Back Propagation Algorithm (BPA) based Mitotic Cell Detection in Breast Histopathology Images

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Abstract - Nowadays, Breast cancer diseases are common cancer among women. It is doubtlessly an abominable and life-threatening disease. If it is distinguished and by rights treated in its early stage, the chance of healing increases. Different imaging techniques are there which plays a critical role in the diagnosing of breast cancer. The proposed system presents mitosis detection in digital histopathology images using Image Processing Techniques by feed forward back propagation Artificial Neural Networks. Mitosis counts in histopathological slides play a crucial role for invasive breast cancer grading using the Nottingham grading system. Pathologists perform this grading by manual examinations of a few thousand images for each patient. Hence, finding the mitotic figures from these images is a tedious job and also prone to observer variability due to variations in the appearances of the mitotic cells. A database of 90 previously verified patient cases are employed and randomly partitioned in to one set for training and five independent sets for testing. Gray Level Co-occurrence Matrix (GLCM) and chip histogram features extracted from the known histopathology images are used to train separately random forest and Artificial Neural Network based detection system. In Testing Phase the extracted features of known and unknown histopathology images are compared for classification of images containing mitotic and non mitotic cells. Feed-forward back propagation Artificial Neural Network structure had been trained for detection. The performance is evaluated on the basis of five-fold cross validation method and Mean Square Error (MSE). The verification results show that the proposed algorithm gives the best classification results of histopathology images using Artificial Neural Network classifier

Index Terms— Histopathology, Nottingham grading system, GLCM, Chip histogram, ANN

I. INTRODUCTION

MITOSIS, the most common form of cell division, is controlled by the genes inside a cell [1]. But due to mutation in the cell DNAs, the mitosis process may go out of control causing the cells to replicate in an abnormal manner. These are the cancer cells [2] which form lumps or tumors that damage the surrounding normal tissues. Sometimes, cancer cells break off from the original tumor and spread in other parts of the body through the blood. This is called metastasis [3].

Thus, generation and spread of cancer is primarily governed by mitosis cell division.The Nottingham Grading System [4], internationally recommended for breast cancer grading by the World Health Organization, is derived from the assessment of three morphological features of tissues, namely: tubule formation, nuclear pleomorphism and mitotic count of which the third one plays the key role [5]. Cancer grading not only offers an insight to the growth of cancer and its spread but also helps in cancer prognosis and treatment planning. Clinically, the grading of invasive breast cancer is performed on the Hematoxylin and Eosin (H&E) stained slides where the pathologists manually mark the mitotic figures present in the slides. But due to huge number of cells in the slides and their widely different appearance, the manual process is cumbersome and prone to observer variability. Hence, an automated mitosis detection method will not only save the time but also make the grading observer-independent.

But there are several challenges in the automatic detection of mitotic figures from the microscopic images of H&E stained histopathological slides. Firstly, mitotic cells have a large variety of shape configurations. During the four different phases of mitosis cell division, namely: prophase, metaphase, anaphase and telophase (see Fig. 1), the shape of the cell nucleus appears differently. The nucleus of mitotic cell gets completely split in the telophase. But, they are still not full individual cells. So, a mitosis in telophase must be counted a Single mitosis, and not as two mitoses. Variation in appearance of the mitotic figures may also be caused by other factors like aberrant chromosomal makeup (such as aneusomy, polysomy, translocations, amplifications, deletions) of many tumors and imperfections of the tissue preparation process for cancer grading.

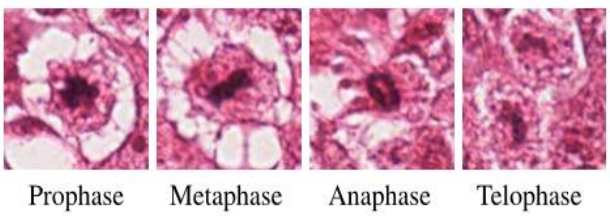

Fig 1. Phases of mitosis

These present a challenge for an automated mitosis detection system. Further, there may be other objects (like

apoptotic cells, lymphocytes, junk objects, and dense nuclei) which may look similar to mitotic cells. So, there is a possibility of mis-classification and hence, manual mitosis detection is prone to observer variability.Also, a clear nuclear membrane may be absent in mitotic cells which may lead to inaccurate cell segmentation. Consequently, the region features, extracted from the segmented object becomes inaccurate and this results in improper classification.

Propose a new method for mitosis detection from histopathological images. This method is based on the fact that although various factors cause significant variation in the shape of mitotic nuclei, their intensity pattern remains closely similar. Again, the intensity pattern of mitotic and non-mitotic cells is generally different due to the fact that at the beginning of mitosis, the chromosomes condense.So, construct a novel Relative-Entropy Maximized Scale Space (REMSS) using area morphological opening and closing. This scale space does not use the entire spectrum of gray levels. Rather, it constructs the scale space by parameter zing only those gray levels which make the Relative-Entropy between the object (cells in our problem) and background maximum. Thus this novel scale space exploits the object-background inter-class information maximization and provides an accurate segmentation of cells. Finally, classify the segmented cells in mitotic and non-mitotic categories using the Random Forest classifier with weighted voting. And then the system is again classified in artificial neural network classifier to exactly and accurately classify the segmented cells in to mitotic and non mitotic category.

II. RELATED WORK

Detection of mitotic cell in the traditional H&E stained histopathological image is a very challenging task since mitotic cells (MC) are small objects with a large variety of shape configurations. In addition, the wide variation in intensity information due to the staining differences and a large number of cytological components which are highly similar to the in terms of the color and morphological appearances make the automatic detection of MC difficult. The first attempt to detect the MCs in traditional H&E stained histopathological images is done Serteletal [13].Serteletal. Proposed an automatic technique for detection of the mitosis and karyorrhexis cells (MKC) in digitized neuro blastoma histological images Irshad et al. [14] proposed an approach to improve the accuracy of mitosis detection by capturing the statistical and morphological features using the best color channels. The algorithm consists two steps; in the first step, candidate cells were detected and segmented using the Laplacian of Gaussian and active contour model on blue-ratio image. In the second step, 143 features including morphological, first order and second order (texture) statistics have been extracted for each candidate in selected channels and decision tree classifier was then used for cells classifications. The proposed algorithm was tested on the MITOS dataset and was reported to achieve 74% and 71% detection rate, 70% and 56% precision and 72% and 63% F-Measure on Aperio and Hamamatsu images, respectively.

Sommer et al.[15] proposed a hierarchical learning workflow for automatic mitosis detection in breast cancer. The proposed method combined two open source user interface equipped biomedical image analysis software The developed algorithm can be divided into two main levels: Segmentation of candidate cells and classification of the segmented cells. At the first level, candidate cells were detected and segmented pixel by pixel using the Bayesian approach. Support vector machine (SVM) is then used to classify the mitotic and non-mitotic cells. At the evaluation phase, the authors used dataset containing more than 300 mitoses in 50 images. The proposed approach achieved an area-under the Precision-Recall curve of 70% on an annotated dataset.

These may be broadly classified into two different categories namely region based cell segmentation and boundary based cell segmentation [16]. Among the region based approaches,Chowdhury et al. applied entropy thresholding for detecting monocyte cells [17]. But this method is noise prone and not suitable for cells of varying size. Marker-controlled watershed has been used by Yang et al. [18] for nuclei segmentation. Since, this method uses morphological operation like erosion, this requires prior knowledge of object size and again not suitable for varying cell sizes. The method proposed in [19] employs multi-scale and multi-class contextual model in a series classifier architecture for segmentation of cells and cellular objects. For background subtraction based cell detection,[20]. Nedzved et al. proposed a morphological approach for segmentation of histopathological cell images [21]. In [22], the authors proposed a graph cut binarization based hybrid model for cell detection. A model based segmentation approach has been used by Lin et al. [23] for segmentation and morphometry of fluorescently labeled cell nuclei.

III. METHODOLOGY

The designed breast cancer detection system using ANN works in two phases: Learning/Training Phase and Recognition/Testing Phase. In Learning/Training Phase the ANN is trained for recognition of breast cancer from known Histopathology Images. Features, extracted from the known Histopathology images, are stored in the knowledge base and given as input to the ANN based Diagnosis System. In Testing/Recognition Phase the

extracted features of known and unknown Histopathology images are compared for classification of images into having mitotic cell and non mitotic cell using ANN. Training phase and testing phase consists of pre-processing, segmentation and feature extraction processes. Finally classify the patient results into mitotic detected and non mitotic detected.

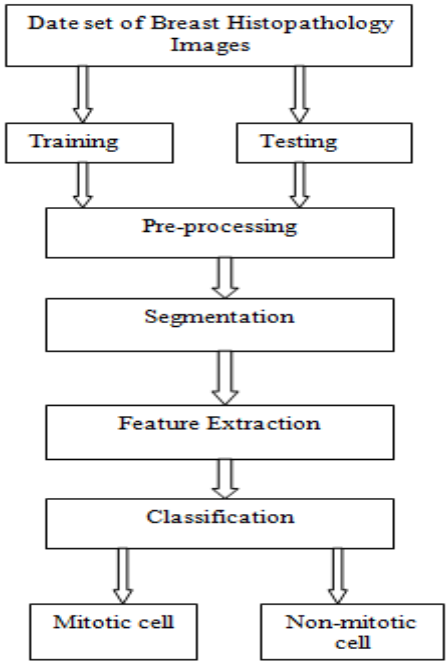

Fig.2 block diagram of methodology

A. Dataset

The images are received in JPEG Format.. The histopathology images were obtained from the MITOS-ATYPIA-14 dataset. The pathology slides are stained with standard hematoxylin and eosin (H&E) dyes and scanned by two slide scanners: Aperio Scanscope XT and Hamamatsu Nanozoomer 2.0-HT. Aperio scanner image data at X40 magnification utilized for experiments. These slide frames are 24-bit RGB bitmap images with a dimension of 1539 × 1376 pixels and resolution of 4.073 pixels/μm.

B. Pre-Processing

The input images are subjected to three different image pre processing techniques, namely, "red channel extraction," "Gaussian filtering," and "entropy based edge preservation," in order to accentuate the region of interest from the acquired images. The intensity pattern on the surface of the cell and background are not exactly homogeneous. But these are much more homogeneous compared to the intensity pattern on the edges of cell and background. The variation of homogeneity on the cell, background and edges is prominent not only on the H&E stained RGB images but also in the red channel images of those slides shown in Figures 3.a and 3.b.Since only the cytoplasm of the cells are stained in red and the nuclei are not, the distinctive features of nuclei like homogeneity in intensity are prominent in the red channel images. Further these red channel images provide the best contrast between nuclei and cytoplasm and thus help to achieve precise detections of the nuclei.prominent in the red channel images. Further these red channel images provide the best contrast between nuclei and cytoplasm and thus help to achieve precise detections of the nuclei.

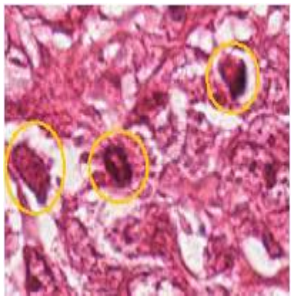

Fig 3.a RGB Image

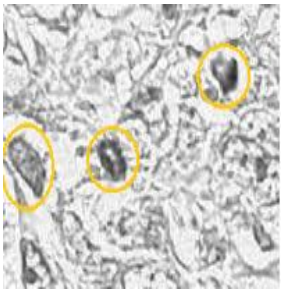

Fig 3.b Red channel image

Proposed Relative-Entropy Maximized Scale Space (REMSS) which is constructed with the help of area morphological opening and closing, but not use the entire spectrum of scale space. Instead the range of the scale to be used is determined by the maximization of relative-entropy between cells and background. Thus the proposed scale space is controlled by the average information between object and background which leads to better object segmentation. The cross entropy is generally minimized between object and the given object prior. In contrast, this method maximizes the relative-entropy between object and background and the method does not require any object prior. Thus this method exploits the maximum separating information between object and background for accurate object segmentation. The pre processing step implements a novel edge preserving filter in an iterative manner. The proposed pre-processing method takes into account the entropy of object and background and tends not to encourage noise. Since the proposed filter smoothes the objects and the background keeping the edges intact, the filter ensures that the relative entropy is contributed only by the edge pixels and not by the pixels of objects or background. Thus the proposed filter subsequently improves the segmentation which relies on relative entropy.

C. Segmentation

The segmentation is done by fuzzy c means clustering method. By this method the final smoothed image is divided in to four different clusters. From these clusters select the best cluster that determines the cells in the histopathology images. Fuzzy c-means ,The algorithm returns value between 0 and 1 called the partition matrix,

which represent the degree of membership between each data and centers of clusters. It is based on minimization of the objective function.

$$Jm(U,C) = \sum_{i=1}^{c}\sum_{k=1}^{n} u \cup_{ik}^{m} ||Xk - Ci||^2 \quad (1)$$

Where m is any real number greater than one. X_1 X_2... X_n are n data sample vectors. C = C_1, C_2...Cc are cluster center. U = $[U_{ik}]$ is a $c \times n$ matrix, where u_{ik} is the i^{th} membership value of k^{th} input sample X_k such that $\sum_{i=1}^{c} uik = 1$. m ∈ [1,∞) is an exponent weight factor that controls the fuzziness of the member ship function . ||∗||is any norm expressing the similarities between any input sample and its corresponding cluster center. Optimization of the objective function shown above with the updating of the membership u_{Ik}, and cluster center C_i.

$$u_{ik} = \frac{1}{\sum_{j=1}^{c} \frac{||Xk-Ci||}{||Xk-Cj||}^{2/(m-1)}} \quad (2)$$

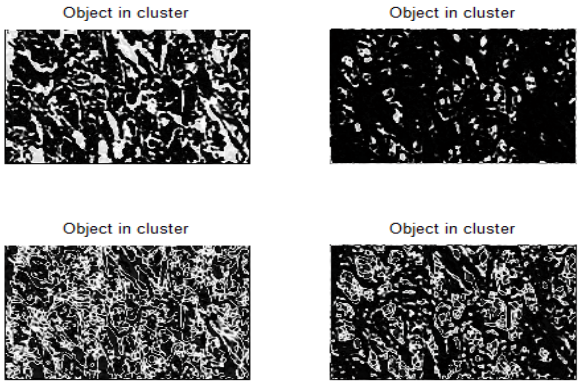

Fig 4 Fuzzy C - means clustering of Histopathology

$$Ci = \frac{\sum_{k=1}^{n} u \cup_{ik}^{m} Xk}{\sum_{k=1}^{n} \cup_{ik} m} \quad (3)$$

The standard FCM consists of following steps:

1. Choosing the number of clusters C.

2. Choosing the exponent weight m.

3. Initializing the membership u_{ik}.

4. Calculating the cluster center C_i (Eq 2).

5. Updating the membership u_{ik} (Eq. 3.14) for i=1,2,....,c and k=1,2,....,n.

6. Repeating steps 4, 5 until the distortion is less than a specified value.

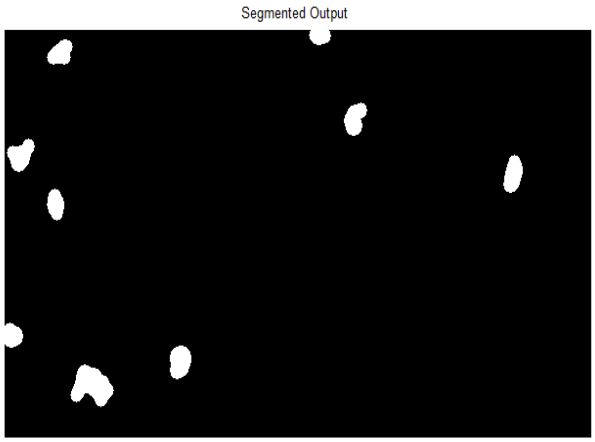

Fig 5: Segmented image of Histopathology

D. Feature Extraction

The medical image categorization procedure consists of two steps: Texture Feature Extraction and Classification. Feature extraction is the most significant step in breast cancer detection. A feature is used to denote a piece of data which is relevant for working the computational task linked to a certain application. Some of the most usually used texture measures are deduced from the Gray Level Co-occurrence Matrix (GLCM) and Chip histogram based texture features.

- Gray Level Coherence Matrix (GLCM)

Gray Level Coherence Matrix (GLCM) is widely employed to characterize texture images. In our experiments, four adjacency directions 00, 450, 900, 1350 and 8 gray levels are applied to figure the GLCM. On the GLCM, 13 Haralick parameters are computed [14]: angular second moment, contrast, correlation, sum of squares, variance, inverse difference moment, sum average, sum variance, sum entropy, entropy, difference variance, difference entropy, information measures of correlation 1, and information measures of correlation 2. Finally, we get a final feature vector by calculating the mean of the 13-dimensional feature vectors in the four directions.

- Chip histogram features

For the image with number of gray levels as 'L', so there exists the gray vector, which varies from 1 to L. The histogram of the image is given as: Histogram= h(rk)=nk,where 'r_k' is the k^{th} gray level,nk the number of pixels in the image having gray level 'r_k' and h(r_k) is the histogram of a digital image with gray level r_k (Kaiwei et al. 2011). The image having the size of MxN, the Gray level probability function is defined as:

Gray level probability = $P(r_k) = h(r_k) / M*N$

E. Classification

The training and testing of the classifier for textural feature set were performed using the cross-validation methodology. Classification of the normal and cancer cases was conducted by using the ANN (Artificial Neural Network) classifier with diagonal covariance matrix estimate. In this paper, breast cancer detection based on ANN has been designed by Feed-forward back propagation Network model. Leven berg–Marquardt back-propagation algorithm was used to train the networks for classification of histopathology images into mitotic and non-mitotic cells.

The most popular Neural Network algorithms is back propagation algorithm, which consists of four main steps:

1. Feed-forward computation.

2. Back propagation to the output layer.

3. Back propagation to the hidden layer.

4. Weight updates.

Initial weights are commonly set at just about random numbers and then they are corrected during NN(Neural network) training. After selecting the weights of the network arbitrarily, the back propagation algorithm is used to compute the essential corrections. During the NN training weights are updated subsequent iterations. If the results of NN subsequent weights updates are better than the former set of weights, the new values of weights are saved and iteration goes on.

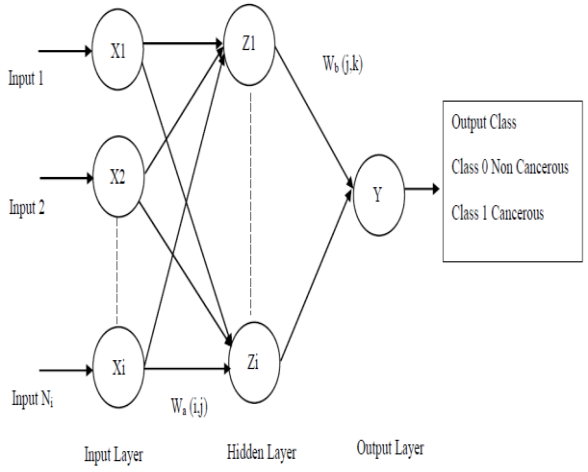

Fig 6 .Block diagram of Multilayer feed forward Neural Network.

The algorithm stops when the value of the erroneousness function has become sufficiently small. Figure 6, shows the architecture of the Neural Network Classifier. In the feature extraction stage, a valid feature vector of seventy-six features is extracted from the red and green channel of segmented cells of histopathology image to represent the breast mass characteristic features. This feature vector is passed to the Neural Network (NN) Classifier, which is the last stage.

IV. RESULT AND ANALYSIS

A total of 90 histopathology images of the breast (54 benign and 36 abnormal patterns) is analyzed. The twenty textural features based on GLCM and chip histogram based features are used to classify breast into malignant by containing masses and benign by containing normal tissues. Every texture feature value was computed as the average of values got from the four GLC matrices matching to four different directions (θ =0°, 45°, 90°, and 135°) and one distanced = 1 pixel. The classifier employed in this research is an Artificial Neural Network.

The performance in identification can be measured by the following factors: Accuracy (AC), Sensitivity (SE) and Specificity (SP) of detection. They are determined as follows,

1. Classification accuracy is dependent of the number of samples correctly classified.

$$AC = \frac{TP + TN}{TP + TN + FP + FN}$$

2. Sensitivity is a proportion of positive cases that are well detected by the test.

$$SE = \frac{TP}{TP + FN}$$

3.Specificity is a proportion of negative cases that are well detected by the test.

$$SP = \frac{TN}{TN + FP}$$

Where, TP is the amount of true positives, FP is the number of false positives, TN is the number of true negatives, FN is the count of false negatives. Figure 4 shows the confusion matrices for the classification results received with ANN classifier. The confusion matrix is defined between target class and output class. The diagonal cells in each table show the amount of cases that were correctly classified, and the off-diagonal cells show the misclassified cases. The blue cell at the bottom right shows the total percent of correctly classified cases (in green) and the total percent of misclassified cases (in red). Gray cells numbered 1 and 2 show sensitivity and specificity, respectively. Gray cells in the third column of

Confusion Matrix represent the Precision or Positive Predictive Value (PPV) and Negative Predictive Value (NPV). The positive and negative predictive values are the proportions of positive and negative answers of classification tests that are true positive and true negative results. Mathematically, PPV and NPV can be expressed as,

$$PPV = \frac{TP}{TP + FP}$$

$$NPV = \frac{TN}{TN + FN}$$

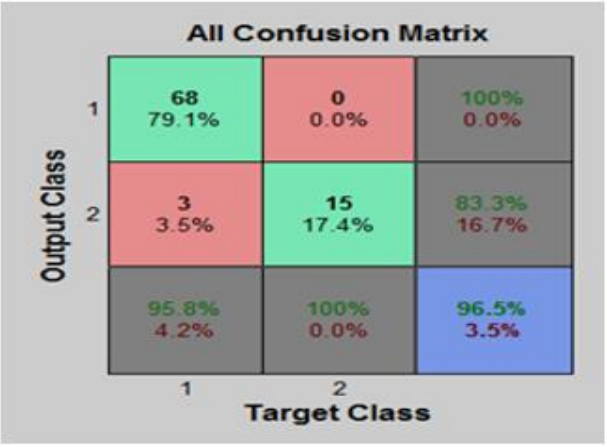

Fig 7. Confusion Matrix of Histopathology

In Figure 4 results indicate that the accuracy of 96.5%, sensitivity of 95.8% and Negative Predictive Value (NPV)of 83.3% are obtained by classifying histopathology using ANN classifier. High sensitivity and high NPV of ANN classification of histopathology indicate that texture features can be parameters for breast cancer screening. The MSE for training, testing and validation of Similarly the Performance graph of Histopathology training process for Feed forward Back propagation is shown in Figure and MSE for training, testing and validation of histopathology is shown in corresponding curves.

The performance is measured on the basis of Mean Square Error (MSE). Figure 8, shows the neural network training performance of histopathology, reaching Mean Squared Error of 0.14459 and the MSE for training, testing and validation of histopathology is shown in corresponding curves.

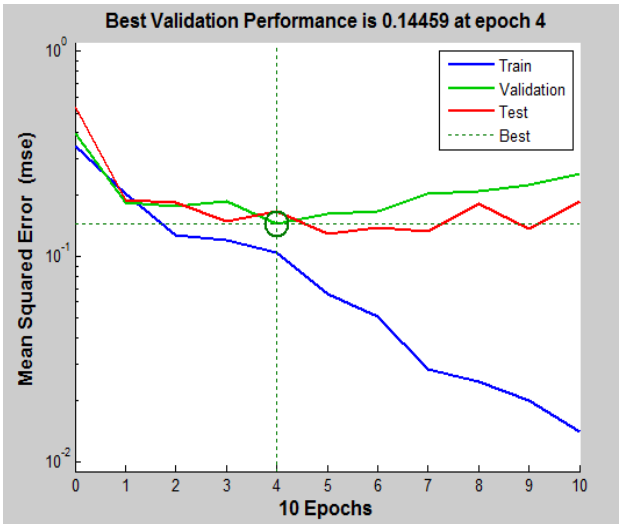

Fig 8: ANN Training Performance of Histopathology.

The gradient, Mutation and validation check graphs for Feed-forward Back propagation neural network training state of histopathology is shown in Figure 9.

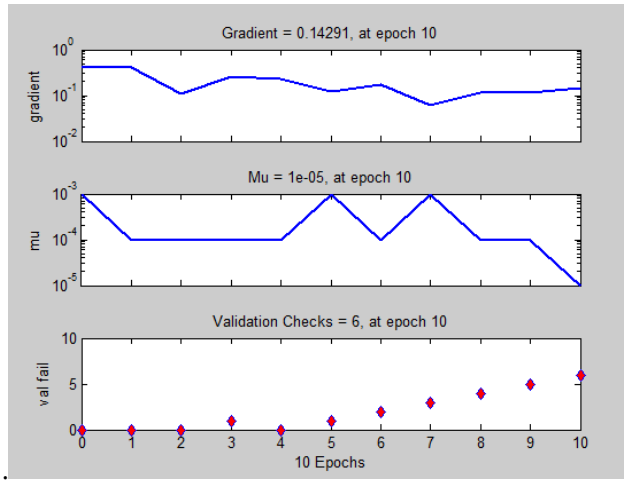

Fig 9. : ANN Training state of Histopathology

V. CONCLUSION

The proposed system is an effective technique for detection of breast cancer in early stages. The project proposes an approach which deals with Analysis of Breast mitotic segmentation and abnormality detection in histopathological images based on Fuzzy C-Means Clustering. The proposed technique is expected to reduce the workload of pathologists when they evaluate the cancer grade.

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