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Multilevel Segmentation Optimized by Physical Information for Gridding of Microarray Images

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ABSTRACT As one of the great advances in modern technology, the microarray is widely used in many fields, including biomedical research, clinical diagnosis, and so on. Evidently, in order to extract the intensity of fluorescence bio-probes accurately, we need to pay special attention to the gridding of microarray at first. To solve the poor effect of the traditional Otsu method for microarray gridding, an innovative algorithm of Otsu optimized by multilevel thresholds is proposed to improve the accuracy and effectiveness of the microarray image gridding and segmentation. The experimental results indicate that considering the physical information carried by microarrays, the improved algorithm of Otsu optimized by multilevel thresholds achieves high-quality gridding and establishes the bio-spot coordinates more precisely. Compared with the traditional Otsu method, its gridding error is reduced to zero, and the integrated relative error of bio-spot coordinates is decreased from 2.89% to 1.05%. This optimization of Otsu combined with physical information of spot-matrix will greatly improve the performance of segmentation so as to make the contribution to extracting the fluorescence intensity of microarray accurately.

INDEX TERMS Microarray image, Otsu method, multilevel thresholds, gridding, physical information.

I. INTRODUCTION

DNA microarray was designed to analyze a large number of gene sequences. It was developed as spot-matrix fixed on the specified position of glass slide to perform thousands of hybridization experiment simultaneously [1]. As one of the great advances in current era, DNA microarray technique is widely applied in many fields including molecular biology, genetics, disease diagnosis, medical treatment, and food safety supervision, etc [2]. There are three important steps, namely, hybridization experiment, image processing and sequence analysis, to determine the success or not of the microarray application. Especially, the image processing plays a potentially tremendous impact on the subsequent analysis [3], [4]. In recent years, a large number of algorithms have been developed in processing the microarray images, and they are mainly focused on image gridding, spot segmentation and bio-probe intensity extraction to analyze the DNA microarray response data [5]. Especially, gridding of microarray is the most important stage in image processing, because it significantly affects the spot segmentation and intensity extraction. Evidently, in order to obtain the accurate intensity conveniently, we also need to pay more attention to the automatic gridding at first.

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Over the past decade, different softwares have been successfully developed to pursuit the perfect gridding for the microarray application, such as ScanAlyze, GenePix, Quant Array, and so on. However, there are serious disadvantages to be tolerated. For instance, the parameters need to be preset manually, and the artificial intervention is a necessary procedure during the segmentation processing [6]. In addition, there are many other related algorithms to be concerned. The Hill-Climbing method for automatic gridding, expressed in [7], can perform gridding properly only if the ideal grids are present. Yet it is difficult to satisfy this ideal situation in practice. And the gridding methods based on pattern classification or intelligence algorithm, such as K-mean cluster, Fuzzy analysis and Genetic algorithm, however, are too computational to be applied [8]–[10]. Other well known approaches are based on histogram segmentation of pixel intensity information. And they have attractive advantages of computational efficiency and few input parameters to automatic gridding, although the optimal threshold is not easy to be searched to distinguish the fluorescence spots from the image background perfectly [11], [12]. Especially, the maximum between-class variance (i.e., the Otsu method) could provide a very simple way to automatic gridding of microarray images [13], [14]. It seems to be a straw for the gridding of microarray automatically. Unfortunately, the Otsu method is only an optimal way to achieve the threshold for histogram with bimodal or multimodal distribution, yet it would fail in confirming the segmentation if the histogram is unimodal or close to unimodal distribution [15]. Worst of all, the area of fluorescent spots is inadequate compared with the entire region of microarray image, which leads to the poor effect on separating the bio-spots from the background.

Though many efforts are focused on this particular gridding problem, they are all limited to scanning the problems in image property alone. Considering the localization information of the fluorescent bio-spots fixed on microarray, a new gridding method is proposed by taking the uniformity of gridding or locating interval as an optimization parameter, to improve the accuracy and the effectiveness of microarray segmentation. Our work employs this novel segmentation algorithm based on Otsu optimized by multilevel thresholds with the physical information, and the results show that this improved Otsu is superior and effective on gridding the microarray image. The rest of the paper is organized as follows: the related knowledge about DNA microarray, Otsu method and novel gridding technique are introduced in Section II. And then, the experimental results and analyses are given in Section III. Finally, the conclusions and discussions are drawn in Section IV.

II. MULTILEVEL OPTIMIZATION METHOD FOR AUTOMATIC GRIDDING OF MICROARRAY IMAGE

A. MICROARRAY

As one of the great advances technology for high-throughput analysis and quantitative detection of DNA sequences, the microarray has a large number of well defined bio-probes fixed at the specified positions on a single glass substrate [16], [17]. It is widely used in many fields. Additionally, traditional microarray usually locates the pre-defined bio-probe as the spots in orderly ranks, like a matrix as shown in Figure 1.

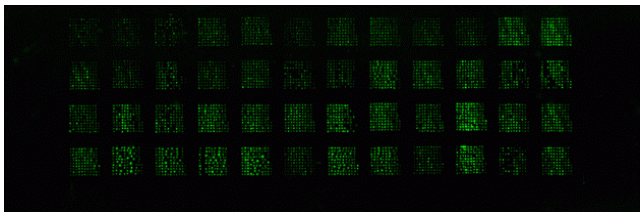

FIGURE 1. Cy3 response image of microarray provided by FZU in 30 *um* resolution.

B. OTSU METHOD

Otsu method provides an optimal threshold, which is selected by the identifying criterion to maximize the separability of the classes in histogram and gray-level [6], [18]. It is a state-of-the-art automatic threshold technique, which determines the optimal threshold value by maximizing the between-class variances of target and signal background [19].

Consider a digital signal $g(x,y)$ which lies in the interval [0, L-1], where L is the number of gray levels. We define the number of pixels with gray value i will be f_i, and denote the total number of pixels as N, so the $g(x,y)$ histogram is defined as a probability distribution p_i

$$p_i = \frac{f_i}{N}, \quad p_i \geq 0, \; u = \sum_{i=0}^{L-1} ip_i \tag{1}$$

where, the u is the average gray-level of $g(x,y)$.

Suppose T is a gray threshold between the target and the background, we could divide these pixels into two classes

$$w_0(T) = \sum_{i=0}^{T} p_i, \;\; w_1(T) = \sum_{i=T+1}^{L-1} p_i = 1 - w_0(T) \tag{2}$$

where $w_0 = \{g(x,y)|0 \leq f_i \leq T\}$ and $w_1 = \{g(x,y)|T+1 \leq f_i \leq L-1\}$. Normally, w_0 is the target or foreground, and w_1 is the background.

Then, there are the foreground mean u_0 and the background mean u_1 shown in the following

$$u_0(T) = \sum_{i=0}^{T} ip_i/w_0(T), \quad u_1(T) = \sum_{i=T+1}^{L-1} ip_i/w_1(T) \tag{3}$$

In Otsu method, it shows that the optimum threshold is determined by considering the most significant distinction between foreground and background. Thus under this criterion, the optimal threshold T^* must make the between-class variance to be maximized [20].

$$T^* = \arg \max_{0 \leq T \leq L-1} \left\{ w_0(T)(u_0(T) - u)^2 + w_1(T)(u_1(T) - u)^2 \right\} \tag{4}$$

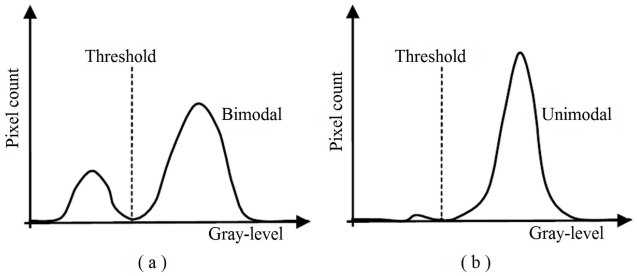

FIGURE 2. Optimal threshold selection in gray-level histogram (a) bimodal distribution and (b) the unimodal or close to unimodal distribution.

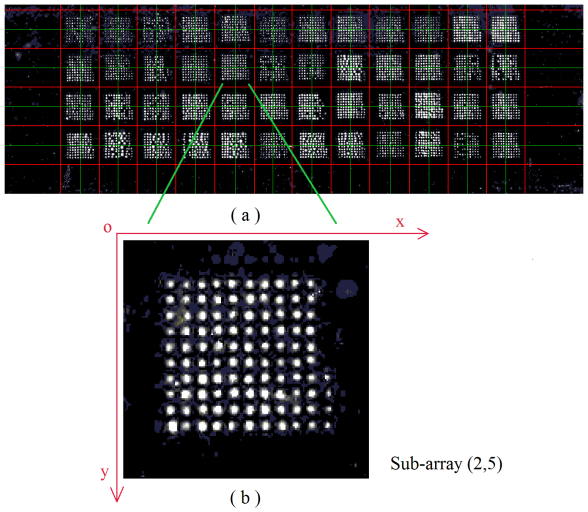

FIGURE 3. The microarray image gridding by Otsu method, (a) Cy3 image of microarray provided by Fuzhou university and (b) sub-array(2,5) of microarray image.

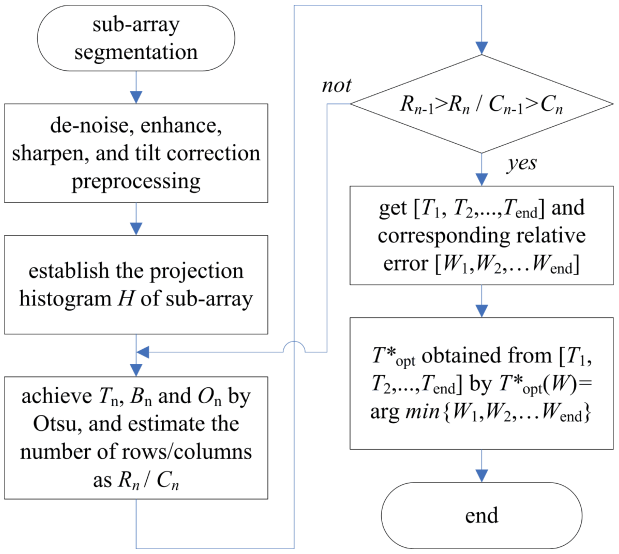

FIGURE 4. Multilevel segmentation method optimized by physical information for gridding of microarray image.

In view of $u = w_0 \times u_0 + w_1 \times u_1$, the (4) could be simply transformed into the following equation [19].

$$T^* = \arg \max_{0 \le T \le L-1} \left\{ w_0(T)u_0^2(T) + w_1(T)u_1^2(T) \right\} \quad (5)$$

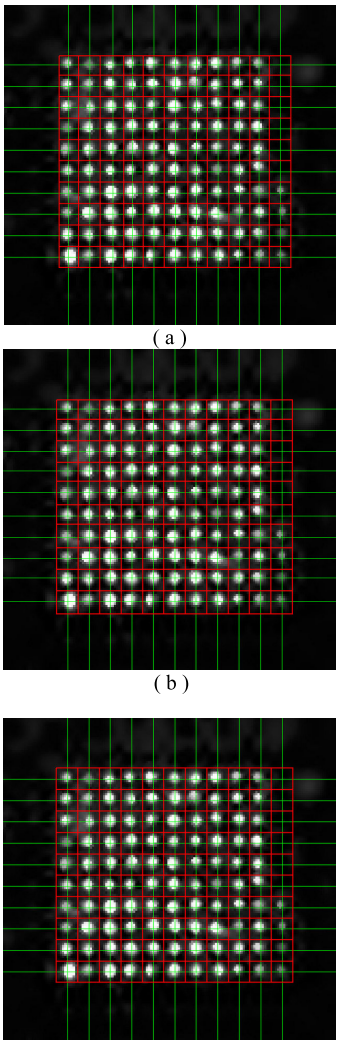

FIGURE 5. Gridding of sub-array(2,5) by Otsu with multilevel thresholds. (a) Gridding of sub-array(2,5) by T_1 threshold. (b) Gridding of sub-array(2,5) by T_{end} threshold. (c) Gridding of sub-array(2,5) by T_{opt} threshold.

However, the Otsu method could achieve an acceptable result when the foreground of image is sufficient different from the background. That is, the image histograms have bimodal or multimodal distributions [19]. Most poignantly, the images of microarray have a large background and the corresponding foreground (i.e., bio-probe region) is very small, which prevents the Otsu algorithm from determining the optimal threshold for efficacious gridding. Therefore, the traditional Otsu is not appropriate for immediate gridding of microarray image.

Several improvements on Otsu method for adapting to the large background have been proposed to overcome the unimodal or distribution close to unimodal. Their basic idea is an addition of a small weight coefficient to adjust the segmentation threshold level which ensures that the ideal threshold should lie at the valley of bimodal, or at the bottom rim of unimodal distribution, as shown in Figure 2, and this improved algorithm is called valley-emphasis method [21], [22].

TABLE 1. Gridding performance of OTSU optimized by mulitilevel thresholds for sub-array(2,5).

Gridding optimized by multilevel	Threshold of row	Threshold of column	Max deviation of W_{rc}	Average deviation of W_{rc}
Otsu threshold of T_1	$T_1 = 44$	$T_1 = 47$	11.24%	3.73%
Otsu threshold of T_{end}	$T_{end} = 29$	$T_{end} = 33$	10.00%	4.50%
Otsu threshold of T_{opt}	$T_{opt} = 39$	$T_{opt} = 33$	0	0

The projection histogram H is condensed to 8 bit gray-level and the integrated relative error $W_{rc} = (W_r + W_c)/2$.

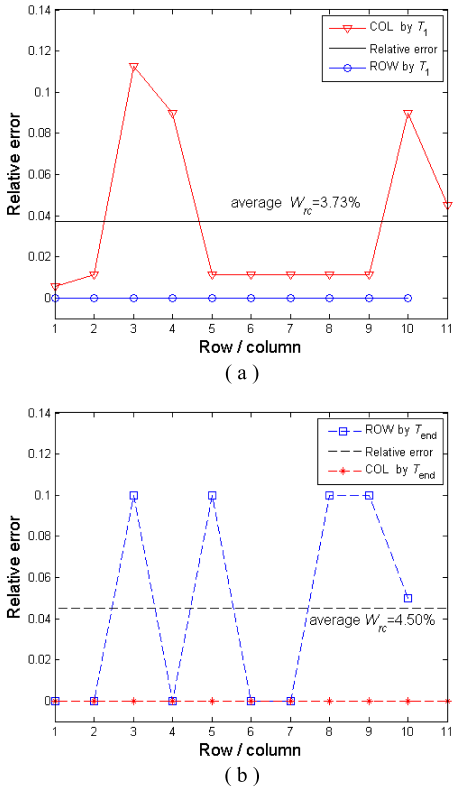

FIGURE 6. Gridding details of relative error under the threshold of T_1 and T_{end}, while (a) is demonstrated by T_1, and (b) is demonstrated by T_{end}.

As Figure 2 shows, corresponding in mathematics, there is a small weight, denoted as τ, adjusting the output threshold of (5), which is demonstrated in (6).

$$T_\tau^* = \arg \max_{0 \le T \le L-1} \left\{ \tau(w_0(T)u_0^2(T) + w_1(T)u_1^2(T)) \right\} \quad (6)$$

C. MULTILEVEL OPTIMIZATION METHOD FOR AUTOMATIC GRIDDING

Valley-emphasis, partially resolves the problem that is the histogram with unimodal or close to unimodal distribution by weighting the threshold function of the Otsu method, but it is also difficult to search an optimal coefficient τ for valley-emphasis algorithm to adjust the acceptable threshold level. So it is still not suitable to apply this improved method for

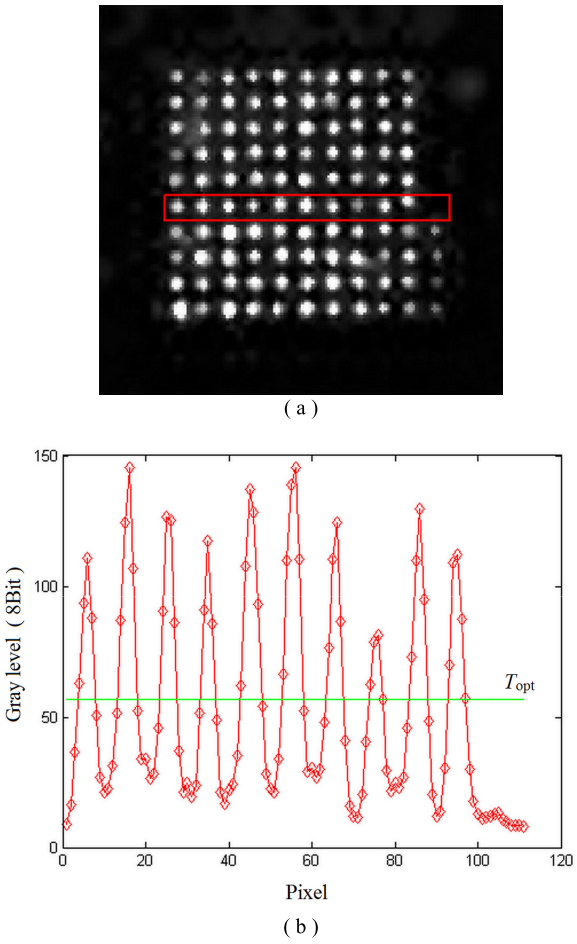

FIGURE 7. Segmentation optimized by multilevel for sub-array(2,5) on the row 6.

gridding in practice. Considering the location information of spot-matrix of microarray bio-probs, we could construct an objective function of optimum criterion for gridding of microarray by uniform interval. In this way, a target function expressed as the average relative deviation W, which is confirmed based on the difference of geometric position between the manufacturing coordinates and them in spatial gridding, would be simply used to determine the optimal threshold. Especially, this innovative solution perfectly avoids pursuing the acceptable τ of valley-emphasis method for optimum gridding.

The proposed gridding method of multilevel optimized by physical information of spots is to be demonstrated as following:

Firstly, we would prepare the microarray image with essential preprocessing, such as de-noise, enhance, sharpen, and tilt-correction, etc [23], [24].

Secondly, in order to reduce the complexity of calculation, we could realize the row and the column projection of microarray image, to establish the projection histogram H_x or H_y, oriented to X-axis or Y-axis.

Thirdly, all the pixels of projection H_x or H_y are taken to be divided into foreground and background, respectively.

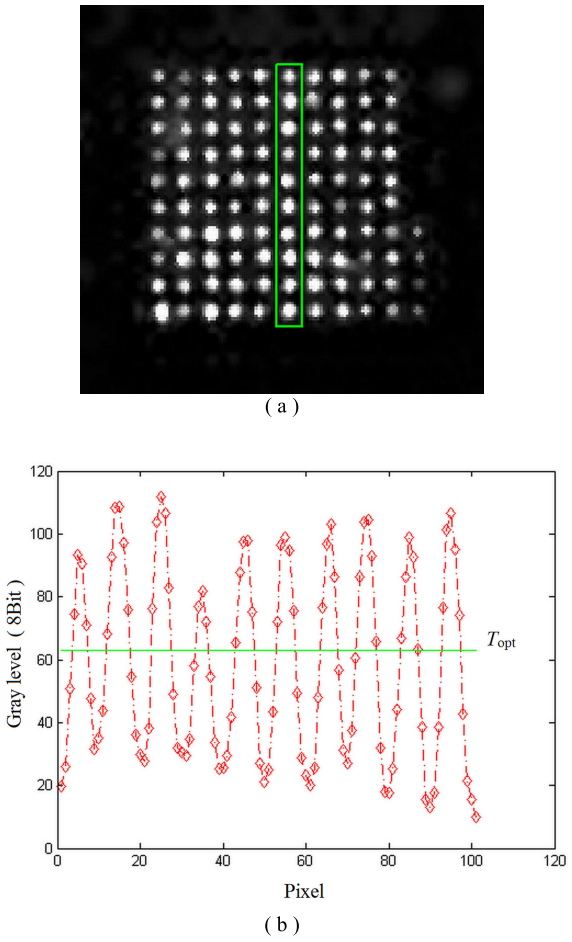

FIGURE 8. Segmentation optimized by multilevel for sub-array(2,5) on the column 6.

Thus we could form a new background by Otsu segmentation, and denote this new background as B_{x1} or B_{y1} while the corresponding Otsu gridding threshold as T_{x1} or T_{y1}. Besides, the number of rows R_{N} and the columns C_{N} would be estimated as spot-matrix parameters for automatic gridding, simultaneously.

Then, under the constraint of spot-matrix row and column parameters, we could continue to separate a new background from B_{x1} or B_{y1} on the above-stated method, and denote them as B_{y2} or B_{y2}, similarly. Furthermore, we also need to estimate the number of rows R_2 and columns C_2 at this time, and sign $R_{\mathrm{N}} = \max\{R_n\}$ and $C_{\mathrm{N}} = \max\{C_n\}$. In this manner, we could also obtain a series of thresholds and store them as $[T_{x1}, T_{x2}, \ldots, T_{x-\mathrm{end}}]$ or $[T_{y1}\ T_{y2}, \ldots, T_{y-\mathrm{end}}]$ until a terminating condition come along with $R_{n-1} > R_n$ or $C_{n-1} > C_n$.

And finally, according to the thresholds $[T_{x1}, T_{x2}, \ldots, T_{x-\mathrm{end}}]$ or $[T_{y1}, T_{y2}, \ldots, T_{y-\mathrm{end}}]$ of projection, we also could get a series of corresponding relative deviations as $W_{x1}, W_{x2}, \ldots W_{x-\mathrm{end}}$, or $W_{y1}, W_{y2}, \ldots W_{y-\mathrm{end}}$, respectively. Therefore, the optimal threshold $T^*_{x-\mathrm{opt}}$ or $T^*_{y-\mathrm{opt}}$ is going to be obtained from $[T_{x1}, T_{x2}, \ldots, T_{x-\mathrm{end}}]$ or $[T_{y1}, T_{y2}, \ldots, T_{y-\mathrm{end}}]$ by solving an equation of $T^*_{\mathrm{opt}}(W) = \arg min\{W_1, W_2, \ldots W_{\mathrm{end}}\}$.

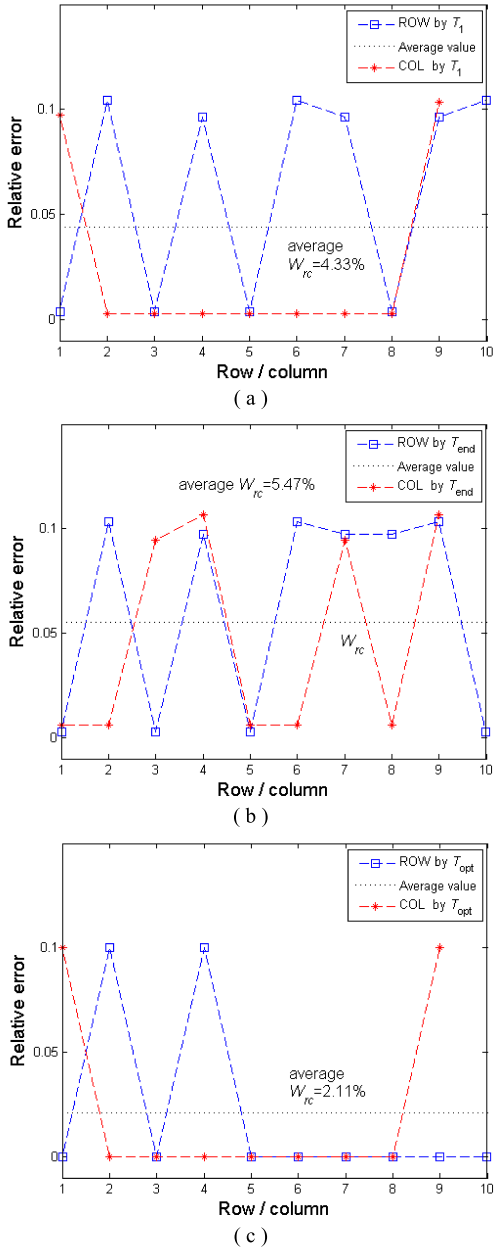

FIGURE 9. Re-gridding of sub-array(2,5) by Otsu with multilevel thresholds. (a) Re-gridding of row 5 and column 5 by T_1 threshold. (b) Re-gridding of row 5 and column 5 by T_{end} threshold. (c) Re-gridding of row 5 and column 5 by T_{opt}, and achieve minimum $W_{rc} = 2.11\%$.

III. EXPERIMENT RESULTS AND ANALYSES

A. GRIDDING OF MICROARRAY IMAGE

After tilt correction, adaptive contrast enhancement, horizontal-vertical projection and morphological smoothness, the sub-arrays image could be separated from the whole image of microarray by Ostu method at first, and a diagram of sub-array segmentation as shown in Figure 3.

When we take the sub-array(2,5) from microarray image of Figure 3, we could confirm the excellent performance of gridding by using this improved Otsu method with multilevel optimization. For considering the combined influence of horizontal and vertical deviation, we define the integrated

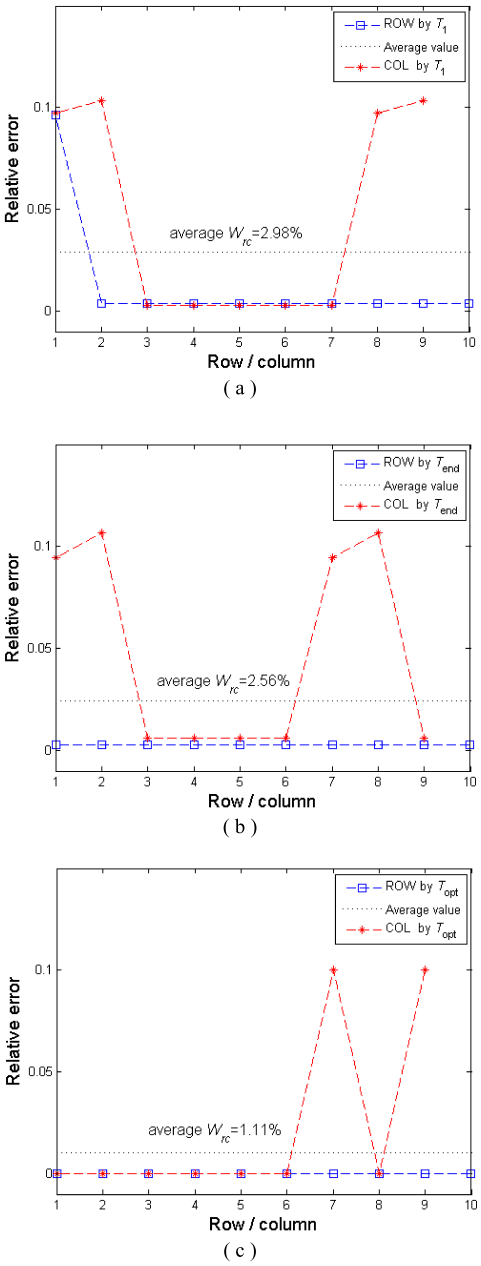

FIGURE 10. Re-gridding of sub-array(2,5) by Otsu with multilevel thresholds. (a) Re-gridding of row 6 and column 6 by T_1 threshold. (b) Re-gridding of row 6 and column 6 by T_{end} threshold. (c) Re-gridding of row 6 and column 6 by T_{opt}, and achieve minimum $W_{rc} = 1.11\%$.

relative error $W_{rc} = (W_r + W_c)/2$, Where the W_r is the relative deviation of line interval while the W_c is the corresponding deviation of column interval [25].

The procedure of multilevel Otsu optimized by the physical information for gridding of microarray image is illustrated as Figure 4.

The Figure 5 demonstrates the sub-array(2,5) image reaches the complete gridding by using the Otsu method of multilevel thresholds with T_1, T_{end} and the optimal threshold T_{opt}.

In order to distinguish the gridding performance of multilevel thresholding conveniently, table 1 shows the comparison of T_1, T_{end} and the optimal status T_{opt}, and the results indicate that the Otsu method optimized by multilevel thresholding could obtain high-accuracy gridding by the T_{opt}.

In table 1, obviously, either the max relative error or the mean relative error of image gridding is reduced to zero for T_{opt}. Moreover, the Figure 6 also indicates that the gridding details of relative error under the threshold of T_1 and T_{end}. It clearly predicts that the optimal threshold T_{opt} would be between T_1 and T_{end} under the constraint by closing W_{rc} to zero.

B. COORDINATE MODIFYING BY MULITILEVEL OPTIMIZATION METHOD

Due to the inevitable manufacturing errors, we should have to reproject each row or column region after gridding, to modify the spot-location for avoiding the interaction of multi-row or multi-column as far as possible.

The Figure 7 indicates the reprojection region and optimal thresholding for sub-array(2,5) segmentation on the row region 6. Correspondingly, the optimal thresholding on the column region 6 is illustrated in Figure 8.

When we iteratively remodify the bio-spot coordinates by reprojection each row and column region, and achieve the re-gridding constrained by the physical information one by one, we could succeed in obtaining all the coordinate of bio-spots accurately. The Figure 9 demonstrates the re-gridding of row region 5 and column region 5 at T_1, T_{end} and T_{opt}, and the good performance was showed for the minimum $W_{rc} = 2.11\%$. Furthermore, the minimum $W_{rc} = 1.11\%$ is achieved at the optimal threshold T_{opt} for row region 6 and column region 6, which is illustrated in Figure 10.

To investigate the advantage and disadvantage of the multilevel segmentation method optimized by physical information, a comparative analysis is to be carried out for the maximum relative error, mean relative error, variance and the failure rate of gridding. Table 2 certifies that the Otsu method optimized by multilevel thresholds to be quite accurate for gridding and segmentation of fluorescent bio-spots of sub-array(2,5).

TABLE 2. Statistical deviation of coordinate center of each bio-probe in sub-array(2,5).

Location parameter of bio-spot	Otsu with T_1 threshold	Otsu with T_{end} threshold	Otsu with T_{opt} threshold
maximum relative error	29.88%	27.31%	20.55%
Average relative error	2.89%	2.44%	1.05%
Variance	3.327	2.054	0.741
Failure rate of gridding	1.00%	1.90%	0

The relative error is defined as $W_{rc} = (W_r + W_c)/2$.

According to the Table 2, Otsu method optimized by T_{opt} achieves all the spot segmentation with minimum deviation, and it shows that the way of Otsu with multilevel optimization

has sufficient advantage in pursuing the bio-spot information on microarray image, although there are inevitable manufacturing errors resulted from the spotting accuracy of genechip array machine.

IV. SUMMARY AND CONCLUSIONS

There are many factors that significantly affect the gridding and bio-spots location of microarray including bio-probe fabrication, fluorescence scanning and gridding algorithm. Yet the existing methods for bio-spots segmentation are always difficult to adapt to the complex features of fluorescent image, which inevitably leads to manual intervention to improve the accuracy of gridding and segmentation. Considering the physical information carried by the microarray image, we proposed a novel way based on Otsu method optimized by the multilevel thresholds to achieve high-precision gridding and establish accurate coordinates of bio-spots on microarray. The experiment results show that the Otsu method with multilevel optimization considering the physical information of spot-matrix parameters, improves the accuracy of gridding and bio-probe locations. In comparison with the traditional Otsu method, its gridding error is reduced to zero and the integrated relative error of bio-spot coordinates is decreased from 2.89% to 1.05%. And this optimization combined with physical information of spot-matrix will greatly improve the effectiveness of segmentation so as to make the contribution to extracting the fluorescence intensity of microarray accurately. However, due to the employ of projection for horizontal-vertical direction, the application of this improved Otsu method to high-density microarray gridding still need to be studied further.

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