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Mathematical Modeling of Choroidal Neo Vascularization

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***Abstract* - In this research paper, an attempt has been made to mathematically model the choroidal neo vascularization and to classify them as normal, occult or classic. The choroidal neo vascularization is disease which is the advanced stage for age related macular degradation. Images diseased eyes are captured by Fluorescein Angiography (FA). Dye is injected and images of the eyes are captured in intervals for a period of ten to fifteen minutes. Mean of intensity of the images at different stages are obtained. Mathematical model is obtained by fitting a sixth order polynomial curve fitting from the mean intensity data. The co-efficients of the polynomial expression is used for the classification of the choroidal neovascularization. The results show the authenticity of this technique for the categorization of the abnormality.**

***Index Terms* — fluorescein angiography (FA), choroidal neo vascularization, macular degradation, polynomial curve fitting.**

I. INTRODUCTION

Choroidal neo vascularization (CNV) is a sever disease which is related with the retina, it's the later stage of age related macular degradation [1]. It is commonly found in elder people (60+) normally the common symptoms are dark, blurry areas in the center of vision and diminished or changed color perception. CNV disease is a major cause of blindness and visual impairment by abnormal growth of blood vessels [2].

The standard method for finding CNV is Fluorescein Angiography (FA) [3]. It is seen that in many medical studies, it is difficult to diagnose a person suffering from this disease. According to the intensity of fluorescence leakage, pattern present in the retina and Choroidal area the lesions can be divided into two types they are classic CNV and occult CNV [1][2]. It might end up in a wrong prognosis and prior medication if the disease is not properly assessed. It is critical to identify the lesion type and size of CNV for the accurate treatment[4].

Ahmed S Fahmy et al. proposed a method for modeling based on image intensity at different time frames and using a novel gamma-variate model that capture the movement of dye in different stages of circulation [5]. Walid M. Abdelmoula, et al. proposed a method for modeling based on the temporal intensity variation at each pixel in image sequences acquired by FA. The model parameters at each pixel are used to form a feature vector of this pixel [6]. Curve fitting can be alluded to as addition or estimation. The goal of the curve fitting calculation is to utilize a base number of cubic curve pieces to surmise the picture's blueprint with least bending [7]. Complex geometric structures incorporate curves, curved surface patches, and quadric surfaces. Framing of the curve is an intelligent procedure. Adding curve goes precisely through the data points. Control Points control the state of the curve by pulling the piece of the curve toward it and indicated as approximating [8].

Hence the usage of engineering techniques will very gently be helpful for the medical practitioners to diagnose CNV with much ease. The fully-automated detection and analysis of changes in retinal images can form a valuable additional diagnostic resource for the clinician and also to analyze changes from Fluorescein Angiograms (FA).

Choroid neo vascularization (CNV) is due to age related macular degradation, as we know every cell will die eventually in humans like other living species there is mechanism for regeneration of the dead cells, due to the age factor this regeneration will also get affected(i.e. will be reduced or completely lost in some cases) due to this condition new blood capillaries will form for supplying blood and oxygen to these parts as we know like any other organ in the body retina also needs fresh blood and nutrients which are to be supplied by the blood vessels due to conditions like diabetic, stress and injury gives rise to a situation such as accumulation of the dead light receptors , when this accumulation occurs, the eye sight will be affected so badly that the patient who is suffering from this will start to get severe headache and eye sight starts to become blurry, this is when the accumulation occurs in retina (other than macular region) .

When this accumulation of dead light receptors is at macular region the patient who is suffering from this condition will lose the straight line vision (i.e. the patient

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will start to see straight lines as wavy lines etc.) this happens because macular region has more number of light receptors than in other part of the eye and it's the only part of eye where 20/20 vision is possible due to the high concentrated accumulation of light receptor cells

II. IMAGE AQUISATION

Retinal Images from twenty one patients suffering from choroid neo vascularization was collected from Vasan Eye Care Hospital using Fluorescein Angiography. The doctor will perform the test by inserting standard dilation eye drops into eyes. These make pupils dilate. Then the doctor will give an injection containing a dye called xanthophyll pigment. The movement of this dye can be tracked using fundus camera (Zeiss FF4; Carl Zeiss Meditec, Oberkochen, Germany) integrated with a digital acquisition system (MRP Systems, Boston, MA). Each frame was captured at 2000x2000 pixels. Each dataset contains a number (20-35) of time frames spanning time intervals from 0 to 15 minutes.

Dye is injected and the circulation of the dye in the eye is captured in regular intervals. Images captured includes, one set from normal patient, 6 samples from patients suffering from classic CNV and 7 samples from patients suffering from occult CNV. Table 1 shows the sample of the retinal images captured using Fundus camera. From the table it is evident that the intensity in the normal eye is minimal, for classic the area of the brighter spots is more and the intensity is high even from the early stages of the images. Whereas in the occult affected retinal image the area affected is much less and the intensity gradually glows from dim to bright spots where new vessels are formed.

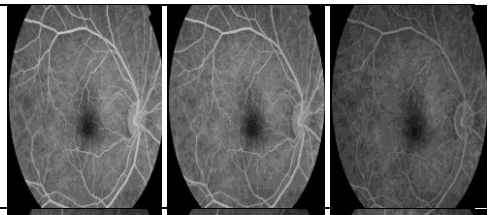
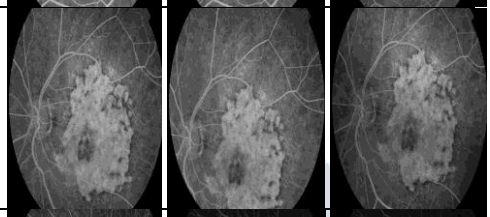
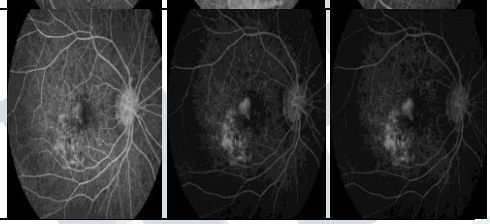
Normal	
Classic	
Occult	

Table 1. Sample normal and diseased retinal images

III. PREPROCESSING

The Fundus Fluorescein Angiography (FFA) image samples are preprocessed. The images are selected in sequence and each patient will have a sequence of 20-35 images recording the movement of fluorescein dye through the veins of retina. The region of interest can be selected by focusing on the accumulation of fluorescein area in FFA. To reduce the computational complexity, the images are cropped with the region of interest (ROI). Since the optic disc will be having the most illuminated area, which could give rise to computational complexity those parts will be excluded in the time of selection of ROI (by cropping process). Quality of the images is improved by adjusting the contrast. The histogram equalization technique is used to enhance the contrast of images by transforming the values on the intensity image so that the histogram will match to the uniform distribution.

Since the lesion size of each patient will be different from other, the ROI size tends to vary which can be overcome by resizing the ROI images (256*256). For the purpose of modeling both normal and abnormal regions are selected in ROI. Table 2 shows the original images and the cropped normal and abnormal portions of the patients under study. Column 1 of the table 2 shows the original FFA images, column 2 shows the normal portion cropped from the retinal images, column 3 shows

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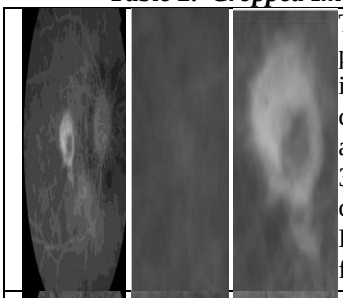
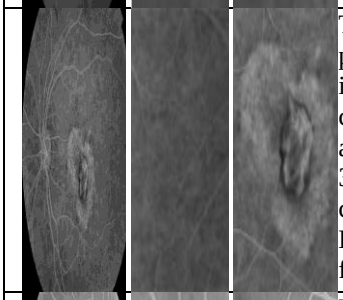
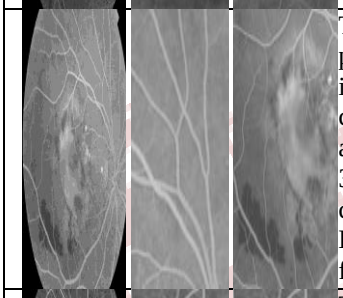
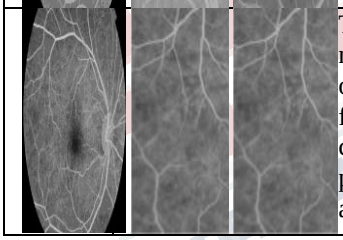
the affected portions in the diseased patients and column 4 gives a detailed idea about the diseased part of the eye.

Table 2. Cropped Images from the FFA

	This is the FFA image of patient1 in which original image is shown in first column, normal and abnormal images in 2nd and 3rd respectively (which are considered as the ROI). Here the patient is suffering from classic CNV
	This is the FFA image of patient 8 in which original image is shown in first column, normal and abnormal images in 2nd and 3rd respectively (which are considered as the ROI). Here the patient is suffering from occult CNV
	This is the FFA image of patient 15 in which original image is shown in first column, normal and abnormal images in 2nd and 3rd respectively (which are considered as the ROI). Here the patient is suffering from occult CNV
	This is the FFA image of a normal patient in which original image is shown in first column, both 2nd and 3rd columns are the normal portion of the image, which are considered as the ROI.

IV. MATHEMATICAL MODELLING OF FA RETINAL IMAGES

The modeling of retinal image is mainly based on the fact that the injected dye (xanthophyll pigment) travels through the feeder vessels to the retina, which will be circulating through it and this circulations can be divided in to three phases like initial phase, middle phase and late phase.

In a normal eye, the retinal blood vessels and the retinal pigment epithelium both act as barriers to fluorescein leakage within the retina. The tight junctions of the endothelial cells in normal retinal capillaries make them impermeable to fluorescein leakage. The tight cellular junctions of the healthy retinal pigment epithelium provide an outer blood-retinal barrier preventing the normal Choroidal leakage from penetrating the retinal tissues.

Due to this for normal patients the intensity of the retinal (FA) images will be more during the initial and middle phase which will gradually reduce during the late phase and the intensity will be distributed uniformly.

But for the abnormal patients there are two types of Choroidal neo vascularization (CNV) they are occult and classic. Both the classic and occult lesions will be have different properties such as, for classic lesions the dye will keep on accumulating until the later phase and decreases gradually.

But in case of occult lesion, ill-defined staining or leakage in the late frames, well-demarcated area of speckled hyper fluorescence with no visible source becomes apparent 2 to 5 minutes after dye injection. The intensity variation is modeled using curve fitting technique.

Intensity Plot

The ROI for the normal and abnormal areas are selected and the intensity of each image is found out .An intensity graph is plotted against time for both normal and abnormal area of the retinal image, as the images are taken in distinctive time interval, so the intensity value can be used to find the amount of the fluorescence dye accumulation with respect to time. It can be found that the intensity values for the normal will be less when compared with the abnormal area due to accumulation. These values for each pixels are found out and by using mean of the pixel intensity values are found so as to get one intensity value for each image. This is done to simplify the values and to give only one value for the image instead of using all pixel intensity values. Using these values three graphs can be plotted one for the normal potion one for the abnormal potion and one for the resultant of this two (affected / normal). Table 4 shows the plot of the mean intensity for the normal, affected and the ratio of the normal to affected.

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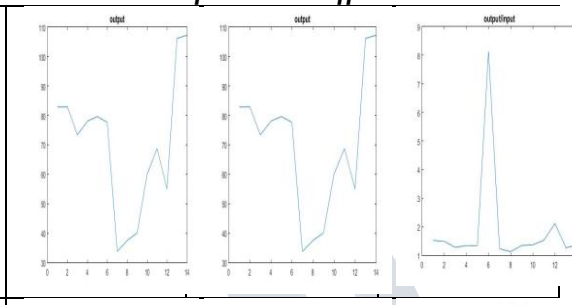
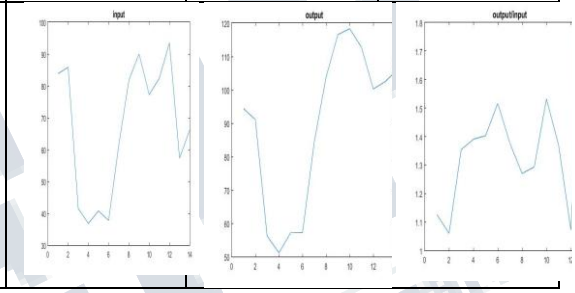
Table 3. The means of intensity values of each image for patient 1 and patient 2

Sl. No.	Mean Intensity for normal portion	Mean intensity for affected portion	Ratio of the normal and affected portion
Patient 1	[54.5033 55.6502 57.4379 58.0871 59.6575 9.5520 27.4364 33.2245 29.7202 43.8501 45.0053 26.0375 83.9370 78.9270]	[82.9043 82.9484 73.3749 78.0280 79.6304 77.6533 33.7201 37.4500 40.0004 59.9538 68.7613 55.0058 106.2218 107.2697]	[1.5211 1.4905 1.2775 1.3433 1.3348 8.1295 1.2290 1.1272 1.3459 1.3672 1.5278 2.1126 1.2655 1.3591]
Patient 2	[83.8245 85.8646 41.4985 36.7926 40.7466 37.7255 61.3232 81.7435 90.0918 77.2422 82.3373 93.5052 57.2713 66.1227]	[94.3921 91.0380 56.1997 51.1568 57.1646 57.2146 84.4193 103.8082 116.5437 118.3133 112.7459 100.2579 102.4336 105.8534]	[1.1261 1.0603 1.3543 1.3904 1.4029 1.5166 1.3766 1.2699 1.2936 1.5317 1.3693 1.0722 1.7886 1.6009]

It can be clearly found that the difference between normal and abnormal potions of mean intensity values. The difference between normal and abnormal values are found to be in the range 10-30 which depends on the severity of the disease, in which phase it is in and the type of CNV. Then the mean intensity values from the table are taken to draw the graph of mean intensity v/s frequency of the image taken.

Table 4. Plot of the Mean Intensity of the normal, affect and the ratio of normal to affected

P 1	
P 2	

Curve Fitting Using 6th Order Polynomial Expression

Each image after preprocessing (from both normal and abnormal) is selected and extracted features from those like mean, standard deviation etc. then these values are used to plot a graph for each of the features selected. These plotted graphs are nonlinear in nature and curve fitting technique are used for determining the characteristic polynomial.

Then using curve fitting technique a polynomial of 6^{th} order is created to fit the curve for the extracted feature plot. After the curve fitting, a polynomial for the plot is generated.

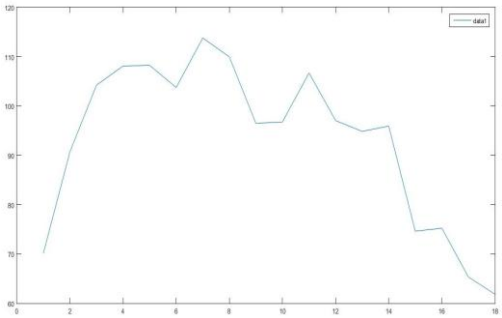


Figure 1 Shows the graph (mean of intensity v/s frequency) of the FA image of patient 5 before using the curve fitting technique

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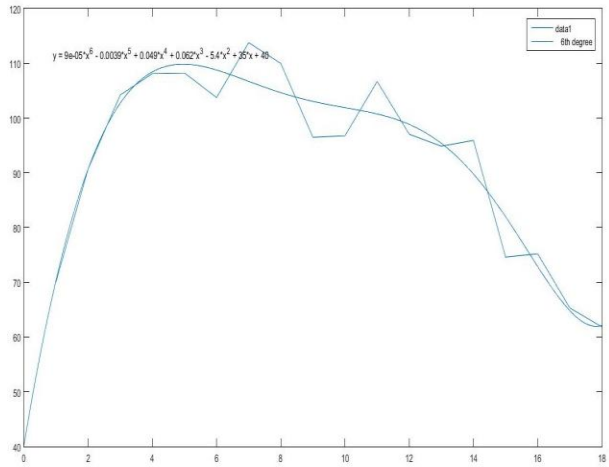

Figure 2 Shows the graph (mean of intensity v/s frequency) of the FA image of patient 5 after using the curve fitting technique

In the Figure 1 is the original curve which is drown from the extracted feature values and Figure 2 is the one in which a curve is fitted using the curve fitting. Forming of curve is an interactive process. Interpolating curve passes exactly through the data points. Control Points control the shape of the curve by pulling the part of the curve toward it this curve is called the approximating curve. By using approximated curve the polynomial for the curve is found out. This is repeated for all the patients and polynomial values are noted.

Table 5. Polynomial values of the curve after curve fitting for all the patients for normal and abnormal mean

	y = p1*x^6 + p2*x^5 + p3*x^4 + p4*x^3 + p5*x^2 + p6*x + p7 ;							
		p1	**p2**	**p3**	**p4**	**p5**	**p6**	**p7**
P1	N_mean	9.01E-05	0.00391	0.04868	0.062478	-5.4061	35.478	0.205
	AN_mean	0.000314	0.01968	0.46439	-5.038	23.736	29.707	78.989
P3	N_mean	0.22866	-6.3492	69.281	-374.41	1030.4	-1308.9	624.02
	AN_mean	0.33394	-9.2429	100.36	-538.39	1466.6	-1838	868.71
	n							
P4	N_mean	0.002299	0.01033	1.76	-13.771	48.49	-71.371	128.7
	AN_mean	0.015741	0.58732	8.4032	-57.925	98.56	-316.78	291.47
P6	N_mean	0.000104	0.00485 14	0.85737	-7.2576	30.109	-45.833	42.389
	AN_Mean	0.000731	0.00355 16	0.64461	5.4113	20.455	18.078	25.033
P7	N_Mean	0.000104	0.00485 14	0.85737	-7.2576	30.109	-45.833	42.389
	AN_mean	0.000731	0.00355 16	0.64461	-5.4113	20.455	-18.078	25.033
P8	N_mean	-7.05E-05	0.00395 1	-0.07367	0.43158	0.71695	-1.8267	27.28
	AN_mean	-6.09E-05	0.00383 5	-0.09019	0.97084	-5.2743	23.19	9.142
P11	N_mean	-8.42E-05	0.00473 4	0.08811 6	0.49173	1.9 55	-16.476	25.764
	AN_mean	-4.38E-05	0.00192	-0.01274	-0.47227	7.8026	-30.297	39.641
P12	N_mean	-9.28E-05	0.00060 23	-0.14807	1.7173	-9.5527	21.798	75.452
	AN_mean	-5.09E-05	0.00328 3	-0.0827	1.0319	-6.5229	17.561	69.889
P	N_	-	0.0	-	3.99	-	85	20.

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13	mean	0.00012	09289	0.27679	94	28.341	.07	457
	AN_mean	1.54E-05	-0.001401	0.048467	-0.79869	6.756	-28.149	134.79
P14	N_mean	-0.00019	0.011892	-0.29652	3.5976	-21.651	58.257	-26.481
	AN_mean	-0.00112	0.065272	-1.444	15.222	-77.905	174.01	-83.859
P15	N_mean	-0.00193	0.008606	-1.4655	12.01	-50.034	108.84	29.969
	AN_mean	-0.00267	0.12233	-2.1792	19.062	-84.856	180.28	-11.781
P17	N_mean	-0.00011	0.008605	-0.25011	3.4307	-22.645	64.168	-18.929
	AN_mean	-0.00015	0.010384	-0.2655	3.1517	-17.236	37.191	2.3764
P18	N_mean	-2.05E-06	0.000193	-0.00592	0.043318	0.93083	-16.108	93.767
	AN_mean	-4.14E-06	0.000456	-0.00187	0.03401	-2.3381	-2.1404	95.947
nrml	mean	0.49952	-8.771	56.921	-162.77	176.27	0	50.203

Table 6. Polynomial values of the curve after curve fitting for all the patients for normal and abnormal standard deviation

	y = p1*x^6 + p2*x^5 + p3*x^4 + p4*x^3 + p5*x^2 + p6*x + p7 ;						
	p1	**p2**	**p3**	**p4**	**p5**	**p6**	**p7**
P1	N_Std	8.71E-06	0.000652	0.01736	0.20158	0.93289	0.2921	20.168
	AN_Std	1.50E-05	0.001886	0.066329	0.98489	6.5915	-17.21	29.498
P3	N_Std	0.028299	0.69794	6.6392	-30.968	74.65	-88.255	55.496
	AN_Std	0.093188	-2.54068	27.119	-141.72	375.04	-462.24	223.74
P4	N_Std	0.000731	0.027893	0.39667	-2.5875	7.7785	-10.433	26.243
	AN_Std	0.00108	0.061289	-1.2307	11.159	-46.975	84.298	-20.792
P6	N_Std	0.00343	0.018807	0.40266	-4.2158	21.839	-48.318	42.935
	AN_Std	0.00286	0.015243	0.31121	3.0424	14.602	-31.14	42.991
P7	N_Std	0.00343	0.018807	0.40266	-4.2158	21.839	-48.318	42.935
	AN_Std	0.00286	0.015243	0.31121	-3.0424	14.602	-31.14	42.991
P8	N_Std	3.11E-05	-0.00023	0.06679	-0.95371	6.7734	-20.214	25.103
	AN_Std	-5.78E-05	0.000414	-0.11444	1.5204	9.9238	29.968	-17.64
P11	N_Std	-6.98E-05	0.000517 6	-0.14658	1.9715	-12.658	33.578	-11.059
	AN_Std	3.64E-05	-0.000194	0.035253	-0.25459	0.75525	-2.046	18.348
P12	N_Std	-1.32E-06	0.000496	-0.0229	0.38646	-2.6072	5.4085	11.207
	AN_	1.89E-06	-2.26	-0.00	0.045434	-0.1	-1.39	16.11

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	Std		E-05	209		394	95	1
P13	N_Std	1.29E-05	-0.00111	0.036373	-0.56352	4.03778	-10.787	13.259
	AN_Std	1.01E-05	-0.00075	0.021656	-0.30544	2.132	-5.2996	10.473
P14	N_Std	-0.00094	0.047744	-0.93743	8.8644	-41.1555	83.965	-35.345
	AN_Std	-0.00008	0.043968	-0.91989	9.2541	-45.801	100.87	-49.328
P15	N_Std	-0.00022	0.010827	-0.20477	1.8879	-8.90001	20.824	-5.59901
	AN_Std	0.00020201	-0.00093	-2.1792	19.062	-84.856	180.28	-11.781
P17	N_Std	-1.65E-05	0.0011154	-0.03371	0.51687	-4.11577	14.185	0.937711
	AN_Std	1.85E-05	-0.00148	0.044118	-0.61567	4.0009	-10.068	19.964
P18	N_Std	-2.20E-06	0.0002224	-0.00857	0.15472	-1.35777	5.2899	12.072
	AN_Std	-2.37E-06	0.0002774	-0.01206	0.25037	-2.44633	9.4241	14.173
nrml	N_Std	-5.20E-02	0.83072	-4.7444	11.414	-9.68338	0	17.331

V. CLASSIFIER

In this work neural network pattern recognition classifier is used to classify between different types of lesions of retina. The neural network pattern recognition classifier has mainly two layers they are one hidden layer and one outer layer.

It is a two-layer feed-forward network, with sigmoid hidden and softmax output neurons (patternnet), can classify vectors arbitrarily well, given enough neurons in its hidden layer. The network will be trained with scaled conjugate gradient back propagation. The performance and the accuracy of the classifier can be calculated using the confusion matrix and the ROC Curve. A confusion matrix is a table that is often used to describe the performance of classifier.

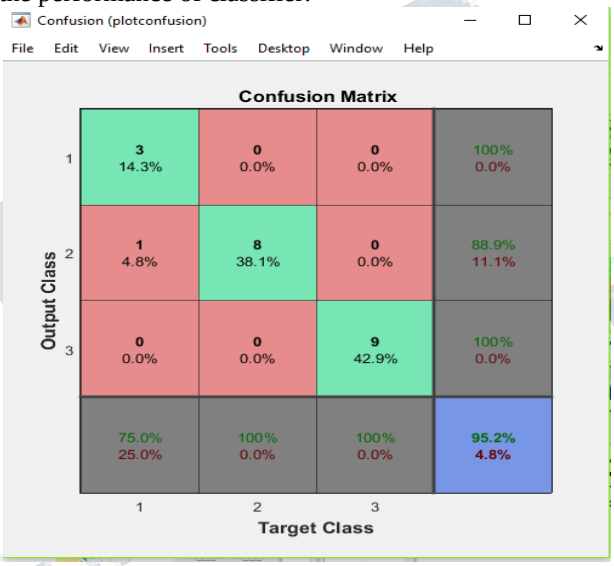

Figure 3. All confusion matrixes

From the All confusion matrix here 21 samples are used for the purpose of classification. In classification of the neural network the sample will be grouped in to three parts (70%-15%-15%) for training, validation and testing respectively.

In this case 15 is selected for training which include samples 1 normal, 7 occult and 7 classic. The classifier classified all correctly but one patient with occult was wrongly classified as normal then the accuracy of training was 93.3%. For validation the classifier used one sample from each class and the result was 100%. And in testing also it used one for each class and got a result of 100%. Here from the overall confusion matrix the accuracy is 95.2%.

***ROC Curve*:** This is a commonly used method to visualize the performance of a binary classifier over all possible thresholds. It is generated by plotting the True

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Positive Rate (y-axis) against the False Positive Rate (x-axis) as you vary the threshold for assigning observations to a given class.

The ROC for testing shows that a small value of miss classification in class 2 other than that the ROC shows high accuracy reading this in comparison with the confusion matrix it can be visualized that it has high accuracy (>90%) which is shows that the classifier is a good one.

In validation ROC and testing ROC it can be seen that there is no misclassification intern sagest that the classifier works effectively.

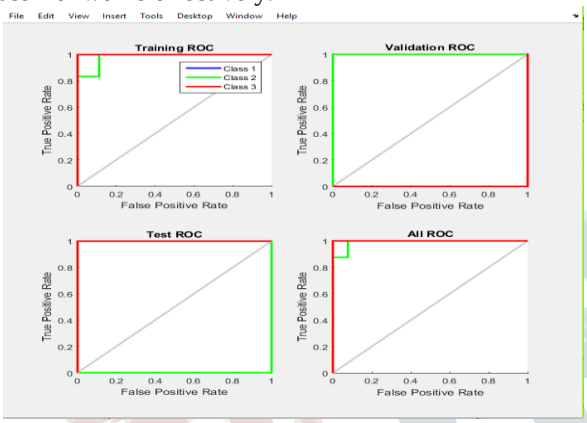

Figure 3. ROC Curve for different sessions of classifier namely training, validation and testing

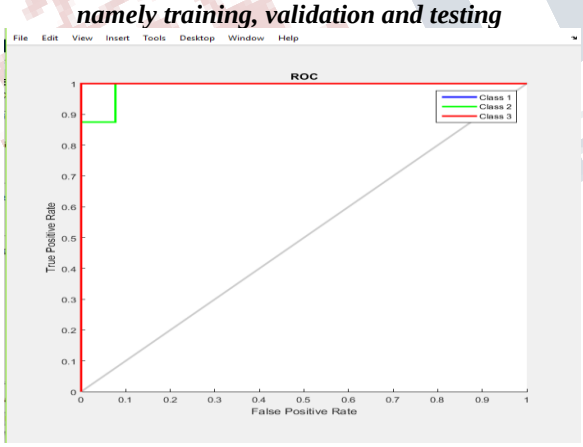

Figure 4. All ROC curve for the neural network classifier

From the Figure 5 all roc shows that a small misclassification in the classifier while classifying the class 2 other than that the classifier works fine and the accuracy is more than 90%.

VI. CONCLUSION

Images of the CNV patients were collected, preprocessed and histogram obtained. The mean value of the image intensities are collected and plotted. Using curve fitting method, a sixth order fitting is performed and the characteristic polynomial got. The co-efficients of the polynomial is used as input to a neural network classifier. The classifier is able to detect the disease with 93% accuracy in the training stage and 100% in testing and validation. The proposed technique is a viable solution for automating the detection of abnormalities in the new vessel formation.

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