Denoising of Microarray Images using the Markov Random Field Model in the Spatial Domain

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Abstract: DNA Microarray technology is a very useful area in bioinformatics research. Microarray gene expression data allow us to quantitatively and simultaneously monitor the expression of thousands of genes under different conditions. Denoising is one of the major pre-processing steps in microarray image analysis. This paper presents a new spatial domain technique for denoising a DNA microarray image. The proposed method uses Markov Random Field model to reduce the noise in the microarray image. The probability mass function for the Markov Random Field uses Quadratic Energy Function. Maximum-a-Posteriori method is used to estimate the noiseless pixel values followed by Quasi-Newton method to solve the unconstrained non-linear optimization problem. Experimental results and analysis illustrate the performance of the proposed method with contemporary methods.

Keywords: Markov Random Field, Microarray image denoising, Energy function, Non-linear Optimization, Minimum mean square error.

Introduction

Microarray is the robotic placement of thousands of cDNAs on a glass microscope slide. It is capable of profiling gene expression patterns of tens of thousands of genes simultaneously. Microarrays containing sequence representatives of all human genes may soon permit the gene expression analysis of the entire human genome in a single experiment, and this will provide unprecedented access to key areas of human health, including disease prognosis and diagnosis, drug discovery, toxicology, aging, and mental illness.Thus,microarray technology is rapidly become a standard platform for functional genomics [1].

The processing of microarray images [2], usually consists of the following steps: (i) gridding and spot finding, which is the process of assigning the location of each spot in the image, (ii) segmentation, which is the process of grouping the pixels with similar features (this step results in the separation of foreground and background pixels), (iii) intensity extraction, which calculates red and green foreground intensity pairs and background intensities.

Noise is inherent in a microarray image because of the very nature of its acquisition. The complex bio-chemical and optical processes involved in the microarray preparation generate substantial amount of noise [3]. The presence of noise in a microarray image will affect subsequent stages of image analysis and finally affects gene expression profile. Therefore, removal/reduction of the noise is an important prerequisite for further processing.

Several methods have been proposed for eliminating and reducing the noise [4], [5] in a microarray image. Two popular techniques are the transform domain approach and the spatial filtering. In the former case, the images are transformed using Fourier or Wavelet transformations and then processed for noise reduction and then inverse transformed to get back the denoised images. In the spatial filtering methods, linear and nonlinear filters are used to reduce the noise. In this paper Markov Random Field (MRF) approach is used to denoise a so that, the first stage of microarray image analysis, gridding becomes easier.

Review of Recent Literature

The literature survey carried out shows that a numerous researches have been proposed by researchers for Denoising the microarray images. In this section, a brief review of some important contributions from the existing literature is presented.

X. H. Wang et al., [6] have proposed a new approach using wavelet theory to provide an denoising approach for eliminating noise source and ensure better gene expression. Denoising method uses stationary wavelet transform to preprocess the microarray images for removing the random noises. R. Lukac et al., [7] have proposed a new vector fuzzy filtering framework to denoise cDNA microarray images. This method adaptively determines weights in the filtering structure and provides different filter structures. Bogdan Smolka et al., [8] proposes a new method of noise reduction, which is capable of removing impulse and Gaussian noises, while preserving and even denoising the sharpness of the image edges. Hara

Stefanou et al., [9] have used a two stage approach for noise removal that processes the additive and the multiplicative noise component that decomposes the signal by a multiresolution transfom. Guifang Shao et al., [10] have developed a new algorithm which includes two parts: edge noise reduction and highly fluorescence noise reduction for noise reduction. J K meher et al., [11] explained noise reduction from microarray image and reduction of error during quantification process for estimating microarray spots accurately by preprocessing techniques such as optimize spatial resolution (OSR) and spatial domain filtering (SDF) to determine expression level of genes. Mario Mastriani et al., [12] described a Noise removal technique using smoothening of coefficients of highest sub bands in wavelet domain. N. Plataniotis et al., [13] have proposed a Denosing switching scheme based on the impulse detection mechanism using peer group concept.

Markov Random Field Model for an Image

Markov Random Field (MRF) is an environment where the probability distribution of a random variable at a point (node) depends only on its immediate neighbors [14]. MRF methods take into account the existence of spatial correlations in the present context.

Consider the pixel location (i, j) of an image as shown in Fig.1, with i representing the row and j representing the column.Let the pixel value at (i, j) be represented by the random variable X(i, j). When image intensities are expressed using 8-bit unsigned integers, the range of the pixel values are from 0 to 255. Therefore, X(i, j) can take any integer value in the range { 0 **:** 255}. Thus X(i, j) is a discrete integer random variable. Let x(i, j) be one of the specific value in the set {0 **:**255}. Then the probability of X(i, j) equal to x(i, j)is represented as p(X(i, j) = x(i, j)) or simply p(x(i, j)). Now consider the conditional probability,

$p(X(i, j) = x(i, j)/X(k,m)=x(k, m))$ for $k \neq i$ and $j \neq m$.

Let the 8-way neighborhood of (i, j) be as shown in grey color in the lattice diagram of Fig. 1. The neighborhood set of (i, j) is represented by N(i, j) and is given by,

$$N(i,j) = \{(i-1,j-1),(i-1,j),(i-1,j+1),(i,j-1)(i,j+1),(i+1,j-1),(i+1,j),(i+1,j+1)\} \quad (1)$$

By definition, the random variable X(i, j) forms an MRF if,

$p(X(i, j) = x(i, j) / X(k,m) = x(k, m))$ for $k \neq i$ and $j \neq m$, is equivalent to,

$p(X(i, j) = x(i, j) / X(k,m) = x(k, m))$ for $(k, m) \in N(i, j)$.

This means, the probability value at location (point) (i, j) depends only on the pixel values of its immediate neighbors.

Probability mass function for MRF

According to, the Hamersley-Clifford theorem [15], the probability mass function for an MRF is given by the Gibbs distribution [16] as,

$$p(x(i,j)) = \frac{1}{Z} * \exp\left(-E(x(i,j))\right) \quad (2)$$

Here, E is the Gibbs *energy function* and Z is the *partition function.* Z is chosen such that,

$$\sum_{x(i,j)\in\{0:255\}} p(x(i,j)) = 1$$

(i−2, j−2)	(i−2, j−1)	(i−2, j)	(i−2, j+1)	(i−2, j+2)
(i−1, j−2)	(i−1, j−1)	(i−1, j)	(i−1, j+1)	(i−1, j+2)
(i, j−2)	(i, j−1)	(i, j)	(i, j+1)	(i, j+2)
(i+1, j−2)	(i+1, j−1)	(i+1, j)	(i+1, j+1)	(i+1, j+2)
(i+2, j−2)	(i+2, j−1)	(i+2, j)	(i+2, j+1)	(i+2, j+2)

Figure 1. Immediate neighbors of (i, j), shown in grey color

In general the energy function can be constructed in several ways.

Quadratic Energy function: In the case of image analysis, the quadratic format for E(x(i, j)) is popular [17]. It is computed as,

$$E(x(i,j)) = (x(i,j) - a(i,j))2 + c1 * \sum_{(e,f)\in HV(i,j)} \big(x(i,j) - a(e,f)\big)^2 + c2 * \sum_{(g,h)\in D(i,j)} \big(x(i,j) - a(g,h)\big)^2 \quad (3)$$

Here, a(i, j) is the present pixel value at (i, j) of a given image. The set HV(i, j) represents the indices of the horizontal and vertical neighbors of (i, j) as shown in Fig.2.Indices (e, f)'s are shown in grey in Fig.2. The set D(i, j) represents the diagonal neighbors of (i, j) as shown in Fig.3. Indices (g, h)'s are shown in grey in Fig. 3. Parameters c1and c2 provide the weights for the respective terms of Eq.(3). The values of c_1 and c_2 are chosen properly for the best performance.

Denoising using MRF model

Let us consider a noisy image whose observed pixel value at location (i, j) is given by a(i, j) as,

$$a(i,j) = x(i,j) + n(i,j) \quad (4)$$

where, x(i, j) is the original noiseless pixel value and n(i, j) is the additive random noise. Our aim is to recover the value of x(i, j) from the known values of a(i, j)'s.

Maximum-a-Posteriori (MAP) Estimation of x(i, j)

In the MRF model under consideration, p(x(i, j)) is given by Eq. (2).According to the principle of MAP, the best estimate of x(i, j) is one which maximizes p(x(i, j)). That means, the best estimate of x(i, j) represented by b(i, j) is,

$$b(i,j) = \arg\max_{x(i,j)} \{p(x(i,j))\} \quad (5)$$

From Eqs.(2) and (5), we see that maximizing p(x(i, j)) is same as minimizing the energy function E(x(i, j)) over x(i, j). Therefore b(i, j) can be expressed as,

$$b(i,j) = \arg\ \min_{x(i,j)} \{E(x(i,j))\} \quad (6)$$

where E(x(i, j)) is given by Eq. (3).

Our objective is to find that (x(i, j) which minimizes E(x(i, j)) given by Eq. (3).

	(i−1, j)	
(i, j−1)	(i, j)	(i, j+1)
	(i+1, j)	

Figure 2. HV(i, j), Horizontal and Vertical neighbors of (i, j)

(i−1, j−1)		(i−1, j+1)
	(i, j)	
(i+1, j−1)		(i+1, j+1)

Figure 3.D(i, j), Diagonal neighbors of (i, j)

Minimization of energy function in quadratic form

The quadratic energy function E(x(i, j)) is minimized by differentiating it with respect to x(i, j) and equating the derivative to zero. From Eq. (3), the derivative is obtained as,

$$\frac{dE(x(i,j))}{dx(i,j)} = 2 * \big(x(i,j) - a(i,j)\big) + 2 * c1 * \sum_{(e,f)\in HV(i,j)} \big(x(i,j) - a(e,f)\big) + 2 * c2 * \sum_{(g,h)\in D(i,j)} \big(x(i,j) - a(g,h)\big) \quad (7)$$

The value of x(i, j) that minimizes E(x(i, j)) is obtained by equating the RHS of Eq. (7) to zero. After cancelling 2, throughout and expanding the summations, we get,

$$x(i,j) - a(i,j) + c1 * \left(\left(x(i,j) - a(i-1,j)\right) + \left(x(i,j) - a(i,j-1)\right) + \left(x(i,j) - a(i,j+1)\right) + \left(x(i,j) - a(i+1,j)\right)\right) + c2 * \left(\left(x(i,j) - a(i-1,j-1)\right) + \left(x(i,j) - a(i-1,j+1)\right) + x(i,j) - a(i+1,j-1)\right) + \left(x(i,j) - a(i+1,j+1)\right)) = 0 \quad (8)$$

On solving Eq. (8) for x(i, j), we get,

$$x(i,j) = b(i,j) = \frac{a(i,j) + c1 * t1 + c2 * t2}{1 + 4 * c1 + 4 * c2} \quad (9)$$

Here,

$$t1 = a(i-1,j) + a(i,j+1) + a(i,j+1) + a(i+1,j) \quad (10)$$

$$t2 = a(i-1,j-1) + a(i-1,j+1) + a(i+1,j-1) + a(i+1,j+1) \quad (11)$$

t_1 gives the sum of the horizontally and vertically adjacent pixels whereas t_2 gives the sum of diagonally adjacent pixels. The values of b(i, j)'s, obtained according to Eq. (9) for all values of (i, j)'s constitute the denoised image. The denoising of a microarray image, using the MRF model, is given below.

Denoising Using MRF (DUMRF) Algorithm.
Input: Noisy spot of the given microarray image.
Output: Denoised spot of the microarray image.

1. Read the given image.
   Get the size (M, N) where M is the number of rows and N is the number of columns of the image matrix A.
   Store the pixels in a(i, j)'s. (for i=1to M and j= 1 to N).
2. Select suitable values for c_1 and c_2.
3. Get b(i, j)'s for all i's and j's using Eqs. (9), (10) and (11).
4. Matrix B of b(i, j)'s gives the denoised image.
5. Exit.

Best estimation of parameters c_1 and c_2.
The denoising performance of our MRF method depends on the correct choice of c_1 and c_2 which are used in Eq. (9). Therefore, we select c_1 and c_2 such that the denoised image obtained using Eq. (9) results in minimum denoising error.
Let us consider a noiseless (clean) image Q of size (MxN), whose elements are q(i, j)'s. To this, we add a known synthetic noise. The noise added could be Gaussian, Poisson, Salt and Pepper so on with appropriate noise parameters like mean, variance etc. Let the noise image be G, whose elements are g(i, j)'s. The resulting noisy image be designated by A whose elements are a(i, j)'s. Then we have,

$$A = Q + G \quad (12)$$

Now, Denoising Using MRF (DUMRF) Algorithm is used to denoise A using Eq. (9), with c_1 and c_2 as decision variables. Then, we solve for c_1 and c_2 using Determination of Optimum values (DOV) algorithm for minimum denoising error. Thus, getting correct c_1 and c_2 is to solve an optimization problem.
Once c_1 and c_2 are obtained by using a known noise source G and a known pure image Q, as in Eq. (12), we assume the same c_1 and c_2 values can be used to denoise other similar images with unknown noises.
1) Mean Square Error in image denoising: Let the denoised image corresponding to A in Eq. (11) be B whose elements are b(i, j)'s. Then the Mean Square Error (MSE) is defined as,

$$MSE = \frac{1}{M*N} * \sum_{i=1}^{M} \sum_{j=1}^{N} \left(b(i,j) - q(i,j)\right)^2 \quad (13)$$

When B is exactly equal to P, the denoising is perfect and the MSE is zero. A low value of MSE indicates that the denoised image B is close to the noiseless image P. In Eq. (13), b(i,j) is a non-linear function of c_1 and c_2.Therefore MSE given by Eq. (13) is a non-linear function of c_1 and c_2. Our objective is to determine c_1 and c_2 to minimize the objective function MSE, using non-linear optimization.

Non-linear optimization
When the objective function to be minimized (or maximized) is a non-linear function of decision variables, then we call it as the non-linear optimization or non-linear programming. In our case, the objective function is MSE as given by Eq. (13), which is a non-linear function of b(i, j)'s which in turn depend on c_1 and c_2. Therefore determination of optimum values, c_1

and c_2 to minimize the MSE forms a non-linear optimization problem. Since there are no explicit constraints in solving for c_1 and c_2, this is an unconstrained non-linear optimization problem.
Several techniques are available to solve the unconstrained non-linear optimization problem [18-20]. A few popular algorithms are, Quasi-Newton [21], Nelder-Mead [22-23] and Trust-region [24].
In this paper, we use the Quasi-Newton method for solving the non-linear optimization problem using the function **fminunc(…)** [25]from Matlab.

Use of fminunc(…)
In using fminunc(…). The decision variables c1 and c2 are represented in the vector form c as,

$$c = [c1, c2] \tag{14}$$

fminunc(…) is basically an iterative method. Therefore we have to supply the initial guess values of c1 and c2. In this case we have taken the initial values as,

$$c0 = [0.0,0.0] \tag{15}$$

The pure image Q and the noisy image A are given as the input parameters to calculate the MSE.The optimal output values of c and MSEopt are obtained as,

[c, MSEopt] = fminunc(@(c)get_mse(c,Q,A),c0,options) (16)

The *options*[25] selected as
options = optimoptions(@fminunc, 'Algorithm', 'quasi- newton', 'Display', 'iter', 'PlotFcns' , @optimplotfval) (17)

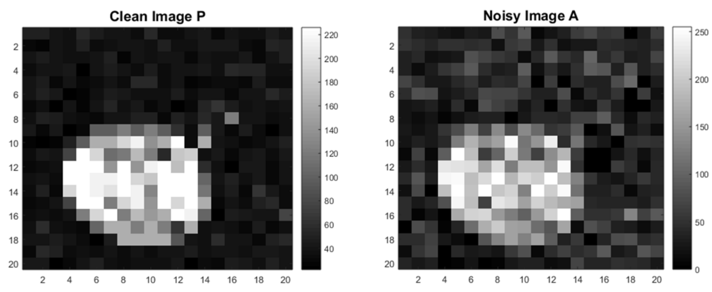
Algorithm (DOV) describes the use of fminunc(…).

Determination of Optimum Values (DOV) Algorithm.
Input : Noiseless image Q, Suitable synthetic Noise matrix G.
Outputs: Best values of c_1 and c_2.

1. Select a suitable synthetic noise matrix G (Gaussian, Salt & Pepper, Poisson and speckle.).
2. Add G to Q to get A as, A = Q +G.
3. Take vector c as, c =[c_1, c_2].
4. Take initial guess value c_0 = [0.0, 0.0].
5. Create the function get_mse(c, Q, A) which gives the MSE value according to Eqs. (13) and (9).
6. Set the options as specified by Eq. (17).
7. Execute the Matlab function **fminunc(…)**as given by Eq. (16).
8. Output is ready in vector c = [c_1, c_2].
9. Over.

Experiments and Analysis

Example 1: Here, we use the Gaussian noise. A sample microarray spot of size 20x20 is taken and is converted to a gray scale image Q. A zero mean, 0.01 variance, Gaussian noise G is added using immnoise [26] function to get A. Noiseless image Q and its noisy version A are shown in Fig. 4a and Fig. 4b. The vertical color bar next indicates the magnitude levels of the grayscale.
Converging values of c_1, c_2 and MSE, from Algorithm DOV, in successive iterations, are shown in Table 1. The final c_1 and c_2 values are, $\mathbf{c_1 = 0.1328}$ and $\mathbf{c_2 = 0.0387}$ at iteration 7.



(a)Noiseless image (b) Noisy Image

Figure 4. Noiseless and noisy microarray spot image

Table 1. Converging values of c1, c2 and MSE

Iterations	C_1	C_2	MSE
0 (at start)	0	0	535.7950
1	0.3179	0.3263	471.7889
2	0.2051	0.0502	329.7417
3	0.1863	0.0096	321.1292
4	0.1773	0.0390	316.9089
6	0.1345	0.0387	316.9086
7	**0.1328**	**0.0387**	**316.9086**
8	**0.1328**	**0.0387**	**316.9086**
9	**0.1328**	**0.0387**	**316.9086**

The MSE values in the neighborhood of optimum values of c_1 and c_2 are plotted and shown in Fig. 5. In Fig. 5, we can see the variation of MSE as c_1 and c_2 are varied around their optimal values. The denoised image of Fig. 4b, using the optimal values of c_1 and c_2, is shown in Fig. 6.

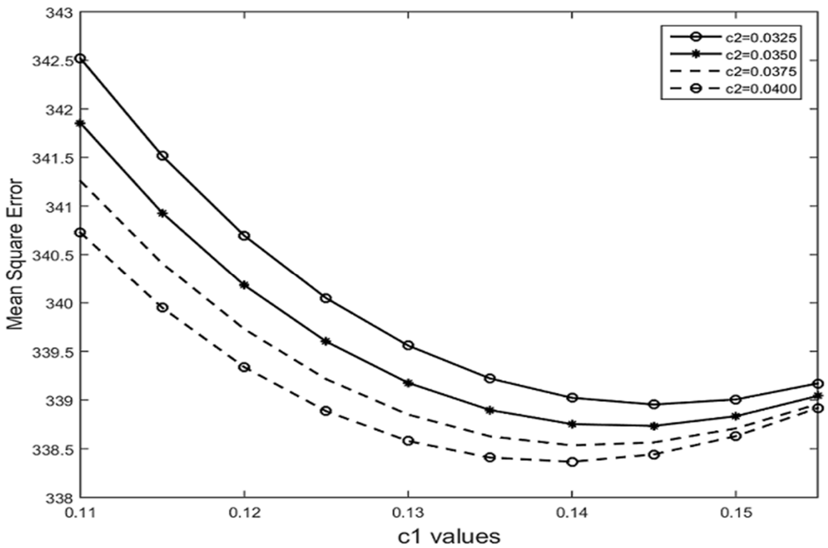


Figure 5. Variation of MSE with c_1 and c_2

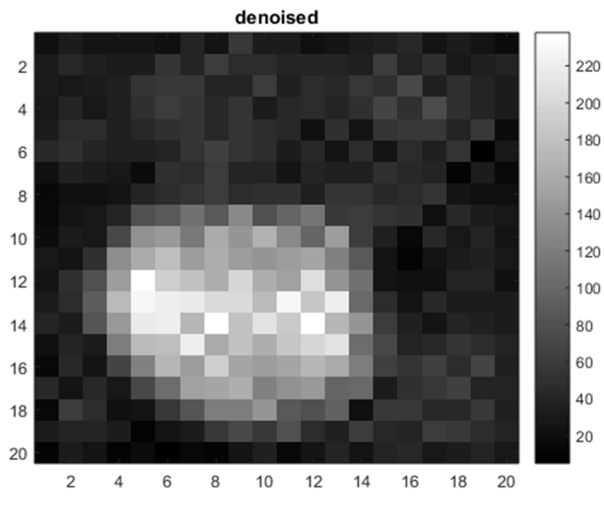


Figure 6. Denoised image using c_1=0.1328 and c_2=0.0387. MSE=316.9086

Example 2: Another sample spot from the microarray image set is taken and denoised using c_1=0.1328 and c_2=0.0387. The given image is assumed to be a degraded and a noisy image. The effect of denoising is shown in Fig. 7. The degree of difference between the noisy image and the denoised image is measured using the MSE between them and is found to be 85.4174.

Denoising performance of the proposed MRF method on different types of noises

The proposed method of denoising is applied to a noiseless sample spot from the microarray image after adding the following types of synthetic noises with default parameters.

1. Gaussian Noise.
2. Salt and Pepper Noise.
3. Poisson Noise.
4. Speckle Noise.

In all the cases, the percentage reduction in the noise level is expressed as,

$$\text{Per}_{\text{red}} = \frac{100*(MSE1 - MSE\ 2)}{MSE1} \tag{18}$$

Where, MSE1 = Mean Square Error without denoising.
MSE2 = Mean Square Error with MRF denoising.

The calculated results are shown in Table 2.

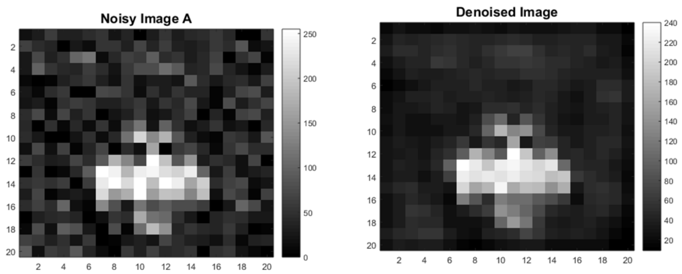


Figure 7. Noisy spot image and its denoised image

Table 2. Percentage Reduction for different types of noises

Type of Noise	Gaussian Noise	Salt & pepper Noise	Poisson Noise	Speckle Noise
Per_red	40.85	32.64	16.69	26.48

From the result of Table 2, we see that proposed method is better suited for Gaussian noise, compared to other types.

Comparison with other methods

Example 3:Gaussian noise with different values of variance are added to a noiseless microarray spot and the resulting noisy images are denoised using the proposed (DUMRF) method and four other standard denoising methods. The methods are,

1. Denoising using MRF with c_1= 0.1328 and c_2 = 0.0387.
2. Denoising using averaging filter [27] of size 3x3.
3. Denoising using SureShrinkwavelet filter [28].
4. Denoising using Soft-thresholding wavelet filter [29].
5. Denoising using SUSAN filters [30].

The successive rows in Table 3 correspond to the increasing values of the noise level in terms of the variance.

Table 3. MSE values for different methods

Noise level (variance)	MSE1 Method1 (DUMRF)	MSE2 Method2	MSE3 Method3	MSE4 Method4	MSE4 Method5
0.001	308.0	462.1	501.7	311.4	327.1
0.002	347.0	464.0	548.0	413.4	416.4
0.003	361.0	458.6	531.7	487.0	506.8
0.004	394.5	476.2	515.1	494.3	646.4
0.005	399.2	486.6	574.0	552.0	768.9
0.006	393.9	498.5	510.3	547.5	710.4
0.007	446.9	495.9	536.6	612.5	850.2
0.008	433.4	505.5	541.6	604.2	1015.0
0.009	470.2	505.6	563.8	556.4	954.3
0.010	494.3	523.7	585.2	649.3	1062.5

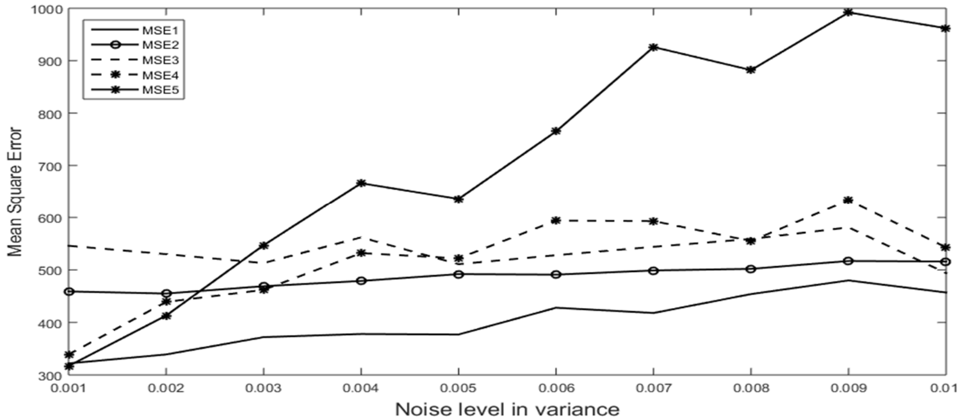


Figure 8. Variation of Mean Square Error with noise level

From Table 3, we see that proposed method produces promising results compared to other standard methods. The bar graph corresponding to the values of Table 3 is shown in Fig. 8.

Conclusion

A new method of denoising microarray spots using MRF is presented. This paper presents two algorithms. In DUMRF Algorithm, Maximum-a-posteriori method is used to estimate the noiseless pixel value. The DOV Algorithm uses non-linear optimization technique to get relevant parameters for DUMRF Algorithm. Experimental results and analysis shows proposed method produces promising results compared to other standard denoising method. This work can be used as efficient pre-processing method in microarray image analysis for accurate gene expression profiling.

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