Review on Image Segmentation Methods in cDNA Microarray Experiments and a Novel Algorithm for Segmentation

Kalesh M. Karun, Binu V. S, Kala M. Karun, Keerthana Prasad, Nair N. S, K. Manjunatha Prasad, K. M. Girisha

Abstract— Microarray experiments are used to measure gene expression levels of thousands of genes at a time. The image analysis has an important role in the microarray data analysis and has potential impact on the identification of differentially expressed genes. Segmentation is one of the important processes in image analysis. The current paper attempts to provide an overview of commonly used segmentation methods in microarray image analysis like fixed circle segmentation, adaptive circle segmentation, the adaptive shape segmentation, histogram-based method and machine learning algorithms. We estimated intensity ratios of selected spots from an image file downloaded from the Gene Expression Omnibus (GEO) database based on the above segmentation methods. It was observed that all these methods give almost similar estimates of intensity ratio value. We are also proposing a new algorithm to identify the spot radius for the adaptive circle segmentation, instead of manual fixing of the radius.

Index Terms—Microarray, Image analysis, Segmentation, Intensity ratio.

I. INTRODUCTION

A cDNA microarray is a glass slide or nylon chip of size that varies from 0.5 x 0.5 cm to 2.5 x 7.5 cm on to which thousands of portions of single stranded DNA (probes) are fixed using robotic spotting. Each spot contains several copies of same known DNA sequence which is reverse complement to a target RNA sequence. In a typical cDNA microarray experiment, the first step is to extract the cellular messenger RNA from diseased and normal celsl. Then reverse transcribed into cDNA and labelled with two different fluorescent dyes, one with fluoresce green (Cy3) and the other with fluoresce red (Cy5).

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These samples are then purified, mixed together and simultaneously hybridized to microarray chip. Then the microarray chips are washed, dried and later passed through two laser beams. A photomultiplier tube (PMT) is used to capture the fluorescent lights emitted from these two lasers and the analogue-to-digital converter (ADC) converts the intensity of the red and green light from each spot into digital signal. The idea behind microarrays is to compute unique signal for each gene that is directly proportional to the quantity of mRNA that was hybridized on the chip [1].

The quantification of gene expression is done by analysing the microarray images, which contains several spots placed in columns and rows. The three important stages of image processing are (i) Gridding- locating the centres and bounding boxes of each spot(ii) segmentation – classifying the pixels of the image into two categories, foreground and background (iii) intensity extraction- calculating the foreground and background pixel intensities [2]. Gridding involves locating the centre as well as the boundary of a spot. Segmentation is the procedure of classifying the pixels in a spot into foreground and background. Intensity extraction involves quantification of the foreground and background pixel intensities.

The aim of segmentation is to distinguish pixels which are part of a spot from the background. In a spot, brightness characteristic of pixels in the regions where probe is located differs from that of regions without probe. Because of change in pH, temperature, voltage etc, the reverse transcribed mRNA may hybridize in regions without probe which is known as non-specific hybridization [3]. The pixels in probe region are called foreground pixels of a spot. Likewise, the pixels in regions other than the probe region within the boundary of a spot are called background pixels. The segmentation procedures results in the identification of foreground pixels and background pixels in a spot. There are various segmentation methods in use and the commonly used methods are fixed circle segmentation, adaptive circle segmentation, adaptive shape segmentation, histogram based segmentation, K-means, Fuzzy C means and PAM [4],[5],[6]. The current article have two parts, in the first part we review the commonly used segmentation methods in cDNA microarray image analysis and also explored how each of these methods affects the ratio of background corrected mean pixel intensities of a spot. In the second part of the article, we are proposing a new algorithm to identify the spot radius for the adaptive circle segmentation, instead of manual fixing of the radius.

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II. MATERIALS AND METHODS OF REVIEW

Commonly used segmentation methods in microarray image analysis are fixed circle segmentation, adaptive circle segmentation, adaptive shape segmentation, histogram based segmentation and Clustering algorithms like K-means, Fuzzy C means and PAM. We discuss how each of these segmentation methods works and their disadvantages.

A. Description of microarray image files used in this study

To explore how the choice of above mentioned segmentation methods affect the values of intensity ratio we used two image files obtained from a dual channel microarray experiment of ‘Atlantic Salmon Head Kidney Study’. The image files of this experiment are publically available in the Gene Expression Omnibus (GEO) database and we downloaded one image file each from infected and non-infected samples for our study (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM16390). Each image file contains 48 blocks with 182 spots arranged in 13×14 rows and columns. For our study we selected the 10 spots from the first block and apply the above mentioned seven segmentation methods on each of these spots. We used GenePix Pro7 software for pixel intensity extraction from the image files and also R package for identifying the foreground and background pixels according to each segmentation methods. The ratio of background corrected mean pixel intensities was obtained for each of the 10 spots based on the seven segmentation methods.

III. RESULTS AND DISCUSSION OF REVIEW

Microarray image segmentation methods falls under two main categories (i) Image processing techniques and (ii) Machine learning techniques. Fixed circle segmentation, adaptive circle segmentation, adaptive shape segmentation and histogram based segmentation are image processing segmentation techniques. Clustering algorithms like K-means, Fuzzy C means and PAM are the important segmentation methods coming under the Machine learning techniques [7].

IV. IMAGE PROCESSING SEGMENTATION TECHNIQUES

A. Fixed Circle Segmentation

This is the simplest segmentation method which uses a circle with fixed radius to identify the foreground and background pixels in all the spots in the image file. Those pixels within the circle are identified as foreground pixels and pixels which lie outside the circle but inside the boundary of that spot as background [8]. This method makes all the spots in the image file with circular shape and of same size. The disadvantage of fixed circle segmentation is that there could be more chance for misclassification of foreground and background pixels. Since this method use fixed circle radius for every spot in a microarray image file, for spots with large region of high intensity, some regions within the high intensity areas are left out of the foreground. Similarly, for spots with small region of high intensity, some regions with the low intensity are included in the foreground regions[9]. Fixed circle segmentation is most commonly used in cDNA image analysis packages like GenePix, ScanAlyze and Quantarray[8].

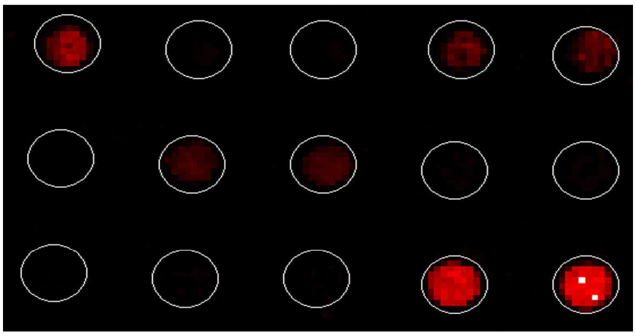

Fig. 1. A portion of image file with fixed circle segmentation

Figure 1 shows a portion of the image file after applying the fixed circle segmentation method with radius of 4 pixels to the TIFF file obtained from the microarray experiment mentioned above. The intensity ratio associated with the selected spots is given in Table 1.

A. Adaptive Circle Segmentation

This method assumes that all spots in an image file are circular in shape but with varying diameters[8]. The radius of the circle for each spot can be fixed manually or by using some software’s like GenePix, ScanAlyze, ScanArray Express, Imagene, and Dapple [9]. Even though manual adjustments of the diameter of the circle are possible in many packages, it is time consuming because of large number of spots in the image file.

Adaptive segmentation using Genepix software applied on the image file used earlier is shown in Figure 2. Here the circle radius ranges from 3 to 9 pixels and the estimated values of the intensity ratios for the 10 spots are shown in Table 1.

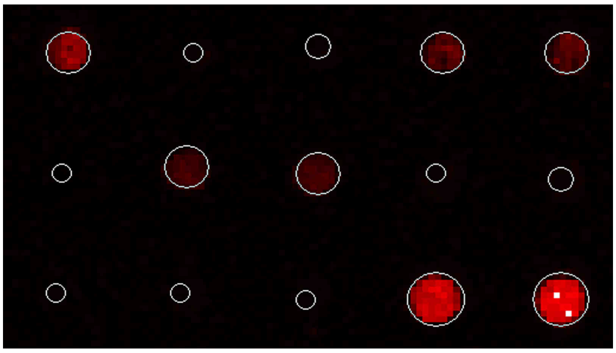

Fig. 2. A portion of image file with adaptive circle segmentation

B. Adaptive Shape Segmentation (Seeded Region Growing)

This segmentation method has no fixed size and shape for spots in an image file. Seeded Region Growing (SRG) method requires an initial point to be known, called the seed which is a pixel in the center of high intensity region of a spot that is considered to belong to foreground region [9]. For example, let us consider a pixel say p as the seed in a spot and let q be an adjacent pixel in that spot. We obtain a similarity measure for these two pixels and if this measure exceeds a pre-defined threshold value, the pixel q is added to the p’s region

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otherwise it is considered as a background pixel. In the next step the similarity measure is obtained for pixel q and a pixel adjacent to q. The similarity measure is compared with the threshold value and if it exceeds the threshold value that pixel is added to the foreground region otherwise considered as background. This procedure is repeated for all remaining pixels in spot. The seeds can be a group of pixels in the high intensity region or can be groups of pixels from the high intensity region as well as regions near to the boundary of a spot. The main benefit of this approach over the adaptive circle segmentation is that noncircular spots can be more accurately defined [2]. The main disadvantage of this method is the selection of seed; if the seeds chosen were not proper, the segmentation results in severe misclassifications. SRG has been implemented in microarray processing package 'Spot', which is the first package to use this algorithm for microarray segmentation [9]. Figure 3 shows the adaptive shape segmentation of a single spot from the above mentioned image file using ImageJ package. The region within the yellow boundary line is the foreground region and the remaining are considered as background. The intensity ratio of 10 spots based on adaptive shape segmentation method is given in Table 1.

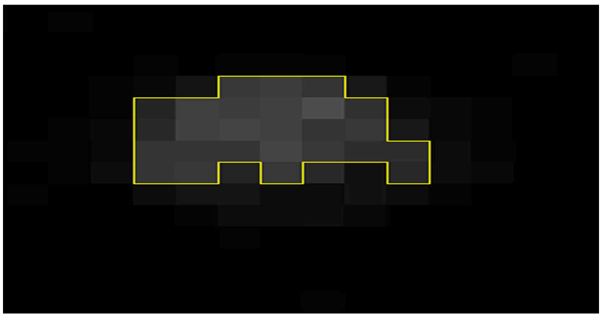

Fig. 3. Single spot with adaptive shape segmentation using ImageJ package

This method is based on percentile distribution of pixel intensities of a spot. Histogram based approach fix a circular mask on each spot, with radius larger than the spot size. The histogram of intensities of pixels within this circular mask is constructed and the percentiles are obtained. Those pixels with intensity value lies between 5th to 20th percentiles are considered as background pixels and those in 80th to 95th percentiles as foreground [9]. The method fails for spots of low intensity as this method always identifies some region as foreground.

The intensity ratios obtained from the extracted foreground and background pixel intensity values using histogram method are given in Table 1. Here we considered a circular mask of 14 pixels diameter for each of the selected spots.

V. MACHINE LEARNING SEGMENTATION TECHNIQUES

A. K- Means Method

Clustering is grouping of objects that are similar to each other. The k-means segmentation method is based on the traditional k-means clustering method. Here the number of clusters k is always two since all pixels in a spot has to be assigned to either foreground or background cluster. This method initially identifies two pixels, the one with minimum intensity and the other one with maximum intensity. The former pixel is considered as the cluster center of the background cluster and the latter one for the foreground cluster. Then based on Euclidian distance measure of intensity values, pixels are assigned to one of the above two clusters. Again new cluster centers are calculated. This algorithm is iteratively repeated until the cluster centers stay unaltered [2],[6],[11]. The intensity ratio estimated for the selected spots after K-means segmentation is given in table-1

B. Fuzzy C-Means Method

Fuzzy C-Means (FCM) introduced by Jim Bezdek in 1981 is an improvement over K means clustering method (Bezdek and James 1981). This method starts with randomly selecting two pixels as centroids of two clusters namely foreground cluster and background cluster. A measure of distance from each cluster centroid to the remaining pixels is computed. These measures are called cluster membership grades. Pixels that lie close to the centroid of a cluster has high degree of membership grade to that particular cluster. Similarly, pixels which are far from the centroid of a cluster will have low degree of membership grade to that cluster. That means, each pixel will have some degree of membership grade with each of the two clusters. Pixels with membership grade higher than 0.5 will consider as one cluster and less than 0.5 as another cluster. Then new cluster centroids are obtained and the cluster membership grades with the new cluster centriods are recalculated for each pixel as before. This procedure is repeated until there is no more change in the cluster centriods. At the end of this procedure pixel with membership grade greater than 0.5 is considered as foreground cluster and below 0.5 as background cluster [11],[12].

The main disadvantage of this method is that it takes longer time compared to K means method, especially if the initial selections of centroids are not proper. The intensity ratio estimated for the selected spots after Fuzzy C-means segmentation is given in table-1

C. Partition Around Medoids (PAM)

Medoid is an object in a cluster, whose average dissimilarity to all other objects in the cluster is minimal. First we randomly select two pixels from the entire pixels as the initial medoids. Calculate the distance of each of these selected pixels from all the remaining pixels. Then calculate median of the distance and add all the distance which are less than median distance separately for both of the initial medoids and later add those two distance sums to get the total distance sum. Similar manner take all the possible pixel pairs as medoids and calculate the total distance sum. At the end, the pixel pair which give minimum sum of distance will be considered as cluster medoids [13]. The pixels which shows the distance less than median distance from the medoids forms one cluster and remaining forms the another cluster. There is a chance that some pixels may shift from one cluster to another cluster depending upon their closeness to medoids. This method will consume lots of time to identify the medoids if number of data points are large.

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We used all the above segmentation methods to each of the selected ten spots in an image file and estimated the intensity ratio of those spots. Table 1 give these estimated ratios and it was observed that the intensity ratio is almost similar for each of the above mentioned segmentation methods.

Table 1. Estimated intensity ratios for selected ten spots based on different segmentation methods.

Spot No:	Intensity Ratio based on						
	Fixed circle	Adaptive circle	Adaptive shape	Histogram	K-means	Fuzzy C-Means	PAM
Spot 3	0.9423	1.0784	1.0226	0.9958	0.9861	0.9797	1.0344
Spot 4	0.9472	0.9504	0.9883	0.9813	1.0104	0.9669	0.9545
Spot 7	1.8300	1.6284	1.4807	1.4442	1.7841	1.5964	1.7070
Spot 8	1.4834	1.4243	1.3173	1.6713	1.8019	1.5672	1.5145
Spot 11	1.1913	1.2637	1.6953	1.1731	1.3605	1.3549	1.4293
Spot 12	1.0680	1.0592	1.6289	1.0729	1.3845	1.4018	1.3714
Spot 19	0.6460	0.8142	0.8253	0.7582	0.7327	0.8005	0.8142
Spot 20	0.6816	0.7438	0.6277	0.7002	0.6880	0.7502	0.7863
Spot 35	1.1805	1.1632	1.2945	1.1805	1.2121	1.2195	1.2619
Spot 36	1.0319	1.0536	1.0963	1.6707	1.0733	1.0875	1.1437

Table 2. Mean and standard deviation of the absolute difference between intensity ratios obtained using various segmentation methods.

	Fixed circle	Adaptive circle	Adaptive shape	Histogram	K-means	Fuzzy C-Means
Fixed circle	.0750 (.0703)	0.2113 (0.1921)	0.1454 (0.2103)	0.1123 (0.1123)	0.1189 (0.1018)	0.1261 (0.0899)
Adaptive circle		0.1651 (0.1852)	0.1383 (0.1844)	0.1314 (0.1221)	0.0834 (0.1012)	0.0926 (0.0913)
Adaptive shape			0.2331 (0.2401)	0.1684 (0.1621)	0.1229 (0.1135)	0.1242 (0.1068)
Histogram				0.1675 (0.1955)	0.1512 (0.1804)	0.1790 (0.1581)
K-means					0.0647 (0.0813)	0.0851 (0.0748)
Fuzzy C-Means						0.0484 (0.0292)

The table 2 gives the mean of the absolute difference of estimated intensity ratios between each of the segmentation methods. Histogram method shows higher variation in the intensity ratio compared to all other methods and Machine learning algorithms gives more or less similar results. Overall the result shows that the choice of segmentation method has small impact on the estimated intensity ratios. Similar results were observed in studies conducted by Antti et al. 2006 and Yee et al. 2001.

Since there is not much difference in the estimated intensity ratios, it is advice to use fixed circle segmentation as this method is simple and can be easily performed with most of the microarray image analysis packages. Also, this method eliminates the selection of pixels from the non- probe regions compared to other methods like histogram and machine learning algorithms.

VI. AN ALGORITHM TO IDENTIFY SPOT RADIUS FOR ADAPTIVE CIRCLE SEGMENTATION

Adaptive circle segmentation assumes that all the spots are in circular shape with varying diameter for the circle. This segmentation has two steps. First is the identification of the center and second is the adjustment of the diameter of the circle. There are different algorithms are available for adaptive circle segmentation approach. A typical edge detection technique (eg: Laplacian transformation), can be applied to automatically estimate the diameter of the circle [9]. Another algorithm considers all pixels above a user-specified threshold value as foreground and finds the circle with the highest percentage of pixels that are foreground [14]. Some packages like GenePix and Dapple allow the adaptive circle segmentation, though the algorithms are different. Manual adjustment of the diameter of the spots is possible in many of the packages, which is time consuming. We are proposing a new algorithm to fix the spot radius which is based on the pixel intensity values. The algorithm is given below.

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Algorithm: SpotRadiusMS( )
Input: Spot Grid, SG
Output: Spot Radius, SR
1. P:=0.1,SIP:=0
2. r:=Max. possible radius for SG
3. Repeat steps 4 to 7 until SIP<=P or r=3
4. PI_IC:=pixel intensities of the perimeter of the circle having radius r-1
5. PI_OC:=pixel intensities of the perimeter of the circle having radius r+1
6. SIP=Wilcoxon_Mann_Whitnney_U (PI_IC,PI_OC)
7. if (SIP>P)
7.1. r:=r-1
else
7.2. SR=r
8. Exit.

First fix a circle with maximum possible radius, r for the selected spot grid SG. Then extract the pixel intensity values from the pixels which are immediately inside the circle, PI_IC and immediately outside the circle,PI_OC. Then find the significance difference SIP, between the pixel intensities obtained in PI_IC and PI_OC by means of Wilcoxon Mann Whitnney U test. If there is no significant difference between the intensities of pixels that are immediately inside the circle and immediately outside the circle, then fix the radius,r one unit(pixel) less than the previous radius and do the same procedure to know is there any significant difference. This procedure repeats up to when we will get a significant difference in the pixel intensities between pixels immediately inside the circle and outside the circle. Fix the radius of the spot, SR where we get a significant difference between pixel intensities. We considered the $p<0.1$ as the statistically significant.

We used R- package version 3.1.1 to obtain the values of pixel intensity from immediately inside the circle and immediately outside the circle for different pixel radius and to check the significant difference also. First we fix the spot radius as 9pixels and repeated up to 3pixel radius for all the 100 selected spots. We identified that among 100 selected spot, 61 were good quality and remaining 39 were bad quality spots. Among the 61 good quality spots, the proposed algorithm identified the cut off radius around 4pixel for 59 spots. The algorithm fails to identify the cut of radius for all the bad quality spots. The results show that the proposed algorithm can be used to identify the good quality spots.

To ensure that the proposed method is able to differentiate the foreground and background pixels, we simulated data for good quality spots and bad quality spots as experimentally obtained data. We simulated data for these two situations 1000 times using R package. We got exactly same results from the simulated data as we expected that is the proposed algorithm is good separate the foreground and background pixels.

VII. CONCLUSION

Various segmentation methods are used in microarray image analysis. The commonly used methods are fixed circle segmentation, adaptive circle segmentation, adaptive shape segmentation, histogram-based segmentation, K means segmentation and Fuzzy C means method. Our study shows that all these methods give similar values of estimated intensity ratio of a spot. The results show that the choice of segmentation method has little impact on the value of the estimated intensity ratio of a spot.

We also propose a method to identify the appropriate spot radius for the microarray spots for the adaptive circle segmentation. The main advantage of proposed algorithm is that it will automatically identify the spot radius for the spots according to the pixel intensity values of the spots. We identified that the proposed algorithm is correctly identifying the spot radius for most of the good quality spots (96%), so the proposed algorithm can also be used as quality measure for spot. If the algorithm fails to identify any cut off radius, the spot is considered as a bad quality spot.

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