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Segmentation of Complementary DNA Microarray Images by Wavelet-based Markov Random Field Model

Emmanouil I. Athanasiadis, Dionisis A. Cavouras, Member, IEEE, Dimitris Th. Glotsos, Pantelis V. Georgiadi, Member, IEEE, Ioannis K. Kalatzis, and George C. Nikiforidis

Index Terms—cDNA Microarray, Markov Random Field (MRF), image segmentation, Wavelet.

I. INTRODUCTION

Complementary DNA (cDNA) microarray chips are used for the qualitative and quantitative identification of thousands of genes at the same time [1]. Biological and technological specifications concerning cDNA microarray technology can be found in [1]. When using cDNA microarray images, the objective is to calculate the fluorescence intensity value for each spot on the chip. This intensity value is closely related with the expression abundance of the specific gene. However, accurate assessment of the spot’s intensity value would require precise segmentation of the spot-pixels from the spot’s background. Although, it has been advocated [1] that an inaccurate segmentation algorithm with a background correction method has no impact on the calculated spot intensity value, nevertheless, it has been recently proved [20,31] that segmentation methods can significantly influence microarray data precision, leading to inaccurate intensity extraction results.

Thus, the exact location and accurate identification of the boundary of each spot are crucial for more precise gene expression measurements.

In order to measure spot intensities, three steps are followed [1]-[2]: 1/ the addressing or gridding step, for the individual localization of cells (spots and their background), 2/ the segmentation step, for the discrimination of the spot from its background in each cell, and finally, 3/ the intensity extraction step, where calculation of the intensity of each spot is performed. The segmentation step is the most crucial due to the fact that errors during segmentation propagate to the intensity extraction step, leading to inaccurate intensity calculations.

In previous studies, several segmentation methods have been proposed in order to overcome limitations of currently used segmentation methods [3]-[7]. More specifically, in the publicly available SCANALYZE [3] and GenePix [4], fixed and adaptive circle segmentation methods have been adopted respectively. According to those two methods, all spots are considered to be circular with a fixed predefined radius; radius is constant in the former and adaptive in the latter technique. This assumption is the main drawback of those techniques due to the fact that spots are not perfect circles but are irregular in shape. Seeded Region Growing (SRG) [8] is one representative method of adaptive shape segmentation and it has been employed by the SPOT® [6] software. However, the limitation of SRG is that all initial seeds must be accurately defined [9]. In the ImaGene [7] software, a histogram based segmentation method is used, where values between the 80th and the 95th histogram percentile contribute to the calculation of the intensity value of the spot. Segmentation algorithms, based on the statistical Mann-Whitney test, that apply a thresholding filter on the cell, have also been introduced [10].
techniques have also been applied [11], where an initial contour is located on the spot-image and a contour deformation is formed for the task of delineating the spot’s boundaries. However, deformation that makes use of spatial information is apt to noise. Mixture Model [12]-[13] algorithms have been adopted for the task of segmenting microarray images using the Bayes’ rule. However, these methods are only based on the intensity and histogram of the image and do not take into account dependences among adjacent pixels (contextual).

In the last decade, Markov Random Field (MRF) [15] models, that use contextual and textural information, have been proposed for the task of segmenting [19] microarray images. In [27], multiresolution approaches have been proposed with the use of the Discrete Wavelet Transform (DWT) for the task of modeling the labels at various scales; label is a binary variable that indicates whether a pixel belongs to the foreground (spot) “1” or the background “0”. That modeling scheme has taken into account interscale and intrascale statistical dependencies. However, during the DWT decomposition process, image size is reduced by half and no further information has been used. Additionally, DWT-wavelet domain images have been used to model only the Energy of labels in the MRF model.

In the present study, we directly deal with the segmentation problem and we assume that the gridding stage has already been done and the location of each cell is known, as explicitly described in a previous study by our group [14]. Here, a new segmentation approach based on the MRF and the Stationary Wavelet Transform (SWT) [16] is proposed. The 1-level SWT of the image was used to form two images, a denoised image, using hard thresholding filter [24], and a magnitude image, from the amplitudes of the SWT’s horizontal and vertical components. The SWT was employed, since it retains the size of the decomposed components and information contained within the wavelet domain is not compressed as in the case of the DWT, and, thus, elements from the denoised and magnitude images could be suitably combined in actual scale to form the proposed wavelet-based MRF (WMRF) model for segmenting spots from their background. In addition, with the use of the stationary wavelet transform, additional textural (i.e., the intensity in the wavelet domain) and contextual information (i.e., the details in the wavelet domain), which are “hidden” in the wavelet domain, were also used to model both the labels and the feature’s Energy.

II. MATERIALS AND METHODS

A. Material

Simulated microarray images were produced, as described in [19], for the task of numerically evaluating the segmentation methods. More precisely, by applying a simple thresholding segmentation technique [19] to an actual cDNA microarray image with 1600 spots, a binary image was produced, which was in turn used as a template for the creation of a simulated image. Thus, the location, boundary, and area of all simulated spots were a priori determined. Moreover, the intensities of each spot (foreground) were formed from intensity values randomly drawn from an exponential distribution, which had a predefined mean intensity value that was randomly picked between 0 and $2^{16}$-1, which is the range of a typical actual microarray image. Additionally, background intensities were similarly produced but from a single exponential distribution with mean intensity value equal to 4000, which is close to the mean background intensity of actual microarray images. Finally, the so formed simulated microarray image was corrupted with additive Gaussian noise [13] with Signal to Noise Ratio (SNR) 1, 3, 5, 7 and 9 dB, thus, producing five different microarray images. The latter were employed for assessing the robustness of the simple Fuzzy C Means (FCM) [18], the conventional MRF, and the proposed Wavelet based MRF (WMRF) segmentation algorithms, in determining the spot’s boundaries.

In addition, the performances of the segmentation algorithms were estimated on five actual microarray images, which were replicates at five different distinct time intervals of the same experiment for both the Red and Green channels [1], [25]. Those microarray images were obtained from a free public available database [25], well established and widely used in the literature concerning Saccharomyces cerevisiae [25]. The software used for the creation of the microarray images was the ArrayMaker (Version 1.8.5). Detailed descriptions may be found in [26]. In the common reference Green channel, normalized spot-image intensities (see section D) are expected to remain constant with time, and this feature is usually employed in assessing the performance (reproducibility) of the segmentation techniques [20]: the steadier the segmentation result, in terms of mean spot intensity value at different time-intervals, the better the segmentation algorithm.

B. Markov Random Field (MRF)

MRFs were first introduced in computer vision by Geman [22]. The main benefit of the MRF model is that it can manipulate textural and contextual information of the image.

Suppose that a feature vector $F$ has been extracted from a random image $X$ and that $Y$ is the result of segmentation (labels “0” for Background and “1” for Foreground or spot) based on the observed features $F$. According to the Bayesian theory, the segmentation problem can be expressed by using relation (1).

$$P(Y \mid F) = \frac{p(F \mid Y) p(Y)}{p(F)}$$  \hspace{1cm} (1)

where, $P(Y \mid F)$ is the a posteriori probability of $Y$ given the observed features $F$, $p(F \mid Y)$ is the conditional probability of $F$ given $Y$, $P(Y)$ is the a priori probability of $Y$ that is used to describe the label distribution, and $p(F)$ is the probability distribution of $F$. \hspace{1cm}
The objective is to find the maximum a posteriori probability $P(Y|F)$ in (1); $p(F)$ in (1) was omitted since it does not vary with respect to any solution [23]. If we assume the energy form of $P(Y)$ to be $E_L$ and of $p(F|Y)$ to be $E_F^c$, where $c$ refers to the class (foreground, background), then the Total Energy can be derived from the sum of the two energies [23].

$$E^c = E_L + aE_F^c$$  \hfill (2)

where $a$ is a weighted parameter used to determine the individual energy percentage contribution in respect to the total energy.

The a posteriori probability may be expressed, using Gibbs distribution [22] and [23], as in (3).

$$P(Y|F) = \frac{1}{Z} e^{-\frac{E^c}{T}}$$  \hfill (3)

where, $T$ is a constant, $E^c$ is the energy function of class $c$ and $Z$ is a normalized constant given in (4) for all possible configurations of $Y$.\hfill (4)

$$Z = \sum_{c=1}^2 e^{-\frac{E^c}{T}}$$

In order to model the labels distribution ($E_L$), the Multilevel Logistic Model [15] has been adopted with 1st order neighbor system [23] as in (5)

$$E_L(y) = \sum_{c=\text{Neighbor}} \delta(y_i, y_{center})$$  \hfill (5)

where $y$ is the value of the label (“1” for the foreground or spot and “0” for the background) $t$ are the neighboring pixels of the $y_{center}$ center, $\delta(y_i, y_{center}) = -1$ if $y_i = y_{center}$ else $\delta(y_i, y_{center}) = I$.

In addition, if we assume that features follow a Gaussian distribution [23], we can model the feature distribution ($E_F$) as in (6).

$$E_F^c(f) = \sum_{k=1}^K \left( \frac{(f^k - \mu^c)^2}{2\sigma^c_k} \right) + \log(\sqrt{2\pi}\sigma^c_k)$$  \hfill (6)

where, $f$ is the feature vector, $\mu$ and $\sigma$ are the mean value and the standard deviation of each feature $k$ of class $c$, and $K$ is the number of features. In our case, $K$ was set to unity due to the fact that only the intensity of the pixel was used.

Finally, for the maximization of $P(Y|F)$ in (1), the Expectation Maximization algorithm was applied according to the following scheme [23]:

1) For each cell, a k-means clustering algorithm [18] was applied in order to make an initial rough estimation of the 2 classes, the foreground (spot) and background classes.

2) For each class, $\mu$ and $\sigma$ were calculated.

3) $E_L$ in (5) and two $E_F^c$ in (6) energies for each class $c$ were calculated by means of a 3x3 moving window within each cell. Next, two total energies in (2) were computed. Finally, based on (4), two a posteriori probabilities were found and classification was performed to the highest a posteriori probability.

4) Label values $Y$ were redefined.

5) The procedure was repeated from step 2 with the updated labels, until $E_{new} - E_{old} < \text{threshold}$.

C. Proposed Wavelet MRF (WMRF) Method

The SWT transform was first applied onto the microarray image, using one-level decomposition as an optimal solution to our microarray data; next the hard thresholding technique, as shown in (7), was employed to the detail images.

$$W_{out} = \begin{cases} W_{in} + Th \cdot (G - 1) & \text{if } W_{in} > Th \\ W_{in} - Th \cdot (G - 1) & \text{if } W_{in} < -Th \\ 0 & \text{otherwise} \end{cases}$$  \hfill (7)

where, $W_{out}$ denotes the output and $W_{in}$ the input coefficient values of the details (Horizontal ($Ho$), Vertical ($Ve$) and Diagonal ($Di$)). $Th$ and $G$ are threshold and gain values respectively. Threshold was automatically calculated by using the principle of Stein’s Unbiased Risk Estimate [30]. In each detail image, an individual threshold value was selected with the use of "thselect" MATLAB command.

Finally, the denoised ($D$) and magnitude ($M$) images were generated (see Fig.1). Images $D$ and $M$ were used in the calculation of the new energies $WE_L$ and $WE_F^c$ (see relations (9) and (11) ) of the labels and features respectively.

![Fig 1: SWT-decomposition of the initial image, filtering by hard thresholding (HT), and formation of the filtered (D) and magnitude (M) images.](image)

The magnitude image [24] was formed as in (8)

$$M = \sqrt{Ho^2 + Ve^2}$$  \hfill (8)

where $Ho'$ and $Ve'$ are the Horizontal and the Vertical wavelet decomposed detail images respectively at the 1st level of decomposition.

Following a trial and error procedure, the biorthogonal 1.5 mother wavelet [29] was chosen as optimum in delineating spot boundaries. For the calculation of $E_L$ in (5), the k-means clustering algorithm was applied to both denoised and magnitude images and, as a result, two binary images were produced, a rough estimation of spot and background pixels. $WE_L$ energy was calculated employing (9)
\[ WE_L(y) = w_1 \sum_{t \in \text{Neighbor}} \delta(y_t, y_{\text{center}})_M + (1-w_1) \sum_{t \in \text{Neighbor}} \delta(y_t, y_{\text{center}})_D \]

where \( w_1 \in [0, 1] \) is a weight constant.

For the calculation of \( WE^c_f \), a smoothing kernel (10) was first applied to the magnitude image \( M \)
\[ L_{\text{mask}} = \frac{1}{9} \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} \] (10)
and \( WE^c_f \) was calculated as follows
\[ WE^c_f = w_2 \left[ \frac{(I_M - \mu^c_M)^2}{2(\sigma^c_M)^2} + \log(\sqrt{2\pi}\sigma^c_M) \right] \\
+ (1 - w_2) \left[ \frac{(I_D - \mu^c_D)^2}{2(\sigma^c_D)^2} + \log(\sqrt{2\pi}\sigma^c_D) \right] \]

where \( I_M \) is the smoothed magnitude image, \( I_D \) is the denoised image, \( \mu^c_M \) and \( \mu^c_D \) are the mean values of class \( c \) of smoothed magnitude image \( M \) and denoised image \( D \), respectively. Finally, \( \sigma^c_M \) and \( \sigma^c_D \) are the standard deviations of \( M \) and \( D \) images of class \( c \), respectively. \( w_2 \in [0, 1] \) is a weight parameter.

The two new SWT-total energies were then calculated by (12),
\[ WE^c = WE_L + aWE^c_f \] (12)

\section*{D. Intensity Extraction and Normalization}

The outcome of each segmentation algorithm was a binary image, in which white pixels (255) corresponded to spots and black pixels (0) to background. In each cell-image (spot with its background) the mean intensities of both spot (foreground) and background were calculated by reference to the corresponding intensities on the original image. All spot mean intensities, on both simulated and actual microarray images, were background corrected by subtracting from each spot’s mean the background’s mean [1]. Regarding actual microarray images, spot intensities were calculated for both Red \( R \) (control) and Green \( G \) (common reference) channels.

Following intensity extraction, a normalization process was essential for removing systematic variations from the measured spot intensities in \( cDNA \) microarray experiments [28] and, consequently, for assessing spot intensities’ variation at different time intervals. In the present study, an intensity dependent normalization method (lowess) [28] was implemented for normalizing spot intensities. More precisely, \( MA \) plots were firstly constructed for one of the five replicate images, where \( M = \log_2(I_R/I_G) \), \( A = (1/2)\log_2(I_R/I_G) \), and \( I_R \) and \( I_G \) are the green and red channels spot mean intensities (see Fig. 2).

\[ MA \] plots have been previously found useful in identifying artifacts and intensity depended patterns [28]. Each \( MA \) plot was next fitted by a polynomial regression function (\( M \): predicted using lowess technique), which was used to normalize \( M \), by subtracting from each value of \( M \) the corresponding predicted \( M \), \( \hat{M} = M - M \). Regarding the green channel, which is the common reference channel, individual \( I_G \) intensity values were normalized according to (13) [...]
\[ \log_2 I_G = A - \frac{M}{2} \] (13)

Normalized green channel mean spot intensity values were calculated for the spots of the five individual images (replicates) and were used for further processing. Regarding red channel spots, mean spot intensities were left intact, since they were not employed in the evaluation of the precision of the algorithm.

\section*{E. Evaluation}

For the simulated microarray images the following metrics were calculated:
1) Segmentation matching factor (SMF) [14],
\[ SMF = \frac{B_{\text{segment}} \cap B_{\text{actual}}}{B_{\text{segment}} \cup B_{\text{actual}}} \] (14)

where \( B_{\text{segment}} \) and \( B_{\text{actual}} \) are the binary versions of the segmented and simulated actual cell-images respectively.

2) Coefficient of determination \( r^2 \) [19]
\[ r^2 = \frac{\sum_{i=1}^{All \ spots} (I_{\text{segment}(i)} - \bar{I}_{\text{actual}})^2}{\sum_{i=1}^{All \ spots} (I_{\text{actual}(i)} - \bar{I}_{\text{actual}})^2} \] (15)

where \( I_{\text{segment}} \) and \( I_{\text{actual}} \) are the mean intensity values of the calculated and simulated actual spots respectively, \( i \) refers to individual cell images \( (i=1...1600) \), and \( I_{\text{actual}} \) is the overall
mean of the spot intensity values of the simulated actual image.

Regarding the real microarray images, the reproducibility of the segmentation techniques was quantified by means of:

1) Mean Absolute Error (MAE) [20].

\[
MAE_{\text{spot}} = \frac{1}{n} \sum_{i=1}^{n} |I_i - \bar{I}|
\]

(16)

where \( n \) is the number of replicates (\( n = 5 \)), \( I_i \) is the normalized mean spot intensity value and \( \bar{I} \) is the spot’s overall mean, calculated from the means of the corresponding spots in the \( n \) replicates.

2) Coefficient of Variation (CV) [21].

\[
CV_{\text{spot}} = \sqrt{\frac{1}{n-1} \sum_{i=1}^{n} (I_i - \bar{I})^2}
\]

(17)

The lower the MAE and the CV values, the better is the reproducibility of the method being evaluated.

Finally, all methods and metrics described in the above sections were performed by means of custom made programs developed in MATLAB® [17].

III. EXPERIMENTAL RESULTS AND DISCUSSION

The most essential task of the segmentation process is the discrimination of each spot’s foreground from its background. Since it is unfeasible to know each spot’s exact location, extend, and outline on real microarray images, simulated data were generated for validating the segmentation algorithms [20]. Five simulated microarray images were formed for quantifying the segmentation performances of the proposed wavelet based MRF technique, the conventional MRF technique as well as the FCM clustering algorithm. The segmentation matching factor (SMF) and the coefficient of determination (\( r^2 \)) were both used for evaluation purposes, since the former concerns segmentation accuracy and the latter intensity extraction precision, and the results are illustrated in Tables I and II respectively. In addition, a graphic representation of the results is shown in Fig. 3 and 4.

### TABLE I

<table>
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<th>SNR (dB)</th>
<th>FCM</th>
<th>MRF</th>
<th>WMRF</th>
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<tr>
<td>1</td>
<td>89.22</td>
<td>92.15</td>
<td>92.66</td>
</tr>
<tr>
<td>3</td>
<td>89.94</td>
<td>92.96</td>
<td>93.53</td>
</tr>
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<td>5</td>
<td>91.25</td>
<td>94.24</td>
<td>94.56</td>
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<td>7</td>
<td>93.81</td>
<td>96.30</td>
<td>96.69</td>
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<tr>
<td>9</td>
<td>94.69</td>
<td>97.20</td>
<td>97.47</td>
</tr>
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Comparative SMF results for the 5 simulated images with different SNR levels. The 2nd, 3rd, and 4th columns indicate the SMF by using FCM, MRF and the proposed WMRF segmentation techniques respectively.

![Fig 3: SMF results on simulated data using FCM, MRF and WMRF for different SNR levels.](image)

![Fig 4: \( r^2 \) results on simulated data using FCM, MRF and WMRF for different SNR levels.](image)

According to our findings on the simulated data, the proposed WMRF algorithm achieved the highest SMF and \( r^2 \) scores as compared to the conventional MRF and FCM techniques at all SNR levels. More precisely, at the 1dB SNR Gaussian noise level (see Table I), the FCM scored 89.22 whereas the MRF and WMRF scored 92.15 and 92.66 respectively. This SMF difference, of about 3%, between the FCM and WMRF was sustained for higher SNR levels. In contrast, in the case of the \( r^2 \), differences among FCM, MRF, and WMRF decreased for higher SNR levels (see Table II).

Furthermore, the proposed WMRF and the conventional MRF techniques were both used to segment five actual microarray images. The algorithms’ performances were assessed by the reproducibility of the results on the green...
channel and they were quantified employing two metrics, MAE (sameness) and CV (variation). Moreover, for comparison reasons, the publicly available software programs SCANALYZE® [3] and SPOT® [6] were employed for segmenting the same microarray images; the SCANALYZE software makes use of the Fixed Circle (FC) segmentation technique and the SPOT of the Seeded Region Growing (SRG). Results concerning MAE and CV for all 6400 spots are illustrated in Table III and Fig 5.

### TABLE III

<table>
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<th>Method</th>
<th>MAE</th>
<th>CV</th>
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<tr>
<td>MRF</td>
<td>1215</td>
<td>1.15</td>
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<tr>
<td>WMRF</td>
<td>497</td>
<td>0.88</td>
</tr>
<tr>
<td>SCANALYZE (FC)</td>
<td>503</td>
<td>0.90</td>
</tr>
<tr>
<td>SPOT (SRG)</td>
<td>1180</td>
<td>0.93</td>
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Results for the four segmentation techniques by means of MAE and CV, applied on five real microarray images.

The lowest MAE and CV measurements were obtained by the proposed WMRF method. More precisely, WMRF scored 497 mean MAE for the 6400 spots, which is close to the score attained by the FC technique. Additionally, the MAE of the proposed WMRF technique was half that of the conventional MRF, which is indicative of the improvement on MRF that wavelet based information may bring about. Additionally, the proposed method achieved a MAE (497) score lower, but close, to SCANALYZE’S FC technique (503), but definitely lower than that of the conventional MRF technique (1215) and of the SPOT’s SRG technique (1180) (see Table III). Additionally, the CV values of WMRF, FC, SRG, and MRF (0.88, 0.90, 0.93, 1.15) were close to unity with the WMRF having the lowest value.

Regarding segmentation processing time, for an actual microarray image of 6400 spots it took approximately 23 minutes for the WMRF against about 20 minutes for conventional MRF on a Pentium IV 3GHZ desktop PC with 1GB RAM. Nevertheless, it should be noted that the algorithms have not been optimized yet, for optimal time-processing results, as compared with SCANALYZE’S fast response times, using the fixed-circle technique. Although our method, as compared to Scanalyze (FC), shows a slight improvement in the precision of reproducibility, its value is on the delineation accuracy of the spots’ boundaries and, hence, of the spot’s expression level, that can significantly influence microarray intensity extraction results [20, 31].

### CONCLUSIONS

A new method (WMRF), based on the SWT and the MRF was proposed, for improving the segmentation of microarray images. The WMRF method was tested on both simulated and actual cDNA microarray images and was compared against the FCM and the ordinary MRF methods and against two publicly available software packets, SPOT and SCANALYZE. Results revealed the potentiality of the proposed method, which may be attributed a) to the employment of the SWT, for retaining the actual scale on the wavelet transformed images, and b) to the formation of novel labels and features, that utilize additional hidden textual and contextual information, to design the proposed WMRF scheme.

### REFERENCES


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