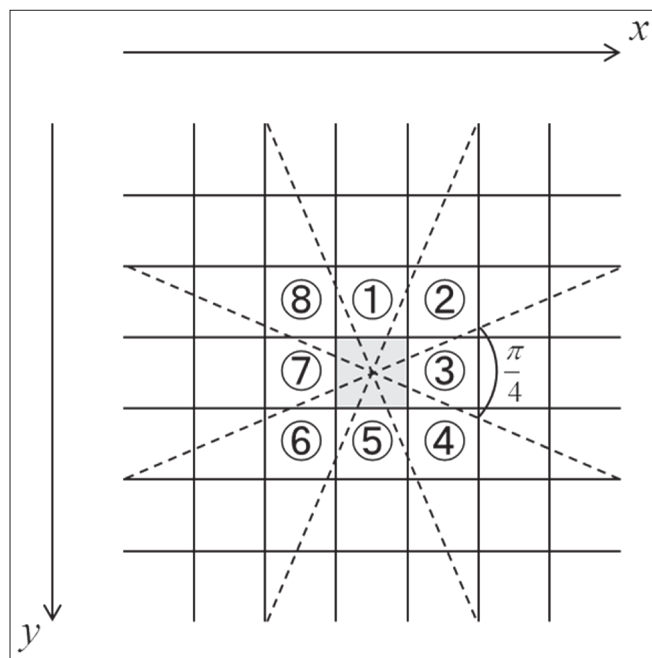
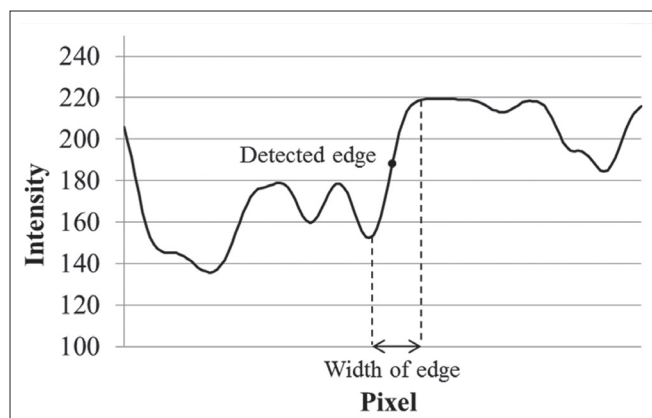**Figure 1: Determination of directions corresponding to *θ* of gradients**

Figure 2: An example of the profile of intensity with a certain direction

Noise Evaluation

Since noise also affects the image quality of scanned slides, the implementation of an evaluation algorithm for noise is also considered. Several authors proposed to estimate noise from the entire image itself,[12-13] but this takes longer time to compute. Similar to reference 14, we proposed a simple algorithm to evaluate the amount of noise present on the assumption that it is an independent random variable. In the noise evaluation, the unsharp masking technique, which is often used in image enhancement, is employed. In this method, the original image is first blurred by using a Gaussian filter and the resulting blurry image is subtracted from the original image. The result of the subtraction produces large values for pixels which belong to edges or if the pixels are noises. To highlight the noise's pixels, the center pixel in

a 3×3 window is replaced with the minimum difference between its surrounding pixels as shown in Figure 3, and this process is repeated on all pixels.

The mean square of the minimum differences of all pixels in the entire image is defined as the evaluation measure for noise:

$$n = \frac{1}{M} \sum_{j=1}^{M} \left[d_{\min}(j) \right]^2 \qquad (5)$$

where *M* is the number of pixels in the image and $d_{\min}(j)$ represents the minimum difference in a 3×3 window at *j*th pixel. Since we assume that noises appear independent of color channels, this process is done on red, green, and blue channels independently, i.e., R, G, and B channels respectively. The average value of *n* for the three color channels is considered as the evaluation measurement for noise. This measurement is expected to be large if the image includes a lot of noises.

Regression Model

The image quality evaluation indices are derived from the previous two evaluation measurements, namely the sharpness and noise measurements. The image quality evaluation index *q* is calculated using the following equation wherein the sharpness and noise measurements are denoted by *s* and *n*, respectively,

$$q = \alpha + \beta s + \gamma n \qquad (6)$$

The coefficients of prediction *α, β,* and *γ* are derived by linear regression analysis using a training data set. The training data set varies depending on the purpose of the image quality evaluation. If the purpose of the evaluation is image analysis, *q* in Eq. (6) is represented by the MSEs of the images in the training data set; we refer to the MSEs as the objective evaluation scores. If we want to obtain an image quality evaluation index for diagnostic purposes, the results of the subjective evaluations are considered for *q*.

RESULTS

We performed evaluation experiments to confirm the validity of the proposed image quality evaluation method. In the experiments we compared the values of the image quality indices calculated from the proposed method with the reference values. The results of the comparison show the effectiveness of the proposed image quality evaluation method. Furthermore, we applied the evaluation method to the entire slide image and we have verified the potential of the proposed method for practical application.

Evaluation Experiment with Objective Method

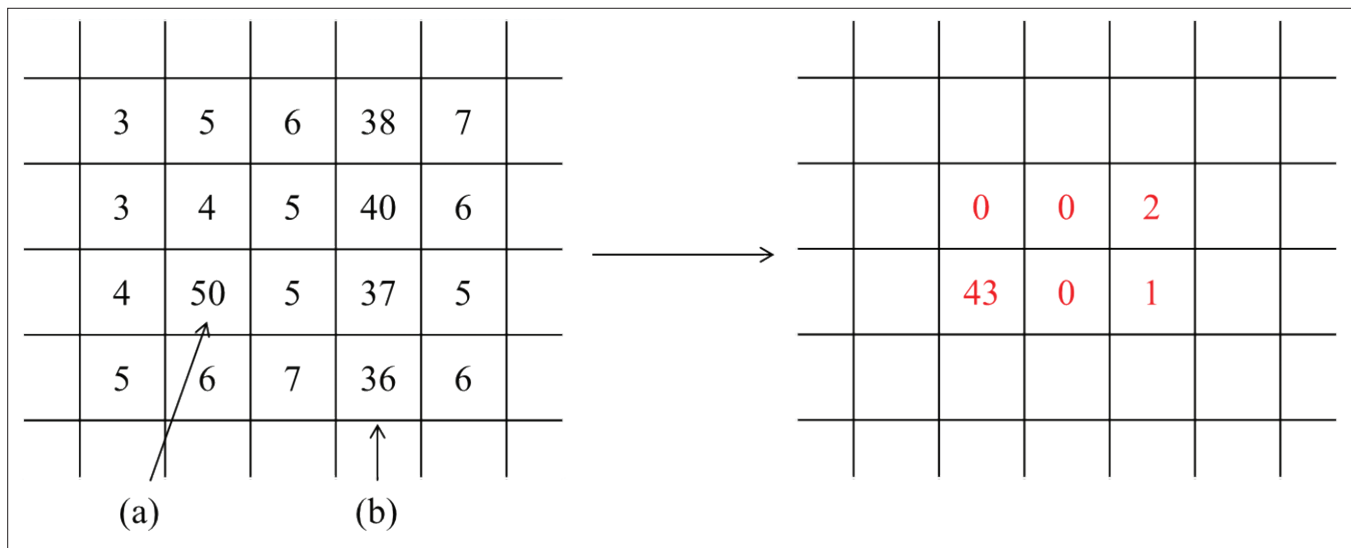First, the evaluation experiment was conducted by using the objective evaluation scores, i.e., MSE. We manually

Figure 3: An illustration of the result of the noise detection process on pixels' intensities. The left figure is an example of the pixels' intensities in a 5×5 neighborhood while the figure on the right shows the result of the detection process. In the right image, a higher value means the pixel considered to be noise. (a) A noise-likely pixel and (b) Edge-likely pixels

selected 100 regions from the mouse embryo slide shown in Figure 4 which was scanned with NanoZoomer 2.0-HT (HAMAMATSU Ltd., Hamamatsu, Japan) at 20× and encoded into the JPEG-compressed image with quality factor 80 (relatively high). The embryo slide contains all types of tissue organs hence we could show the validity of the evaluation method regardless of the type of tissue organs.

The extracted regions were exported into bitmap format and trimmed to 1,200×800 pixels (20×, 0.46 μm/pixel). Then, we simulated blurry images by applying Gaussian filter (5×5 pixels) and noisy images by adding Gaussian noise. An excessively sharpened image appears unnatural and could be regarded as a degraded image, so we also simulated artificially sharpened image by applying unsharp masking. The standard deviations for the Gaussian filter and Gaussian noise were varied from 0.2 to 2 at 0.2 intervals and 2 to 20 at 2 intervals, respectively. On the other hand, the coefficient of the mask for the unsharp masking was varied from 0.2 to 2 at 0.2 intervals. These processes generated a total of 3,000 degraded images. The examples of digitally degraded images are shown in Figure 5. We used 300 degraded images, which were selected from the digitally degraded images at random, and 100 original images to comprise the training data. The MSEs of these training images were used for q in the regression analysis. The MSE of an M-pixel gray-level image is calculated by the following equation:

$$\text{MSE} = \frac{1}{M}\sum_{j=1}^{M}\left[I_{\text{tar}}(j) - I_{\text{ref}}(j)\right]^2 \qquad (7)$$

where $I_{\text{tar}}(j)$ and $I_{\text{ref}}(j)$ represent the pixel intensities at

the jth pixel for the target image and reference image, respectively.

The regression analysis resulted in values of -631, 105, and 15.1 for the coefficients of prediction, α, β, and γ, respectively. The adjusted coefficient of determination R^2 was 0.895, and the standard error was 46.6. The graph illustrating the relation between the evaluation index q and the actual MSE for the test and training data is shown in Figure 6. Pearson's correlation coefficient between the calculated image quality index q and the actual MSE was found to be 0.946. The calculated quality indices q have a high correlation with the actual MSE with small variations depending on the image content or types of degradations. There results show that we can evaluate the image quality based on the images' MSEs as implemented in the experiment. By choosing the effective threshold value for image analysis, we could acquire the image which has sufficient image quality.

We also investigated the effectiveness of the proposed image quality evaluation method when the magnifications of the images vary, and when the images are scanned by different scanners. The same embryo slide used in the previous experiment was scanned with MIRAX SCAN (3DHISTECH Ltd., Budapest, Hungary) and 20 regions, similar to the regions which were selected in the previous experiment, were captured and trimmed to 1,200×800 pixels (20×, 0.61 μm/pixel). Then, 600 degraded images, which consisted of blurry, noisy and sharpened images, were generated in similar manner to the pervious experiment as well. Using the regression coefficients obtained in the previous experiment when the training images were scanned with NanoZoomer 2.0-HT, Pearson's correlation coefficient resulted to 0.888. When half of the training images were changed to the images scanned
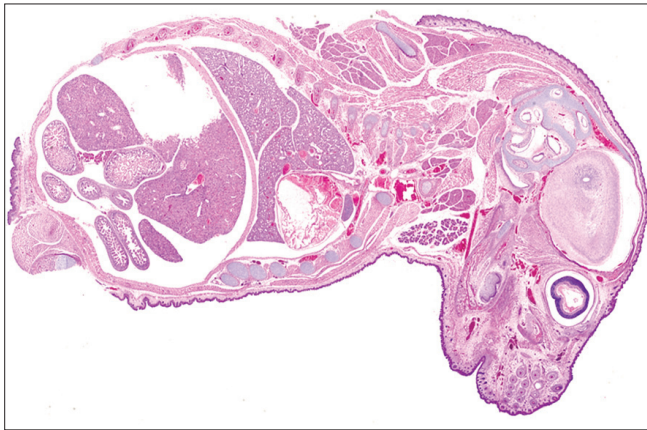
Figure 4: Whole slide image of the H and E stained embryo slide used in the experiment. The training and test images were extracted from this image
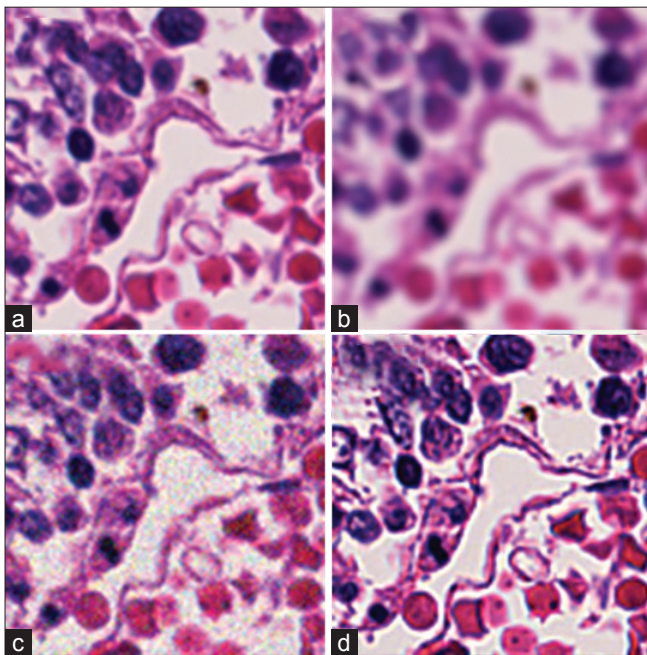

Figure 5: Digitally degraded images: (a) original, (b) blurry, (c) noisy, and (d) excessively sharpened images
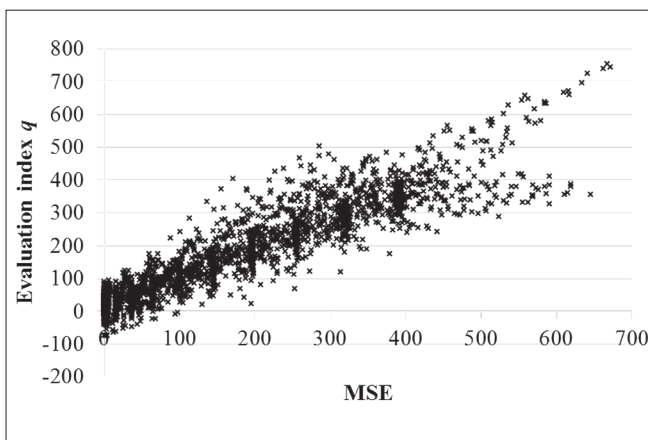

Figure 6: Relation between the evaluation index and MSE using the data scanned by NanoZoomer 2.0-HT

by MIRAX, Pearson's correlation coefficient was 0.892 and the standard error was 62.6, which are closed to the results in the previous experiment. The graph showing the relation between the evaluation index q and the actual MSE is displayed in Figure 7. This plot shows that a change in the scanning device hardly affects the prediction accuracy of the evaluation index. Therefore, provided that the test and training images have the same resolution, we could use the same regression coefficients regardless of the scanner model by which the images were scanned.

In the next experiment we investigated the effect of image resolution to the proposed image quality evaluation method. Again, 20 regions were extracted from the WSI of the mouse embryo scanned with Nanozoomer 2.0-HT, at 40× magnification. The extracted regions were trimmed to the same pixel size 1,200×800 pixels (40×, 0.23 um/pixel), then 600 degraded images, which consisted of blurry, noisy, and sharpened images. Pearson's correlation coefficient between evaluation index q and the actual MSE was 0.507 when the regression coefficients derived from the images scanned at 20× were used. We included half of the 40× images in the training data, and calculated new regression coefficients. The regression coefficients α, β, and γ, resulting from this new set of training data were -264, 35.5, and 17.4, respectively. In this case, Pearson's correlation coefficient for the 40× images with respect to MSE was 0.965 and the standard error was 25.1. Figure 8 illustrates the relation between the evaluation index q and MSE. This shows that we can improve the accuracy of the evaluation index by aligning the training data depending on the resolution of the test images.

Evaluation Experiment with Subjective Method

For images which will be used for undertaking diagnoses, we considered the results of the subjective evaluation score given by human observers to calculate the regression coefficients, which are to be used to derive the image quality evaluation index, q of a test image. The survey to get the subjective scores was conducted through internet. All participants were invited to this survey by e-mails from the authors. The participants were composed of four pathologists, two physicians, two technologists, 21 image engineers, and three other professionals. At the beginning of the survey, instruction for scoring the test images was shown to all observers with a few examples. The observers were then shown with images of different conditions for them to rate. Figure 9 shows the typical screen shown to the observer via the internet.

Fifty 400×400 pixel images were extracted from whole slide images of different tissue slides, such as breast or liver, scanned by NanoZoomer 2.0-HT wherein half of them were chosen as the good-quality images and the others were subjectively labeled the bad ones. These

images were rated by the participant with scores from 1 (worst) to 5 (best). The scores given to each image were averaged and used as the subjective scores. The variance of the subjective scores given to each image was calculated in order to investigate the variability of the scores. The averaged variance for all sample images was found to be relatively small, 0.619. We evaluated the effect of the training data on the accuracy of the
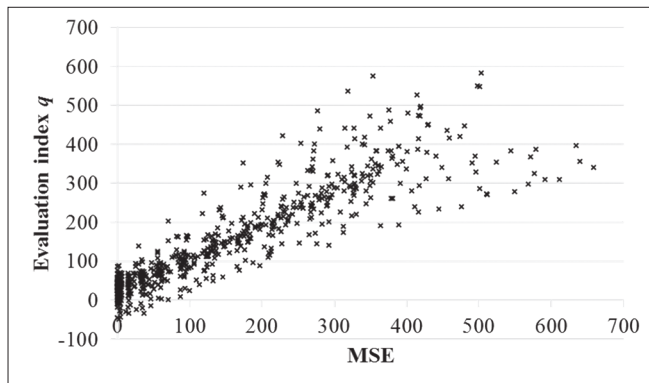

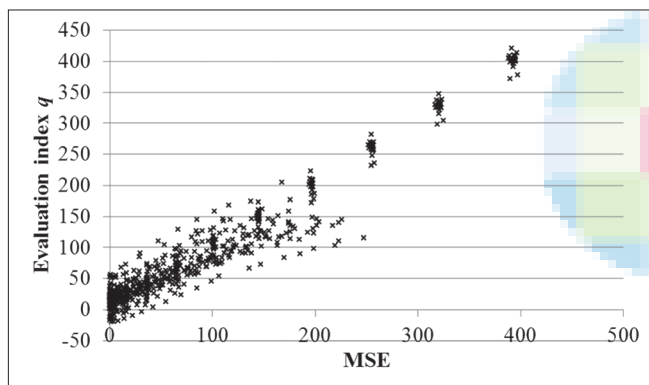**Figure 7:The relation between the evaluation index and MSE using the data scanned by MIRAX SCAN**

Figure 8:The relation between the evaluation index and MSE using the data scanned by NanoZoomer 2.0-HT at 40×.The training and test data consist of 40× images

linear regression analysis, Eq. (6), to predict the image quality of a given image. For this purpose, half of the images were used for regression analysis while the other half was used as test data. To ensure that the result was independent from the selected data, the analysis was conducted 10 times wherein the training data were randomly selected at each run. In this experiment, the average Pearson's correlation coefficient between the calculated evaluation index q and the subjective score was 0.874 and their variance was 0.00098, while the standard error in the regression analysis was 0.471. This shows that the evaluation index q have a high correlation with the subjective scores regardless of the composition of the training data.

An experiment using only the subjective scores, which were given by four pathologists, was also performed; the average variance of the subjective scores was found to be 0.527. Regression analysis was also performed 10 times, and the average of correlation coefficients between the evaluation index q and the subjective score was 0.839 with variance of 0.0013. The evaluation index shows relatively strong correlation with the subjective scores given by pathologists. This implies that we can use the proposed image quality evaluation method for clinical application with pathologists specifying the threshold value for the quality evaluation index.

Application to WSI Scanning
We next illustrate the application of the current image evaluation method to the image quality management of the WSI scanner. In the image quality management, only the regions which were detected to be of bad quality will be rescanned. This makes it possible for the WSI scanners to perform the scanning efficiently. To simulate this process, the entire WSI is divided into blocks and the image quality evaluation algorithm is performed on each block. This procedure is illustrated in Figure 10.
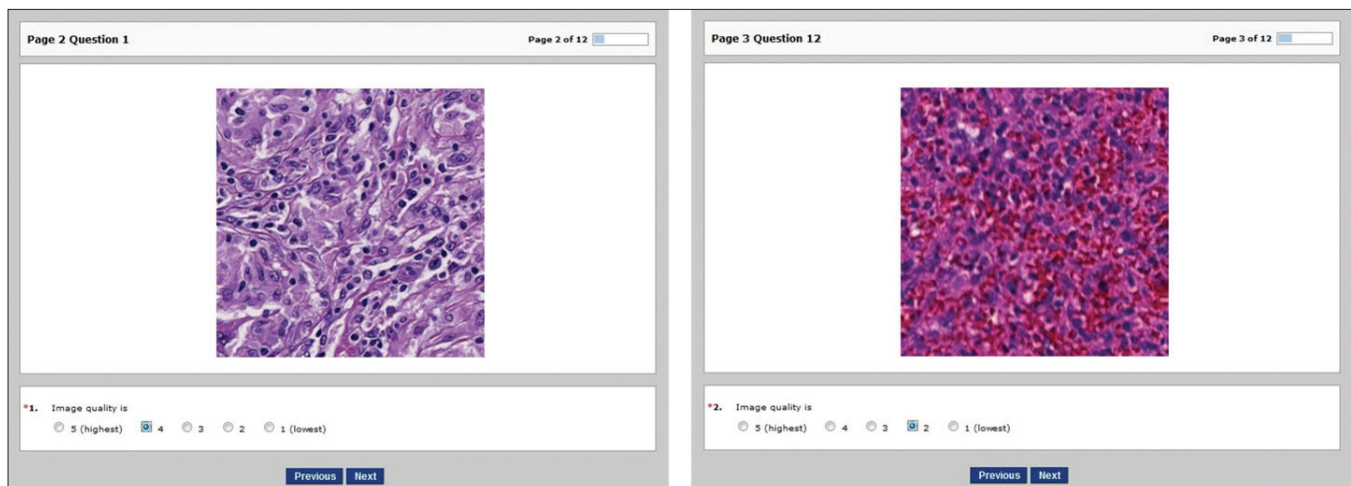
At first, the WSI is divided into 400×400 pixel image

Figure 9: Screenshots of the survey

blocks, and then the block which is dominated by white pixels is regarded as the region of noninterest and ignored in the evaluation process. Here, the white pixel was defined as the pixel whose intensity is larger than 200. If the block has less number of white pixels, the block is processed and evaluated for sharpness and noise. Then, the evaluation index q for each block is calculated according to Eq. (6). In addition, by visualizing each block according to the evaluation index q, we would be able to observe the regions whose image quality are bad. If the detection of the bad-quality region is integrated in the WSI scanning process, rescanning of tissue slides would be more efficient. In this experiment, the subjective scores obtained in the previous experiment were used as the objective values in the linear regression analysis, so the image which perceptually looks bad was evaluated as a low-quality image. At this time, all 50,400×400 pixel images, which were used in the previous experiment, were used for the linear regression analysis to determine the regression coefficients. The computed regression coefficients α, β, and γ, were -3.34, -0.214, and 0.364, respectively. Figure 11 shows the relationship between evaluation index q and the subjective scores; Pearson's correlation coefficient between these parameters is 0.869.

The WSI of the serial section of the embryo slide used in the first experiment was employed as the test image for the image quality management experiment in WSI scanners. The whole slide image of the tissue slide is shown in Figure 12.

This slide was scanned at 20× in automatic mode. In this mode the scanner selects several points for focusing and determines the optimum focus point automatically. The threshold value for q to determine whether the image quality is good or not, was set to 3.5 since most of the evaluation indices of the good-quality images were more than 3.5 from Figure 11. The blocks with evaluation indices of more than 3.5 were visualized in their original brightness. Otherwise they were shaded darker. The intensities of the regions whose evaluation indices were below 3.5 were varied at different degree. For example, the intensity of a block with an evaluation index that is within 3.5-3 was multiplied by $\frac{7}{8}$ and a block whose evaluation index is within 3-2.5 was multiplied by $\frac{3}{4}$. The background regions, i.e., regions with no tissue or the white areas in the image, were visualized in their original state. Visualization of the image quality evaluation results Figure 13, wherein good-quality regions are indicated with lighter shades, while the bad-quality regions are indicated with darker shades. It is to be noted that the background pixels, i.e., white areas, were excluded in the image quality evaluation.

Most of the regions in this image were evaluated as of good quality. For example, the evaluation indices of 85.6% of the nonbackground regions are higher than 3.
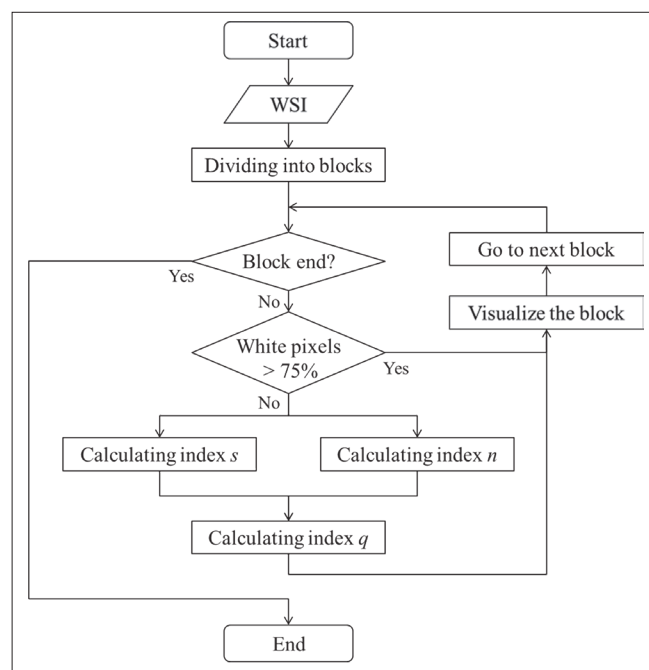

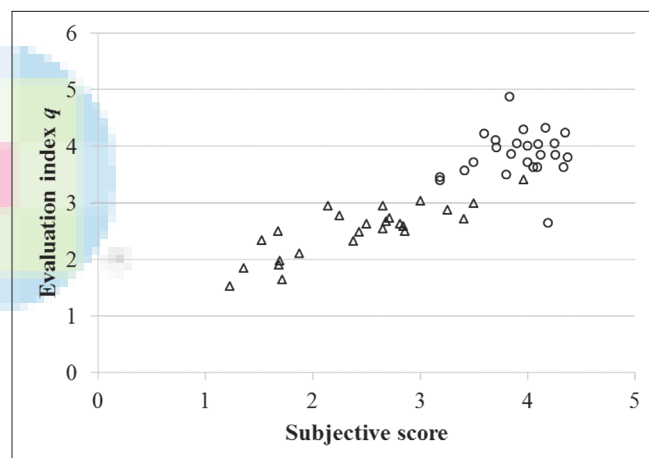**Figure 10: The procedure of image quality evaluation for WSI**

Figure 11: The relation between the evaluation index and subjective score. Circular plots indicate images captured as the good images and triangular plots are bad images which are mainly blurred
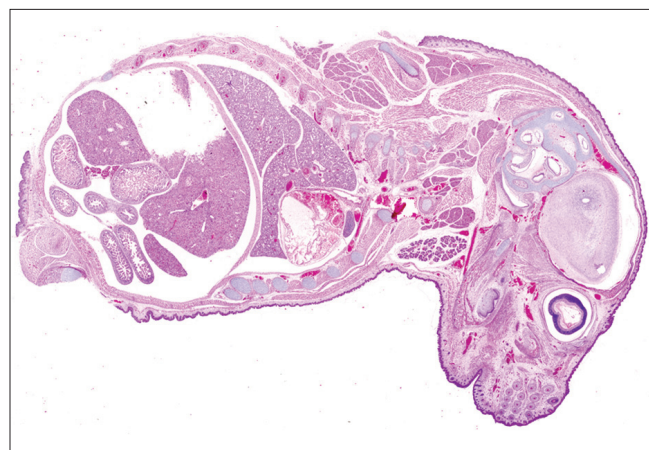

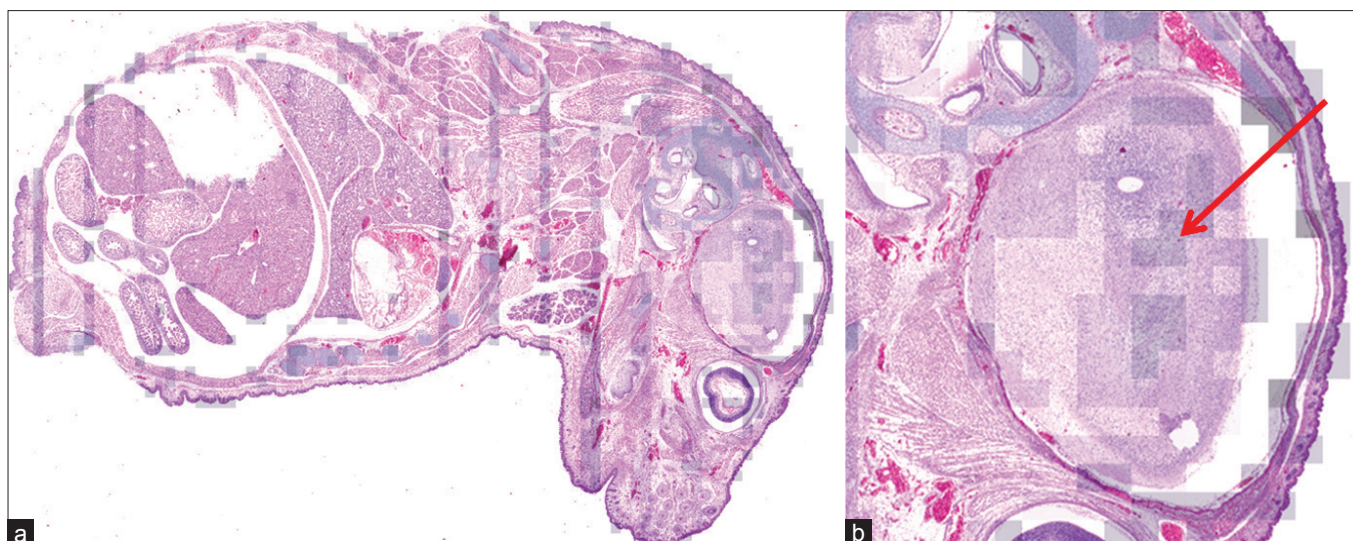**Figure 12: The embryo slide used in the application to WSI**

Figure 13: Visualization of the image quality of a scanned embryo slide. The shaded regions correspond to an evaluation index below 3.5. (a) The whole slide image and (b) the magnified version of the low-quality region
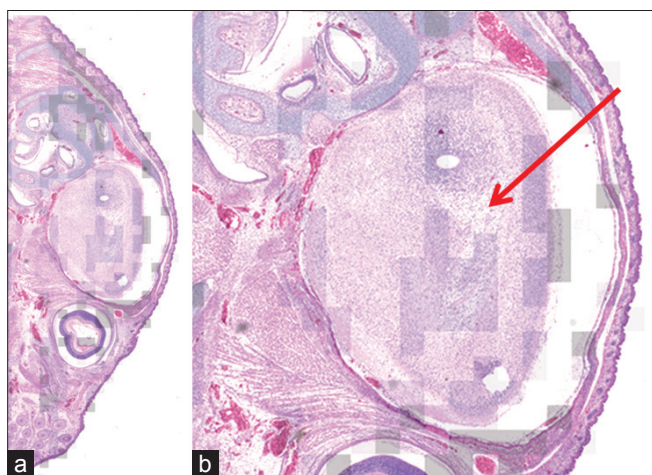

Figure 14: The quality-visualized image of the rescanned slide. (a) Part of the entire image wherein the image quality index was low before and (b) the magnified version of the region specified for autofocusing point

The low-quality area pointed by an arrow in Figure 13 (shaded area) was manually selected for focusing points, then we rescanned this area of the slide. Figure 14 shows the image quality evaluation results of such area from the WSI after rescanning.

The evaluation results of the region, which were evaluated as bad quality in the first image, have been improved. Although the blocks pointed by an arrow in Figure 13b were shaded so dark, the same blocks of the rescanned slide became lighter in comparison to the previous image, as shown in Figure 14b. If the image quality evaluation method we proposed in this paper can be implemented on WSI scanners, only the low-quality regions have to be rescanned.

As the numerical result, in the right $10,000 \times 24,000$ pixels of the image (Figure 14a), 90.7% of the blocks

whose evaluation indices were less than 3 in the first scanned image were dramatically improved. The average increment of evaluation index in the improved region was 0.434, which was very close to the standard error in linear regression analysis, 0.471. This shows the validity of the proposed method in WSI application and its capability to efficiently implement whole slide scanning when it is integrated to the scanning process.

DISCUSSION

We proposed an image quality evaluation method which can quantify the image quality of scanned slides without any reference images. We confirmed the validity of the proposed evaluation method by using the objective and subjective scores. There are a number of WSI scanners available in the market, and each of them has its own hardware specifications, e.g., sensor, optics, etc. Hence the images produced by these scanners have their own unique image quality characteristics. It would have been ideal to investigate the specifications of these scanners such that the evaluation method would be more robust. However this seems difficult at the current stage. Hence, we proposed the evaluation method on a simple assumption where sharp images have large gradients on edge pixels and noises appear independently of spatial relationship, and utilized two different scanners to validate the proposed image quality evaluation method. Although the proposed method has shown to be effective there is still a need for improvement to enhance its applicability to other whole slide scanner models. For example, this paper proposed an evaluation method using linear regression model which employed blur and noise metrics. However, we could further improve the robustness and effectiveness of the method by considering nonlinear models or utilizing other metrics.

This work was an initial investigation on image quality evaluation of whole slide images. In the work we used a mouse embryo slide as we can confirm the robustness of the proposed evaluation method for different kinds of tissue organs with the slide alone. However, using more samples for specific tissue type of different staining will be a subject in the next work.

The automatic determination of regions of interest (ROI) would be also addressed. In this paper, we determined ROI easily on the basis of the white pixels where we regarded a region with a lot of white pixels as the background region. This is considered important because in reality only selected image regions are examined closely. For example, artifacts such as tissue folds and bubbles should be ignored in evaluation process, and detection of an artifact has been developed.[17] Therefore, the determination of ROI has to be improved for efficient and precise image quality evaluation.

CONCLUSION

In this paper, we presented a no-reference image quality evaluation algorithm and its practical usage to WSI scanning. The proposed method can evaluate the image quality of an image without any reference images; the method utilizes the image's sharpness and noise information itself. The image quality evaluation index is derived by regression analysis using a training data, which varies depending on the user's requirement. In our experiments we confirmed the validity of the proposed method wherein we could see strong correlations between the evaluation indices to both objective scores and subjective scores. Furthermore, we illustrated the application of the proposed image quality evaluation algorithm to WSI scanning. We applied the quality evaluation method to the entire WSI and showed its capability to improve the efficiency whole slide scanning.

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