

# AN INTELLIGENT SEGMENTATION ALGORITHM FOR MICROARRAY IMAGE PROCESSING

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**Abstract**— Microarray technology consists of an array of thousands of microscopic spots of DNA oligonucleotides attached to a solid surface. It is a very powerful technique for analyzing gene expressions as well as to explore the underlying genetic causes of many human diseases. There are numerous applications of this technology, including environmental health research, drug design and discovery, clinical diagnosis and treatment and in cancer detection. The spots, which represent genes in microarray experiment contains the quantitative information that needs to be extracted accurately. For this process, preprocessing of microarray plays an essential role and it is also influential in future steps of the analysis. The three microarray preprocessing steps include gridding, segmentation and quantification. The first step is gridding, refers to the identification of the centre coordinates of each spot. The second step is segmentation, refers to the process of separating foreground and background fluorescence intensities. Segmentation is very important step as it directly affects the accuracy of gene expression analysis in the data mining process that follows. Accurate segmentation is one of the vital steps in microarray image processing. A novel method for segmentation of microarray image is proposed which accurately segment the spots from background when compared with adaptive threshold, combined global and local threshold and fuzzy c-means clustering methods. Experimental results show that our proposed method provides better segmentation and improved intensity values than the above existing methods.

**Keywords**-Microarray; Gridding; Segmentation; Quantification; Fuzzy c-means clustering; Soft Threshold

## I. INTRODUCTION

Microarray is one of the most exciting genomic tools that obtain genomic information in a comparative and parallel way. The Deoxyribonucleic acid (DNA) strands are fastened at fixed spots on glass or plastic slides or silicon chips that can be used for monitoring thousands of genes or entire genomes simultaneously [1]. This approach is much more efficient than the traditional experiment method which only focuses on a few genes at a time. Messenger ribonucleic acid (mRNA) is first extracted from cells and converted to single-stranded complementary DNAs. Fluorescent labels are then attached to the complementary DNAs and afterwards they are allowed to hybridize, on a microarray, with their respective complimentary probes. The resulting fluor-tagged hybrids are detected through excitation of the attached fluors, and image formation is carried out using a scanning confocal microscope. Relative RNA abundance is obtained using the measurement of signal intensity from the attached fluors. This intensity is obtained by image processing. The resulting microarray image intensities are subject to statistical analysis with particular attention towards the detection of high/low expressing genes, expression based phenotype classification, and the discovery of the multivariate inter-gene predictive relationships. As such, microarrays have truly revolutionized molecular biology research, and genomic clinical diagnosis.

Measurement of spot intensities is a major step in microarray analysis. The three steps in preprocessing of

microarray images are i) Gridding ii) Segmentation and iii) Quantification (Intensity extraction). Gridding or spot addressing which consists of assigning coordinates to each spot, segmentation allows the identification of the foreground (spot signal) and background, and quantification is the information extracted from the red (Cy5), green (Cy3) fluorescence intensity and background intensities. The accuracy of these steps determines the quality of microarray data. In this processing pipeline, segmentation of cDNA spots is the most challenging task.

Segmentation process divides an image into foreground and background region based on pixel intensities. Microarray images are difficult to handle in general, due to factors such as variability from experiment to experiment, noise and image artifacts. Segmentation step is essential in order to decide which pixels form the foreground signals, which pixels form the background signals and which pixels are just noises or artifacts and should be eliminated. Robust segmentation is significant for accurate classification of gene's expression and to extrapolate an assortment of spot quality measures.

The paper is organized as follows. Section 2 describes the basic methods, thresholding techniques and fuzzy c-means clustering used in the segmentation of microarray images, Section 3 illustrates the related works carried out on segmentation, Section 4 presents our proposed method and Section 5 presents our results and conclusions.

## II.METHODS FOR MICROARRAY IMAGE SEGMENTATION

### A. Basic methods of segmentation

Certain studies on microarray have been shown that segmentation methods can significantly influence microarray data precision. Several methods have been proposed for the segmentation of microarray images. These methods are based on image processing and machine learning techniques [2]. The image processing techniques include Fixed circle, Adaptive circle, Histogram-based and Adaptive shape based methods. On the other hand, the machine learning techniques include Clustering and Classification methods.

### B. Thresholding techniques

A threshold value to turn a gray-scale image into a binary image. Three types of thresholding techniques are global thresholding, local thresholding and adaptive or dynamic thresholding. Thresholding can be based on several image attributes such as the histogram or local properties such as mean, standard deviation, or gradient. When only one threshold is selected for an entire image, the technique is said to be "Global". If the techniques dependent on say a local average gray value, it is "local". Further, if local thresholds are selected independently for each pixel (or group of pixels) is it said to be a "dynamic" or "adaptive" technique.

### C. Global Thresholding

Global thresholding assumes that an image has a bimodal histogram. Therefore, the object can be extracted from the background by a simple operation that compares image values to a threshold value  $T$ . The object and the background pixels have gray levels grouped into two dominant modes. An obvious way to extract the object is to select a threshold which separates these two values

$$g(x, y) = \begin{cases} 0 & f(x, y) < T \\ 1 & f(x, y) \geq T \end{cases}, \quad (1)$$

where  $f(x,y)$  is the gray level of the image

1. Using mean gray level of the image as  $T$ , the image is segmented. This will produce two groups of pixels:  $G1$  consisting of all pixels with gray level values  $>T$  and  $G2$  consisting of pixels with values  $<T$ .
2. Compute the average gray level values  $\mu1$  and  $\mu2$  for the pixels in regions  $G1$  and  $G2$ .
3. Compute a new threshold value:
 
$$T = \frac{1}{2}[\mu1 + \mu2] \quad (2)$$
4. Repeat step 2 through 4 until the difference in  $T$  in successive iterations is smaller than a predefined parameter  $T_0$  (initial  $T$  value).

### D. Local thresholding

Local threshold is determined by splitting an image into sub-images and calculating thresholds for each sub-image. These techniques are computationally more expensive and could be used for images with varying backgrounds.

### E. Adaptive thresholding

A more complex thresholding algorithm would be to use a spatially varying threshold. This approach is very useful to compensate for the effects of non-uniform illumination. If  $T$  depends on coordinates  $x$  and  $y$ , this

referred to as Dynamic Thresholding or Adaptive Thresholding. [31]. There are two main approaches for finding the threshold, the Chow and Kaneko approach and local thresholding. The assumption behind both methods is that smaller image regions are more likely to have approximately uniform illumination, thus being more suitable for thresholding. Chow and Kaneko divide an image into an array of overlapping sub images and then find the optimum threshold for each sub image by investigating its histogram. The threshold for each single pixel is found by interpolating the results of the sub images. The drawback of this method is that it is computational expensive and, therefore, is not appropriate for real-time applications.

An alternative approach to finding the local threshold is to statistically examine the intensity values of the local neighborhood of each pixel [30]. The statistic which is most appropriate depends largely on the input image. Simple and fast functions include the mean or median of the local intensity distribution, or the mean of the minimum and maximum values. The size of the neighborhood has to be large enough to cover sufficient foreground and background pixels, otherwise a poor threshold is chosen. On the other hand, choosing regions which are too large can violate the assumption of approximately uniform illumination. This method is less computationally intensive than the Chow and Kaneko approach and produces good results for some applications.

#### F. Fuzzy c-means clustering for segmentation

This Fuzzy c-means clustering algorithm works as follows [21]:

- i. Make random initialization for the membership matrix,
- ii. Loop through the following steps until a stopping condition is satisfied,
  - a. Compute the centroid values for each cluster,
  - b. Compute the membership values belonging to clusters for each pixel.

By implementing FCM, we have clustered the pixels such that each pixel has a degree of membership belonging to foreground or background clusters. In the nature of fuzzy logic, each point has a degree of membership to clusters rather than belonging to only one cluster. The membership degree of a pixel is a value such that  $u_{ij} \in [0,1]$ .

The sum of membership values of a pixel belonging to clusters equals to 1:

$$\sum_{j=1}^C u_{ij} = 1, \forall i=1,2,\dots,n \quad (3)$$

In this study, an objective function for fuzzy c-means method can be defined as follows:

$$J_m^f = \sum_{i=1}^N \sum_{j=1}^C u_{ij}^m \|x_i - c_j\|^2, m \in (1, \infty) \quad (4)$$

where  $m$  is a real number greater than 1 and is chosen 2, and  $u_{ij}$  is the degree of the membership of pixel  $x_i$  belonging to designated cluster. The  $\|x_i - c_j\|$  above expresses the distance measured between data and the center. An absolute value of the difference between two consecutive objective functions,  $J_{m+1}^f$  and  $J_m^f$ , is sought to be minimized iteratively until a stopping condition that is less than a user-specified parameter  $\mathcal{E}^f$  reached,

$$\text{i.e., } |J_{m+1}^f - J_m^f| \leq \mathcal{E}^f$$

At each iterative step, the membership  $u_{ij}$  is updated as follows:

$$u_{ij} = \frac{1}{\sum_{k=1}^C \left( \frac{\|x_i - c_j\|}{\|x_i - c_k\|} \right)^{\frac{2}{m-1}}} \quad (5)$$

and the cluster centers  $c_j$  are updated according to the following:

$$c_j = \frac{\sum_{i=1}^N u_{ij}^m x_i}{\sum_{i=1}^N u_{ij}^m} \quad (6)$$

### III. RELATED WORK

Researches had carried out different works for microarray image segmentation which are discussed below. (Kasif I.Siddiqui et al., 2002) stated the extraction of spot features from a gene microarray image, which along with the spot intensity can be used for statistical analysis of spot shape and intensity variations. (Chiao-Ling Shih et al., 2003) demonstrated the automatic spot detection of cDNA microarray images using mathematical

morphology methods. (O.Demirkaya et al., 2003) proposed an approach based on the markov random field modeling of the microarray spot regions in which the contextual information is also considered. (Mathias Katzer et al., 2003) proposed markov random field (MRF) based approach to high level grid segmentation which is robust to common problems encountered with array images and does not require calibrations. They also proposed an active contour method for single spot segmentation that describes objects in images by properties of their boundaries. (Radhakrishnan Nagarajan 2003) stated that the target intensity of the spots are extracted using clustering-based segmentation (Wang Yu-Ping et al., 2005) demonstrated clustering based approaches such as fuzzy c-means clustering for automated spot segmentation. (Th. Margaritis et al., 2006) presented a fully automatic segmentation method for improving the spot segmentation result. The method uses both information channels and does not make any assumptions concentrating the number of classes present in each image spot and also it's not driven only by the most intense features.

(Jinn Ho et al., 2007) proposed an integration of active contour approach and Fisher criterion to capture respectively, the boundary and the region information of microarray images. (Tsung-Han Tsai et al., 2007) stated a method to reduce the error of the edge detection which is influenced by noise and tilt array. (Bogdan Belean et al., 2008) proposed an acquisition system for microarray image on an FPGA based platform, together with a hardware implementation of image segmentation for c-DNA microarray images. (Hu Yijun et al., 2009) presented a method which combines K- means clustering algorithm and mathematical morphology for extracting image components. (Deepa J et al., 2009) described the segmentation of microarray images using an improved seeded region growing method. (Shenghua NI et al., 2009) presented a segmentation method based on ACWE with applications in c-DNA segmenting. (N. Karimi et al., 2010) proposed a graph-based method which automatically performs the segmentation.

(A.Sreedevi et al., 2009) presented a novel automatic approach to locate the spots without the formation of grids. An approach using Genetic algorithm is proposed, in which searching for the spots in sub image is done and the relevant information of the spot is extracted and the process is repeated for the entire image.

(Kaustubha A. Mendhurwar et al., 2009) proposed a new approach for segmentation of the microarray images. In this work, Chan-Vese approximation of the Mumford-Shah model and the level set method are employed for image segmentation. (Emmanouil I. Athanasiadis et al., 2009) demonstrated a wavelet-based modification of the Markov random field (WMRF) model for segmenting complementary DNA (c-DNA) microarray images. (A.Sri Nagesh et al., 2010) proposed a methodology to investigate the accuracy of spot segmentation of a microarray image, using morphological image analysis techniques and watershed algorithm. (Volkan Uslan et al., 2010) demonstrated two clustering methods, fuzzy c-means and k-means algorithms and the results of both are compared. The experimental results showed that fuzzy c-means has ensured a sensitive classification of the weak spots when compared with k-means algorithm. (Weng Guirong et al., 2010) presented a novel technique for removing gene's noises based on the offset vector field and segmenting genes using the expectation maximization algorithm. (Dr.P.V.Lakshmi et.al., 2012) proposed a Fuzzy C-means with Bi-dimensional Empirical Mode decomposition (FCMBEMD) for segmenting the microarray image in order to reduce the effect of noise. (Nikolaos Giannakeas et al., 2007) proposed a supervised method for the segmentation of microarray images. The proposed method employs the Bayes classifier which classifies the pixels of the image in two classes, foreground and background pixels. (Sotirios A. Tsaftaris et al., 2007) used Principal Component Analysis (PCA) to de-correlate the signal from the noise, by projecting each spot on the space of eigenvectors, called eigenspots. (Eleni Zacharia et al., 2010) proposed an original and fully automatic approach to accurately segment the spots in a cDNA microarray image. (Biju V G et al., 2012) proposed a Genetic algorithm based Fuzzy C Mean (GAFCM) technique to segment spots of complimentary DNA (c-DNA) microarray images for finding gene expression. (Kadam A.B. et al., 2012) presented a paper for detecting the spot using morphological segmentation technique.

#### IV.PROPOSED WORK

##### A. *Soft Thresholding*

A new soft thresholding method is proposed. The method is based on considering each pixel in the image to the different regions through a membership function, instead of hard decisions [29]. The membership function is derived for each of the regions using the histogram of the image. As a result, each pixel will belong to different regions with a different level of membership. The thresholding is made robust to noisy environments by exploiting feature through spatial processing. Let  $I(x)$  be an image with histogram  $h(I)$ . We will assume that the image is confirmed by  $L$  different regions. We want to extract via thresholding. We will denote  $\mu_l(x)$ ,  $l = 1, \dots, L$  to the membership function of the area  $l^{\text{th}}$ .

The proposed algorithm is as follows:

- 1) Calculate the normalized histogram of the image  $I(x)$ .

2) Maxima search: The number of maxima will correspond to the number of classes in the image. The number of regions:  $L = N_{max}$ . To avoid local values, the histogram of the image is low pass filtered:  $h_f(I) = h(I) * K$ .

3) Fit a sum of known distributions to the histogram. A sum of  $L$  weighted distributions is fitted to the histogram.

$$h_f(I) = \sum_{l=1}^L \omega_l \cdot p_{l(x)} \tag{7}$$

with  $p_{l(x)}$  a probability distribution and  $\omega_l$  some weights. The fitting is done using some minimization algorithm, such as minimum mean square error (MMSE):  $\arg \min |h_f(I) - \sum_{l=1}^L \omega_l \cdot p_{l(x)}|^2$

4) From probability to membership. The distribution  $p_{l(x)}$  fitted to the histogram can be seen as estimation of  $p(R_l | x)$  i.e. the probability of a pixel with value  $x$  to belong to region  $R_l$ :

$$p(R_l | x) = \frac{p(x|R_l) p(R_l)}{\sum_{l=1}^L p(x|R_l) p(R_l)} \tag{9}$$

The membership is used instead of probability values.

5) Membership to the regions: The membership of the image  $I(x)$  to the region  $R_l$  is defined by  $\mu_l(I(x))$ .

The PTS (Pseudo Trapezoid-Shaped) membership function is defined by

$$\sum_{l=1}^L \mu_l(I(x)) = 1 \tag{10}$$

A first segmentation of the image could be done:  $M(x) = \arg \max_l \mu_l(I(x))$

with  $M(x)$  a threshold image. However, to take advantage of the membership values in a neighborhood we do one more step of the process.

6) Adding local information. To make the method more robust in noisy environments, spatial information is used. We propose a nonlinear processing using the median in each channel:

$\mu_l^s(I(x)) = med(\mu_l(I(x)))$  with  $med(.)$  the local median in a neighborhood around each pixel. Note that this neighborhood can be oriented in order to better find structures in one particular direction. Finally, the threshold image can be obtained using a maximum operator:  $M(x) = \arg \max_l \mu_l^s(I(x))$ .

*B. Steps involved in proposed method*

The block diagram for the proposed method is shown in Figure 1. Microarray image shown in Figure 2 is marked with two dyes Cy5, red and Cy3, green and each microarray image consist of large number of  $n$  sub microarrays and each sub microarray contains  $A$  columns and  $B$  rows of gene spots with each spot corresponding to the location of a cDNA probe to which mRNA from the cells of interest have been bound. There are approximately 4800 spots on a slide, arranged in a 4 by 12 grid of sub microarrays, with each sub microarray being a 10 by 10 gene spots. Matlab software is used for implementation.

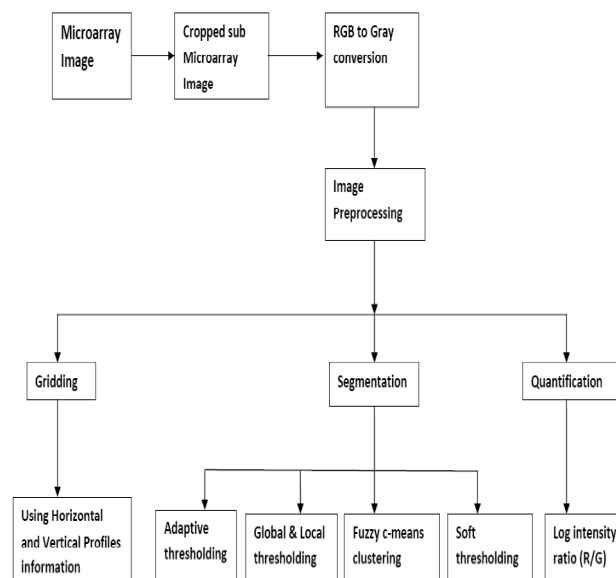


Figure 1. Block diagram of the proposed method

The input microarray image is then cropped to get 10 x 10 gene spots, which is converted into gray scale image. Then it is given as an input image for preprocessing. The first step in preprocessing is gridding. The horizontal and vertical profile information is used to obtain the gridded image shown in Fig.3.

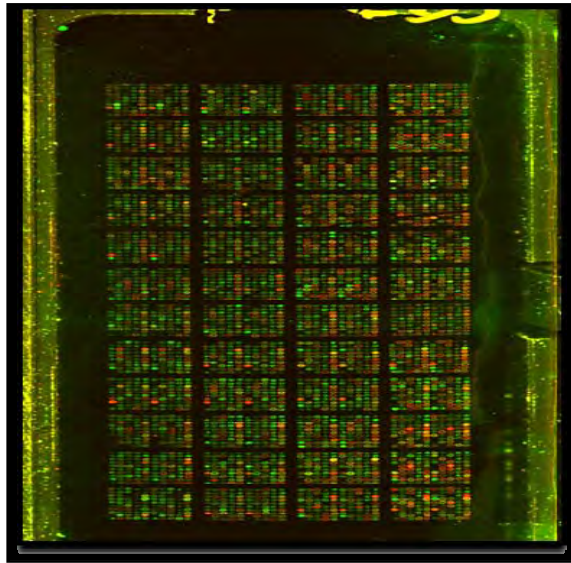


Figure 2. Input Microarray Image

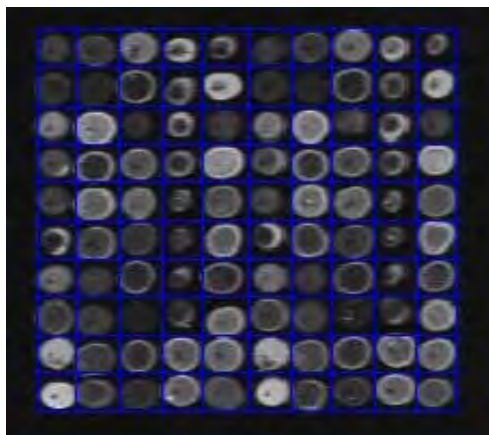


Figure 3. Gridded Sub Microarray Image

## V.RESULTS AND CONCLUSION

The next step in microarray image processing is segmentation. This step is vital, as it influence the next step, quantification to extract intensity values. If the segmentation part is efficient, then the next step is also efficient. So we have proposed a new soft thresholding method for segmentation, which gives improved results. In this paper, we have compared four types of segmentation methods, which includes

- i) Adaptive threshold method
- ii) Combined Global and Local threshold methods
- iii) Fuzzy c-means clustering method and
- iv) Soft thresholding method

The algorithms are explained in section II and IV. These algorithms are simulated using MATLAB. The segmentation output for each method is given below:

### *i) Adaptive threshold method:*

The output segmented image for adaptive threshold is shown in Figure .4

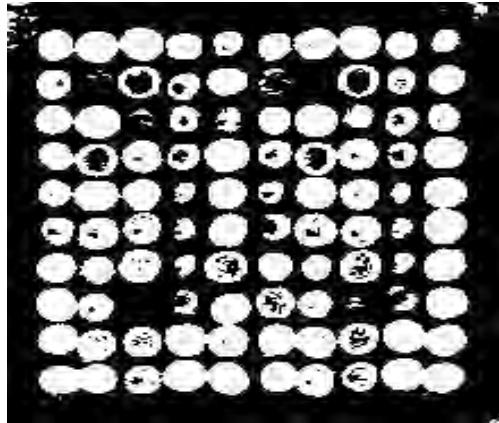


Figure 4. Adaptive Threshold Segmentation

The segmentation results are not that much good as we can see at the bottom of the image, the spots are over segmented.

**ii) Combined Global and Local threshold method:**

The segmentation is good with donut spots. There are also some spots which are over segmented as shown in Figure 5.

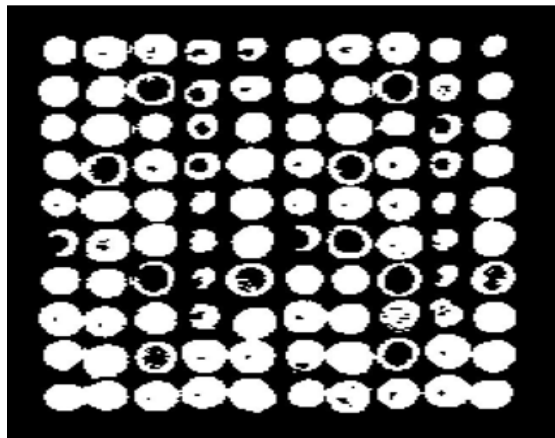


Figure 5. Combined Global and Local Threshold based Segmentation

**iii) Fuzzy c-means segmentation:**

The output is shown in Figure 6. The segmentation results are not good.

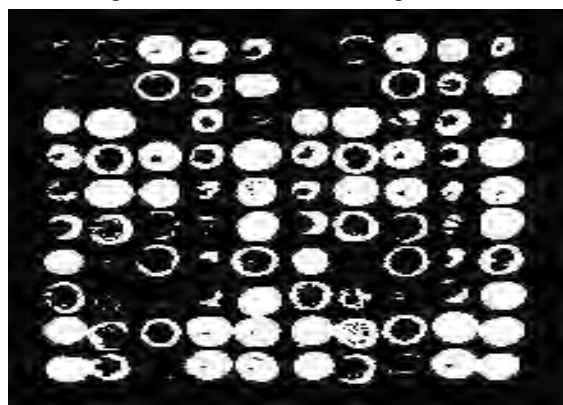


Figure 6. Fuzzy c means Segmentation

**iv) Soft thresholding method:** From the result, it is clear that soft threshold provides better segmentation output. According to varying spot sizes of input image, the output segmented spot sizes also get varied.

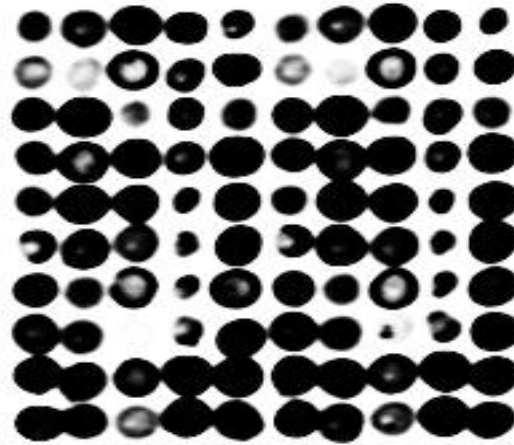


Figure 7. Soft thresholding method.

The last step is quantification, in which the red and green mean intensity values are obtained and then the log expression ratio is the ratio of red mean intensity value to green mean intensity value. The table below gives the log intensity values for spot 20 and 52 using different methods for segmentation.

Table 1. Spot intensity values for different segmentation methods

S.No	Log Intensity Values			
	Adaptive threshold	Combined Global & Local threshold	Fuzzy c-means clustering	Soft threshold
1.Spot 20 Value	0.50	0.36	0.75	0.98
2.Spot 52 Value	-1.29	-1.01	-0.11	0.12

The table shows that our proposed soft threshold method yields improved log intensity values when compared with other methods. As segmentation is effective, the log intensity ratio has been improved.

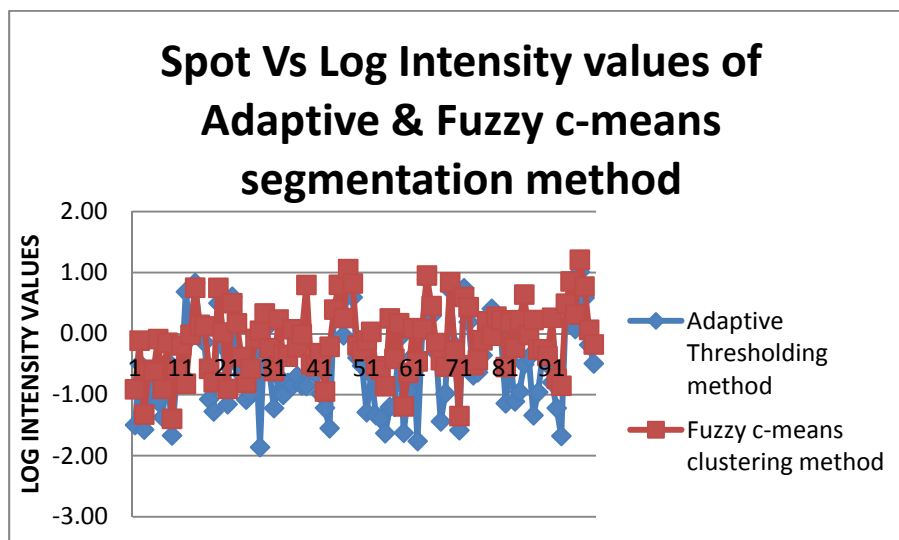


Figure 8. Spot data (100 spots) Vs log intensity values for adaptive and fuzzy c-means segmentation methods.

From Fig.4, it is clear that, fuzzy c-means clustering performs well when compared with adaptive threshold method of segmentation.



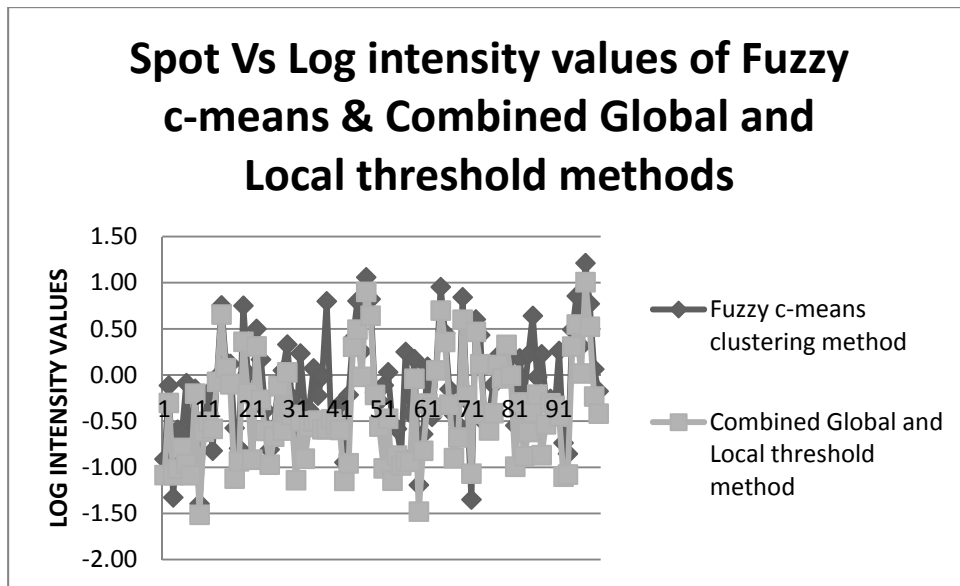


Figure 9. Spot data Vs log intensity values for fuzzy c-means and combined global and local threshold method of segmentation.

From Fig.5, it is clear that fuzzy c-means clustering is better when compared with adaptive and combined Global and Local thresholds.

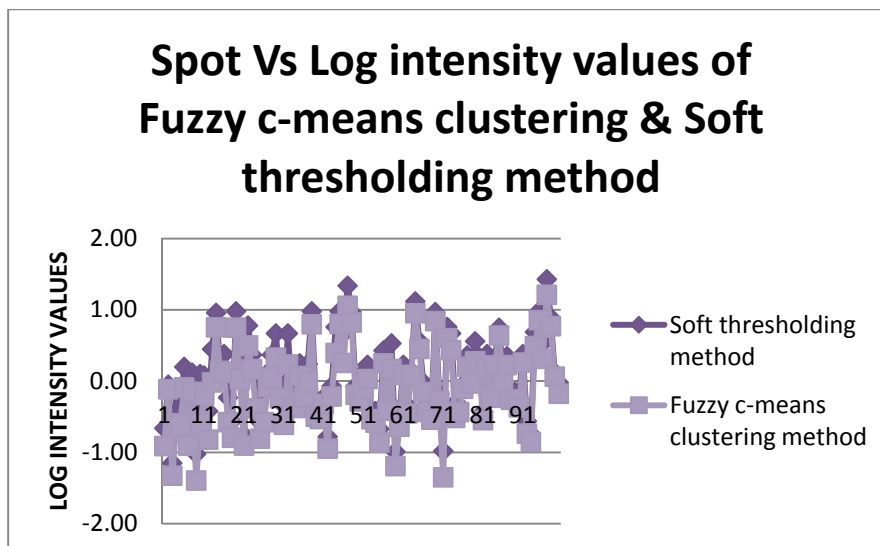


Figure 10. Spot data Vs log intensity values for fuzzy c-means and soft thresholding method.

From Fig.6, it is clear that the soft thresholding gives good segmentation and improved log intensity values when compared with all other methods. Thus our proposed method provides accurate segmentation of spots in microarray images.

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