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An Integrated System for Assessing Stroke Risk

Utilizing Clinical Risk Factors and Noninvasive Investigations Plus Carotid Plaque Texture Analysis

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Stroke is the third leading cause of death in the Western World and the major cause of disability in adults. Carotid stenosis is the largest single etiological factor known to produce focal cerebral ischemia, but in those with carotid bifurcation disease only a minority gives warning symptoms, with the majority having their stroke from previously asymptomatic lesions. Since morbidity and mortality after acute stroke is unacceptably high, it is very important to recognize and to treat patients with carotid bifurcation disease before they develop symptoms [1].

High-resolution ultrasound (duplex scanning and color flow imaging) can determine the degree of stenosis. Ultrasound image plaque characterization, ulceration, and brain CT scanning have been demonstrated to be individually associated with an increased risk of stroke. However, the combination of these findings with clinical data and risk factors has not been utilized to identify patients at high risk of stroke, making the management of these patients a difficult task.

High-resolution ultrasound has made possible the noninvasive visualization of the carotid bifurcation, and for that reason it has been extensively used in the study of arterial wall changes; these include measurement of the thickness of the intima media complex (IMT), estimation of the severity of stenosis due to atherosclerotic plaques, and plaque characterization [1], [2]. Ultrasound provides information not only on the degree of carotid artery stenosis but also on the characteristics of the arterial wall including the size and consistency of atherosclerotic plaques. Several studies have indicated that “complicated” carotid plaques are often associated with ipsilateral neurological symptoms [1], [3]. These symptomatic plaques share common ultrasonic characteristics, being more echolucent (weak reflection of ultrasound and therefore containing echo-poor structures) and heterogeneous (having both echolucent and echogenic areas). In contrast, “uncomplicated” plaques that are often asymptomatic tend to be of uniform consistency (uniformly hypoechoic or uniformly hyperechoic) without evidence of ulceration [1], [3].

The objective of this article is to present an integrated system for the assessment of risk of stroke based on two modules: 1)

clinical risk factors and noninvasive investigations, and 2) carotid plaque texture analysis. The system supports the data collected from the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) natural history study that includes the following groups of data [1], [2], [4]: 1) clinical, biochemical, and electrocardiographic risk factors associated with cardiovascular deaths, and 2) whether any independent risk factors can be used to identify a high-risk group for cardiovascular death. Furthermore, the carotid plaque texture analysis module supports the normalization, despeckling, segmentation, texture feature extraction, and classification of ultrasound plaque images.

Clinical Risk Factors and Noninvasive Investigations Module

Material

The ACSRS is an ongoing international multicenter study under the auspices of the International Union of Angiology aiming to study patients with asymptomatic 50–99% stenosis in relation to the carotid bulb diameter as documented in the European Carotid Surgery Trial (ECST) [4] and to follow them up for at least five years to identify subgroups at high and low risk for future neurological events. Approval has been obtained from the Multiregional Research Ethics Committee (North Thames, London, United Kingdom) and local ethics committees. Patients were admitted to the study after informed consent. The methodology used in the ACSRS study, eligibility of participating centers, and quality control have been published in detail [2]. Patients with internal carotid artery (ICA) stenosis greater than 50% (ECST) on duplex scanning who had never had any ipsilateral hemispheric or retinal symptoms and did not have any neurological abnormality on examination were eligible for admission to the study [2], [4].

Risk Factors and Noninvasive Investigations

The following clinical risk factors and their duration and severity were recorded for each patient [1], [2], [4]: age, gender, height and weight, hypertension, cardiac status, diabetes, smoking, fibrinogen blood level, fasting total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and creatinine blood levels and hematocrit; also, cardiac status including any history of myocardial infarction of cardiac failure, myocardial

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ischemia on ECG, and left ventricular hypertrophy (LVH) on ECG. Myocardial ischemia was considered to be present in one or more of the following as seen at any lead except aVR: flat T wave, negative T wave amplitude, and significant horizontal or downsloping S-T depression. The criteria of LVH included one or a combination of the following: the Sokolow-Lyon voltage criteria of sum of R wave amplitude in V5/V6 and S wave in VL greater than 35 mm, R wave amplitude in aVL greater than 13 mm, R wave amplitude in V5/V6 greater than 27 mm, or S wave amplitude in V1/V2 greater than 25 mm.

Duplex scanning was performed on admission to the study and subsequently every six months to grade ICA stenosis and also to study plaque morphology (see next section). Velocity criteria for grading the degree of stenosis are summarized in references [1], [2], [4]. The entire duplex examination was recorded on videotape. Ultrasound images of the plaques were classified into the following types [2]. Type 1: Uniformly echolucent (black), where bright areas occupy less than 15% of the plaque area. Type 2: Mainly echolucent, where bright echoes occupy 15–50% of the plaque area. Type 3: Mainly echolucent, where bright echoes occupy 50–85% of the plaque area. Type 4: Uniformly echogenic, where bright echoes occupy more than 85% of the plaque area. Type 5: Calcified cup with acoustic shadow so that the rest of the plaque cannot be visualized.

Endpoints

Primary endpoints were ipsilateral hemispheric stroke (including fatal stroke) defined as a hemispheric neurological deficit lasting for more than 24 hours, any stroke, ipsilateral hemispheric transient ischemic attacks (TIA), amaurosis fugax (AF), and death from cardiovascular causes other than stroke [1], [2], [4].

Online Analytical Mining System

An online analytical mining (OLAM) system was developed in Microsoft SQL with HTML and JSP functionality based on the following components. 1) Data collection: The data were collected under the ACSRS study using forms covering the aforementioned groups of data. 2) Data cleaning: The fields were identified, duplications were extracted, and missing values were filled. 3) Data coding: All the aforementioned risk factors were selected and coded. 4) Data mining. a) Classification by decision tree induction: The C4.5 algorithm [5], which uses a divide-and-conquer approach to decision tree induction, was employed. The algorithm uses the information gain criterion and the gain ratio. It works top-down, seeking at each stage an attribute to split on, that which best separates the classes, and then recursively processing the sub-problems that result from the split. The algorithm uses heuristics for pruning, derived from the statistical significance of splits. b) Rule extraction using the association algorithm: The original set-oriented mining of association rules (SETM) [6] algorithm that generates candidate item sets as the database is scanned was used [7]. After reading a transaction, the item sets that were found to be frequent in the previous pass contained in this transaction are derived. New candidate item sets are generated by extending the frequent item sets with other items in the transaction. A frequent item set L is extended with only those items that are frequent and occur later in the lexicographic ordering of items than any of the items in L . The candidates generated from a transaction are added to the

set of candidate item sets maintained for the pass. Each rule is characterized by confidence and support. 5) Pattern evaluation and knowledge representation: Following the run of the C4.5 and the SETM algorithms, rules extracted were sorted for $p = 1, \dots$, maximum number of risk factors investigated, based on the frequency of stroke events. Rules with consecutive numbers of risk factors were compared and the importance of the $p + 1$ risk factor based on the frequency of stroke events was derived. Based on the above procedure, rules to enable the following pattern evaluation and knowledge representation were carried out:

- hierarchical classification of risk factors
- minimal number of risk factors that should coexist for a stroke episode to occur
- a specific risk factor can be modified in order to reduce the risk of stroke.

Extracted frequency (or percentage) per rule was assumed to represent the percentage of the risk of stroke.

Carotid Plaque Texture Analysis Module

Material

Ultrasound images from a cross-sectional study of 274 images (137 asymptomatic and 137 symptomatic) were collected for texture analysis. A subset of 80 images from this dataset was used for the plaque segmentation, as well as an additional 100 images that were captured for the IMT segmentation. Images for plaque segmentation and texture analysis were captured at the Irvine Laboratory for Cardiovascular Investigation and Research, St Mary's Hospital, United Kingdom, whereas the IMT segmentation images were captured at the Vascular Clinic of the Cyprus Institute of Neurology and Genetics. Patients with cardioembolic symptoms or distant symptoms (> 6 months) were excluded from the study. Asymptomatic plaques were truly asymptomatic if they had never been associated with symptoms in the past. Carotid plaques were labeled as symptomatic after one of the following symptoms was identified: stroke, TIA, or AF. The ultrasound images were collected using an ATL (model HDI 3000, Advanced Technology Laboratories, Seattle, Washington) duplex scanner with a 5–10 MHz multifrequency probe. Longitudinal scans were performed using duplex scanning and color flow imaging [2]. Ultrasound was at right angles to the adventitia and the image was magnified or the depth adjusted so that the plaque would fill a substantial area of the image, giving approximately a resolution of 20 pixels/mm.

Normalization and Despeckle Filtering

Brightness adjustments of ultrasound images were carried out in this study. It was shown that this method improves image compatibility by reducing the variability introduced by different gain settings, different operators, different equipment, and facilitates ultrasound tissue comparability [2]. Algebraic (linear) scaling of the image was performed by linearly adjusting the image so that the median gray level value of the blood was 0–5 and the median gray level of the adventitia (artery wall) was 180–190 [1], [2], [4]. The scale of the gray level of the images ranged from 0–255. Thus, the brightness of all pixels in the image was readjusted according to the linear scale defined by selecting the two reference regions. It is noted that a key point to maintaining a high reproducibility was to ensure that the ultrasound beam was at right angles to the adventitia,

adventitia was visible adjacent to the plaque, and that for image normalization a standard sample consisting of half of the width of the brightest area of adventitia was obtained.

In addition, to address noise issues, we applied despeckle filtering to the normalized images. Speckle is a form of multiplicative noise that corrupts medical ultrasound imaging, making visual observation difficult. It limits the contrast resolution, thereby limiting the detectability of small, low-contrast lesions and making the ultrasound images generally difficult to interpret [8]. It was therefore important to despeckle the images prior to further image analysis. A linear scaling filter (lsmv) [8], utilizing the mean and the variance of a 7×7 pixel neighborhood, was used in this study. The filter was applied iteratively five times on each image, as documented in [8].

Segmentation

Following image normalization and despeckling, the Williams and Shah and the Lai and Chin snakes for segmenting the IMT [9] and atherosclerotic plaque [10] were used, respectively. For the IMT segmentation, initial contour estimation was carried out by selecting the area of interest (carried out manually by the user [9]), whereas, for the plaque segmentation, the initial contour estimation was carried out without user interaction using the blood flow image [10].

Feature Extraction and Selection

Following the segmentation of the atherosclerotic carotid plaque, the following texture feature sets were computed [11]: 1) statistical features (SFs): a) mean, b) variance, c) median value, d) skewness, e) kurtosis, f) energy, and g) entropy. 2) spatial gray level dependence matrices (SGLDMs): a) angular second moment, b) contrast, c) correlation, d) sum of squares: variance, e) inverse difference moment, f) sum average, g) sum variance, h) sum entropy, i) entropy, j) difference variance, k) difference entropy, and l) information measures on correlation 1 and 2. For a chosen distance d (in this work $d = 1$ was used) and for angles $\theta = 0^\circ, 45^\circ, 90^\circ, \text{ and } 135^\circ$, we computed four values for each of the above 13 texture measures. In this work, the mean of these four values was computed for each feature and it was used for classification. 3) Gray level difference statistics (GLDSs): a) homogeneity, b) contrast, c) energy, d) entropy, and e) mean. The above features were calculated for displacements $\delta = (0, 1), (1, 1), (1, 0), (1, -1)$, where $\delta \equiv (\Delta x, \Delta y)$, and their mean values were taken. 4) Neighborhood gray tone difference matrix (NGTDM): a) coarseness, b) contrast, c) busyness, d) complexity, and e) strength. 5) Statistical feature matrix (SFM): a) coarseness, b) contrast, c) periodicity, and d) roughness. 6) Laws texture energy measures (LAWS): LL – texture energy from LL kernel, EE – texture energy from EE kernel, SS – texture energy from SS kernel, LE – average texture energy from LE and EL kernels, ES – average texture energy from ES and SE kernels, and LS – average texture energy from LS and SL kernels. We averaged the matched pairs of energy measures in order to obtain a degree of invariance with respect to rotations. 7) Fractal dimension texture analysis (FRACTALS): The Hurst coefficients (H) for dimensions 4, 3, and 2 were computed.

Principal component analysis (PCA) was carried out in order to reduce the dimensionality of the feature vector. This method can be used in cases when the input features vector is large but the components of this vector are highly correlated. After applying PCA, the data set is represented by a reduced number of uncorrelated features, while retaining most of its

information content. In this study feature sets were reduced to smaller dimension sets by using only the components that contributed to 98% of the variance in the data set.

Classification

Classification models were developed based on the texture features for differentiating between asymptomatic plaques or symptomatic plaques associated with retinal or hemispheric symptoms (stroke, TIA, or AF); i.e., unstable plaques. The probabilistic neural network (PNN) and support vector machines (SVM) classifiers were used and are briefly described below.

PNN Classifier: A PNN classifier was used for developing classification models for the problem under study. The PNN falls within the category of nearest-neighbor classifiers [12]. For a given vector w to be classified, an activation a_i is computed for each of the two classes of plaques ($i = 1, 2$). The activation a_i is defined to be the total distance of w from each of the M_i prototype feature vectors $x_j^{(i)}$ that belong to the i th class.

SVM Classifier: The SVM classifier was also investigated. The method is initially based on a nonlinear mapping of the initial data set followed by the identification of a hyperplane that can separate the data into two categories [12]. The SVM network was investigated using Gaussian radial basis function (RBF) kernels. This was decided since the rest of the kernel functions could not achieve reasonable results. The SVM with RBF kernels was investigated using 10-fold cross validation in order to identify the best classification parameters, such as the spread of the RBF kernels.

The leave-one-out estimate was then used for validating the classification models. This method calculates the error or the classifications score by iteratively using $n - 1$ samples in the training set and testing or evaluating the performance of the classifier on the remaining sample. In the experiments carried out in this study, this was repeated for 274 subsets of size 273 for developing the PNN and SVM classification models. It is known that for large n , this method is computationally expensive; however, it is approximately unbiased, at the expense of an increase in the variance of the estimator [12].

The performance of the classifier systems was measured using the following receiver operating characteristics (ROC) measures: 1) the number of true positives (TPs), where the system classifies a plaque as symptomatic in agreement with medical diagnosis; 2) the number of false positives (FPs) decisions, where the system classifies a plaque as symptomatic while the subject is normal (asymptomatic); 3) the number of false negatives (FNs), where the system classifies a plaque as negative (asymptomatic) and the subject is symptomatic; 4) the number of true negatives (TNs), where the system identifies a plaque as asymptomatic in agreement with the subject's condition; 5) sensitivity (SE), which is the likelihood that an event will be detected given it is present; and 6) specificity (SP), which is the likelihood that the absence of an event will be detected given that it is absent. In addition, we define the number of correct classifications (CCs) to be the sum of TP and TN, divided by the total number of cases.

Results and Discussion

Clinical Risk Factors and Noninvasive Investigations

A total of 1,101 subjects were recruited with a follow up of 6–84 (median 38) months. In this dataset, 117 ipsilateral ischemic hemispheric events had occurred: 19 were AF, 46 were TIAs,

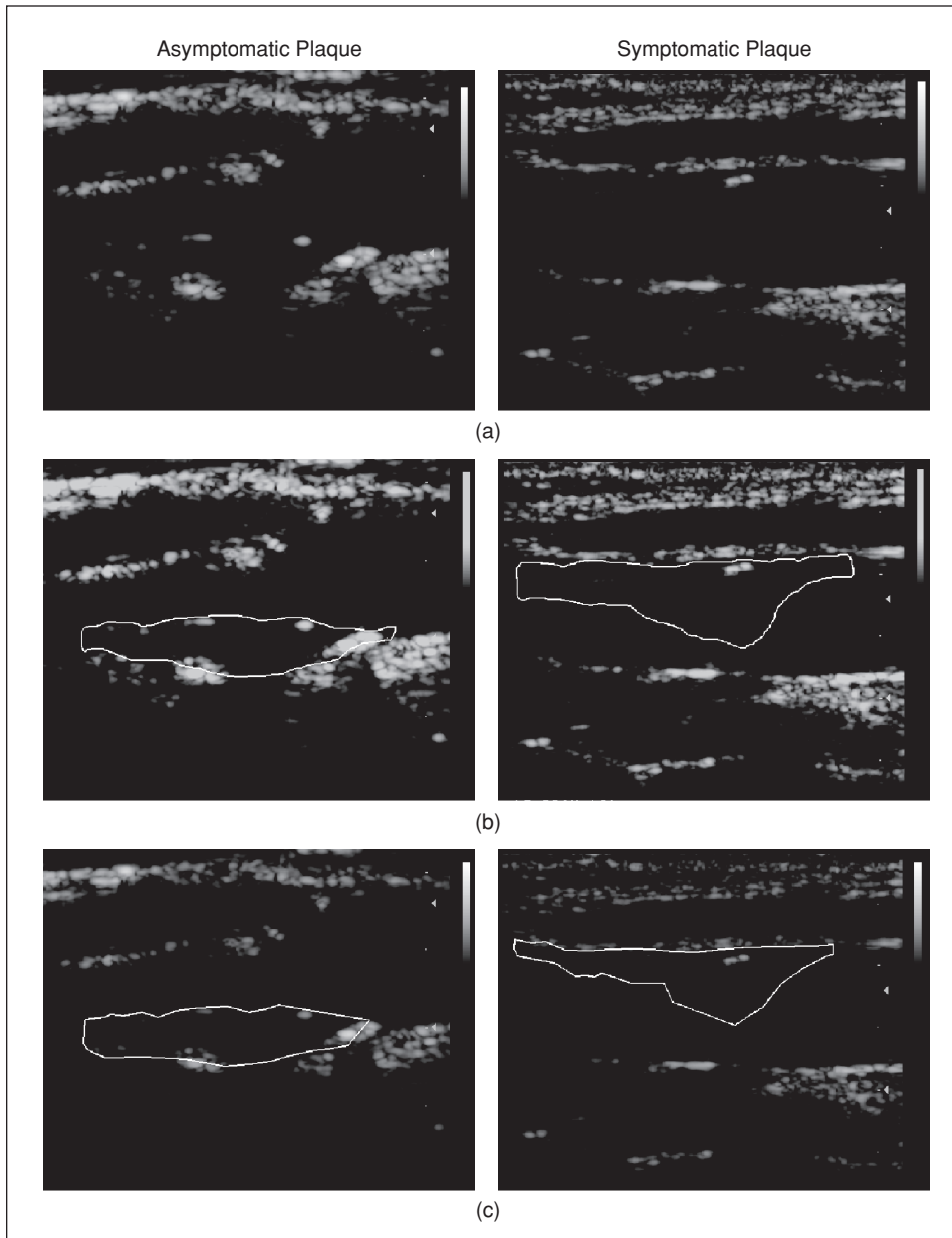


Fig. 1. Segmentation of atherosclerotic carotid plaque in asymptomatic (left column) and symptomatic (right column) cases using manual and automated segmentation. (a) Original image, (b) manual plaque delineation by the expert, and (c) automated snakes plaque segmentation.

and 52 were strokes. There had been a total of 162 deaths, of which 104 (64%) were due to cardiovascular causes [1], [4].

The only criterion that is now well established and currently used in clinical practice for the assessment of the risk of stroke is the degree of ICA stenosis [4]. It has recently been demonstrated that the stenosis in relation to the carotid bulb diameter is linearly related to the risk of stroke. This is not the case with the stenosis in relation to the diameter of the distal ICA [4]. Other risk factors include gender, the presence of cardioembolic silent infarcts on the CT-brain scan, hypertension, and blood levels of creatinine [1], [4].

Recent work has demonstrated that the type of plaque is an additional risk factor. Uniformly hyperechoic plaques (types 4+5) are associated with a low risk in contrast to heteroge-

neous plaques (types 2+3), which are associated with high risk [1], [4]. Uniformly hyperechoic plaques occupy an interim position [13]. We also believe that texture feature analysis of the plaques can also be used to assess the risk.

Traditional risk factors such as age, cholesterol, and smoking are not good predictors, probably because they are also present in the majority of plaques with asymptomatic carotid stenosis.

The OLAM system allows the user to select attributes of the ACSRS database along with the frequency of a rule. It then scans the database and generates frequent item sets based on the user's input. Both the C4.5 and SETM algorithms were run for a selected number of risk factors and all their combinations. The classification outcome for each rule was the frequency of stroke and no stroke events expressed in percentage format. The preliminary results of the OLAM system are in agreement with the above findings. However, further systemic evaluation is still needed. The system is simple to use and user friendly, secure, and it runs in real time.

Carotid Plaque Texture Analysis

The results of this study showed that the proposed IMT and plaque segmentation methods performed on the normalized despeckled images were very satisfactory without requiring manual correction in

more than 90% of the cases. More specifically, it was shown in [9] that there was no significant difference in the IMT measurements between the manual and the snakes segmentation measurements. The $IMT_{mean} \pm$ standard deviation results for the first expert were 0.67 ± 0.16 mm, 0.68 ± 0.17 mm, and for the second expert were 0.65 ± 0.18 mm, 0.61 ± 0.17 mm on the original and normalized images, respectively. The $IMT_{mean} \pm$ standard deviation snakes segmentation results on the normalized despeckled images were 0.68 ± 0.12 mm. Better snakes segmentation results with smaller inter-observer variability, smaller coefficient of variation, and smaller Hausdorff distance were obtained for the normalized despeckled images, when compared with the manually segmented images [9]. The plaque segmentation results showed that the

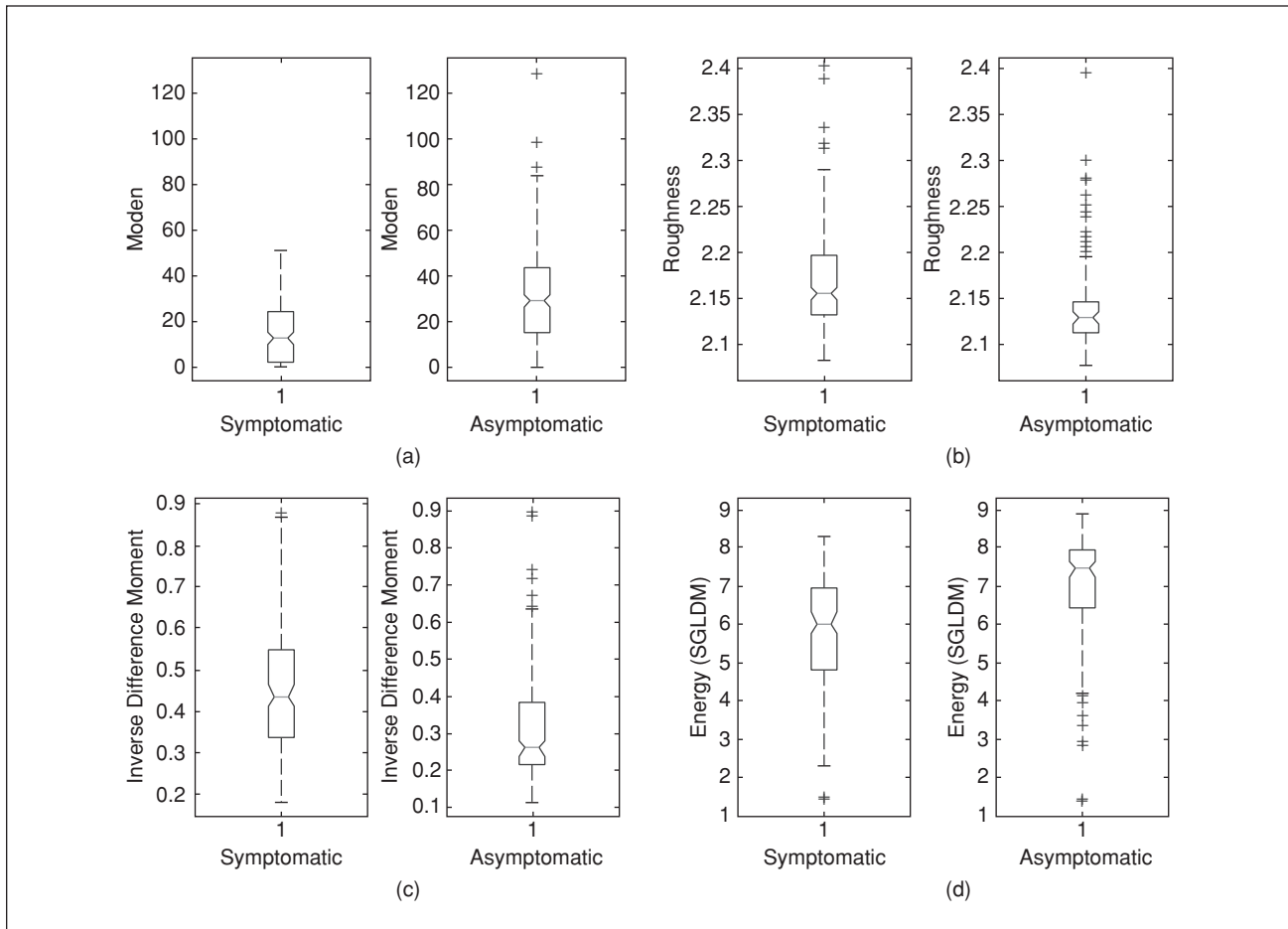


Fig. 2. Box plots of texture features for symptomatic (N=137) and asymptomatic (N=137) plaques: (a) SF: median, (b) SFM: roughness, (c) SGLDM: inverse difference moment, and (d) SGLDM: entropy. The notched box shows the median, lower, and upper quartiles and confidence interval around the median for each feature. The dotted line connects the nearest observations within 1.5 of the inter-quartile range (IQR) of the lower and upper quartiles. Crosses (+) indicate possible outliers with values beyond the ends of the $1.5 \times \text{IQR}$.

Lai and Chin snakes segmentation method agrees with the expert by correctly detecting no plaque (TNF) in 80.89% of the cases, by correctly detecting a plaque (TPF) in 82.70% of the cases, disagrees with the expert by detecting no plaque (FNF) in 15.59% of the cases, and by detecting a plaque (FPF) in 5.86% of the cases [10]. Figure 1 illustrates two examples of the manual and automated segmentation methods of the atherosclerotic carotid plaque.

Statistical analysis and interpretation of the texture features extracted from the plaque ultrasound images (see also the box plots in Figure 2) showed that, in general, texture in symptomatic plaques tends to be darker [SF: median, see Figure 2(a)], with higher contrast, more rough [SFM: roughness, see Figure 2(b)], more heterogeneous (SGLDM: inverse difference moment, see Figure 2(c)), less periodical, less coarse (i.e., less local uniformity in intensity), and less complex [SGLDM: entropy, see Figure 2(d)], whereas in asymptomatic plaques texture tends to be brighter, with less contrast, more smooth, more homogeneous, more periodical, more coarse, and more complex with large areas with small gray tone variations [11]. These results are in agreement with the original visual observations that smooth surface, echogenicity, and homogenous texture are characteristics of

stable plaques, whereas irregular surface, echolucency, and a heterogeneous texture are characteristics of potentially unstable plaques.

The SVM and PNN classifiers were investigated for developing models for differentiating between symptomatic and asymptomatic plaques based on texture features and PCA analysis. Results from all classifiers and texture sets are presented in Table 1. Results of SVM models were better than those achieved with PNN models. The highest percentage of correct classifications score was 73.4% and was achieved using the SVM classifier on all texture features. For PNN, the highest percentage of correct classifications was 72.3% for all texture features. The system allows for both a personal workstation interface and a Web interface that is secure and runs in real time.

Concluding Remarks and Future Work

In this article, an integrated system for the assessment of the risk of stroke based on clinical risk factors and noninvasive investigations and carotid plaque texture analysis was presented.

The large dataset made available for this study supports the complex analysis of a significant number of stroke risk factors. The proposed OLAM system could be a powerful tool in

Table 1. Diagnostic performance of PNN and SVM models for classifying asymptomatic (N = 137) and symptomatic (N = 137) plaques using the leave-one-out method.

Feature Sets	SF	SGLDM	GLDS	NGTDM	SFM	LAWS	FRACTALS	ALL
A. PNN MODELS								
%CC	69	66.1	65.7	59.5	58.0	58.4	58.4	72.3
%SE	78.8	70.8	67.1	55.5	37.2	64.2	54.7	75.9
%SP	59.1	61.3	64.2	63.5	78.8	52.5	62.0	68.6
%FP	40.9	38.7	35.8	36.5	21.2	47.4	38	31.4
%FN	21.2	29.2	32.8	44.5	62.8	35.8	45.3	24.1
B. PCA PNN MODELS								
%CC	69	66.1	65.7	59.5	58.0	58.4	58.4	69.7
%SE	78.8	69.3	67.1	55.5	37.2	64.2	54.7	74.4
%SP	59.1	62.8	64.2	63.5	78.8	52.5	62	65
%FP	40.9	37.2	35.8	36.5	21.2	47.4	38	35.0
%FN	21.2	30.7	32.8	44.5	62.8	35.8	45.3	25.5
C. SVM MODELS								
%CC	69.3	69.3	71.2	65.3	70.8	70.4	66.4	73
%SE	81.7	75.9	83.2	78.1	73	80.3	63.5	82.5
%SP	56.9	62.8	59.1	52.5	68.6	60.6	69.3	63.5
%FP	43.1	37.2	40.9	47.4	31.4	39.4	30.7	36.5
%FN	18.2	24.1	16.8	21.9	27	19.7	36.5	17.5
D. PCA SVM MODELS								
%CC	68.2	68.6	68.6	66.1	70.8	69.7	66.1	73.4
%SE	80.3	77.4	75.9	78.8	72.3	75.9	56.9	81
%SP	56.2	59.8	61.3	53.3	69.3	63.5	75.2	65.7
%FP	43.8	40.1	38.7	46.7	30.7	36.5	24.8	34.3
%FN	19.7	22.6	24.1	21.2	27.7	24.1	43.1	19

CC: correct classifications, FP: false positives, FN: false negatives, SE: sensitivity, and SP: specificity.

the hands of a clinician dealing with subjects at risk of stroke. The results for each category could be used to predict and then (through clinical intervention) reduce the number of stroke episodes and hopefully the number of deaths as well. On the other hand, carotid endarterectomy could be avoided in cases where the risk of stroke is reduced after treating one or more of the treatable risk factors. However, more work is still needed in achieving this.

Both the IMT and plaque segmentation methods referred to in this study can reduce significantly the time required for image analysis, but they can also reduce the subjectivity that characterizes manual measurements. These methods will be further evaluated on ultrasound images of the carotid collected from a large-scale epidemiological study carried out by our group as well as for the segmentation and measurement of curved segments of the bifurcation or bulb of the carotid artery. Moreover, these methods will be validated by multiple experts.

Texture features provide useful information for differentiating between asymptomatic and symptomatic plaques. The investigation of how morphological features [13] and clinical findings can

be utilized to enhance the diagnostic yield of the classification models proposed in this study is currently being performed.

We are also investigating video image analysis methods for accurate plaque motion estimation. We hope to find distinguishing plaque motion characteristics that can be used to predict rupture in the symptomatic cases. The new video motion estimation system will rely on an automated segmentation system to identify the plaque and the plaque surface. Furthermore, we will investigate the use of video image despeckling in providing more accurate motion estimation. Preliminary results from optical-flow methods for video motion estimation indicate that this approach can provide accurate motion estimates.

It is anticipated that the major outcome of this ongoing study will be the establishment of a standardized methodology facilitated via the integrated system for the evaluation of cardiovascular risk and carotid plaque texture analysis for the identification of subjects at high risk of stroke. However, more work is needed mainly for validating the rules generated by the OLAM system as well as in the integration of both modules proposed in this study.

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