Ultrasound Plaque Enhanced Activity Index for Predicting Neurological Symptoms

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Abstract. This paper aims at developing an ultrasound-based diagnostic measure which quantifies plaque activity, that is, the likelihood of the asymptomatic lesion to produce neurological symptoms. The method is rooted on the identification of an "active" plaque profile containing the most relevant ultrasound parameters associated with symptoms. This information is used to build an Enhanced Activity Index (EAI) which considers the conditional probabilities of each relevant feature belonging to either symptomatic or asymptomatic groups. This measure was evaluated on a longitudinal study of 112 asymptomatic plaques and shows high diagnostic power. In particular, EAI provides correct identification of all plaques that developed symptoms while giving a small number of false positives. Results suggest that EAI could have a significant impact on stroke prediction and treatment planning.

Keywords: Ultrasound, Carotid plaque, Enhanced Activity Index, Neurological symptoms

1 Introduction

Carotid plaques are one of the commonest causes of neurological symptoms due to embolization of plaque components or flow reduction. Numerous studies report that plaque morphology, besides patient's clinical history and degree of stenosis, is an important ultrasound marker that positively correlates with symptoms [1, 6]. However, such studies are focused on classifying plaques as symptomatic or asymptomatic and very few aim at identifying those stable lesions at high risk of becoming symptomatic. In fact, this information would be extremely useful for the physicians since they would be able to observe an asymptomatic lesion and quantitatively evaluate if such lesion is prone to developing neurological complications. As a consequence, the identification of a subset of "dangerous"

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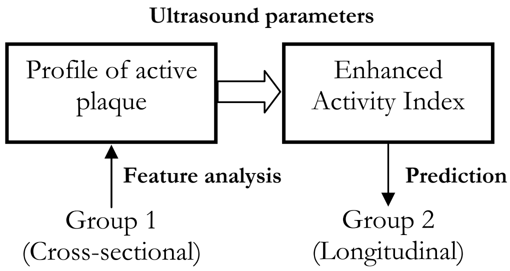

Fig. 1. Framework of proposed method.

or "active" plaques, featuring high neurological risk would help in the indication of treatment. Needless to say, this decision has important clinical and economical consequences for all the parts involved in this process.

Major trials reported that the absolute benefit of surgical intervention based on the degree of stenosis alone as a decision making criterion is low in the asymptomatic disease and in symptomatic disease with moderate obstruction [2, 4]. This clearly motivates the need for developing new strategies for plaque risk prediction. One such strategy [6] aims at combining quantitative (e.g. the degree of stenosis and histogram features) and qualitative information (e.g. textural appearance) obtained from ultrasound B-mode images. This study enabled to develop a diagnostic score, called Activity Index (AI), which could possibly correlate with clinical findings. Statistical analysis identified the most significant parameters as being the grey-scale median (GSM), percentage of echolucent (GSM<40) pixels (P40), surface disruption, severe stenosis, plaque heterogeneity and presence of juxta-luminal echolucent area. Hence, the AI consists of summing the scores for each significant variable. Results suggest that AI is an objective technique to assess plaque instability [6].

This paper uses ultrasound image processing as a first step for predicting the occurrence of plaque symptoms. In recent years, the importance of speckle in B-mode ultrasound images as well as its statistical modeling for tissue characterization has been reported [9]. This issue was also suggested in a recent work [7] where the application of a de-speckling algorithm was able to split the image in its noiseless and speckle components. These image sources were then used for extracting distinct echo-morphology and texture parameters, which contributed to a better analysis of the symptomatic plaque, and differentiation from the asymptomatic lesion [7].

Here, it is argued that an optimal method for identifying vulnerable lesions should include morphological and textural features, extracted from pixel intensity information, and information regarding plaque structure and appearance (e.g. stenosis, evidence of surface disruption and presence of echogenic cap) given by experienced physicians. The combination of this information is expected to produce a more comprehensive description of the profile of an active plaque, potentially providing the identification of lesions that would developed symptoms in the future. This paper proposes a diagnostic tool, named Enhanced Activity Index (EAI), which uses an ultrasound feature set that positively correlates with symptoms. Here, the EAI technique is used to predict the occurrence of neurological complications in a longitudinal study conducted in asymptomatic subjects. Moreover, its diagnostic performance is compared to other well-established strategies for identifying plaques at high risk, including the degree of stenosis (DS) [4] and the AI [6].

2 Methods

This paper employs a two-step method outlined in Fig. 1. The first step consists of feature analysis which identifies an optimal feature set to discriminate between symptomatic and asymptomatic plaques. This step is based on ultrasound images of carotid plaques ($n = 221$, 70 symptomatic and 151 asymptomatic) acquired at a fixed time frame (cross-sectional study). Consequently, the ultrasound profile of the "active" plaque is used to compute the EAI in a longitudinal study conducted in asymptomatic subjects ($n = 112$).

2.1 Ultrasound profile of "active" plaque

Prior to feature analysis, ultrasound images are processed according to [7]. Image processing includes normalization [3], estimation of envelope Radio-Frequency (RF) image and de-speckling. Moreover, each region of interest (ROI) containing the plaque is delineated by an experienced physician. This processing step provides different image sources from where features having different meanings can be extracted (Fig. 2):

- **Histogram features**, computed from pixel intensities in normalized image;
- **Rayleigh mixture models**, are used to describe echo-morphology in envelope RF images [8], consisting of a combination of individual Rayleigh distributions. The weights of each distribution and corresponding parameter are used as echo-morphology descriptors [8];
- **Rayleigh parameters** are theoretically obtained from the noiseless image;
- **Textural features** are obtained from grey level co-occurrence matrices (GLCM), Autoregressive models (ARM) and Wavelet models;
- **Morphological features** are given by the physician during consultation (e.g. evidence of plaque disruption, presence of fibrous cap, degree of stenosis and plaque echo-structure appearance).

A considerable amount of features ($l = 114$) were collected after ultrasound image processing. Naturally, not all the features are important to accurately characterize the plaque status, whether it is symptomatic or not. Hence, at this point an attempt is made to identify the most relevant ultrasound parameters for this particular problem. Hypothesis testing is a common method of drawing inferences about one or more populations based on statistical evidences from population samples (features). Here, we want to investigate if the statistical

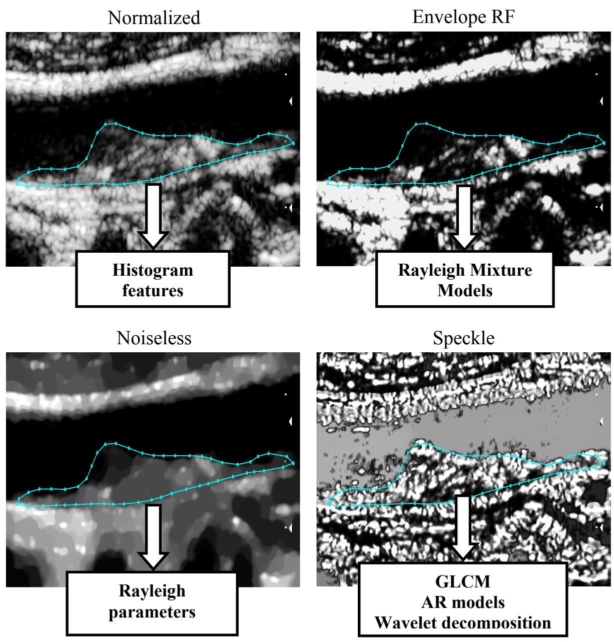

Fig. 2. Ultrasound image processing, resulting in normalized, envelope RF, noiseless and speckle images. Features are extracted from these distinct image sources.

properties of a given feature significantly differ from the symptomatic to the asymptomatic group. Among different hypothesis tests, the application of the Mann-Whitney U-test yields a feature set that produces the most promising classification results with the AdaBoost classifier. This method performs a two-sided rank sum test of the null hypothesis that feature values in symptomatic and asymptomatic populations are independent samples from identical continuous distributions with equal medians, against the alternative that they do not have equal medians. Moreover, the *p-value* is the probability of rejecting the null hypothesis assuming that the null hypothesis is true. Clinically significant features will have a *p-value* which is typically lower than 0.05 or 0.01. In this work, features were considered to be relevant for differentiating between symptomatic and asymptomatic groups when the *p-value*< 0.05.

Table 1 presents the parameters and corresponding sources and *p-values* of the so-called *optimal feature set*. A closer look at the 16-element feature set allows to verify that both subjective and image-based parameters are useful for plaque description. In particular, features from different image sources, namely the normalized image, the envelope RF image and speckle field are considered statistically relevant. This preliminary observation justifies the use of an ultrasound pre-processing set of operations since it enables to obtain useful parameters for plaque classification.

Feature	**Source**	$p - value$
evidence of plaque disruption	morphology	5.5×10^{-18}
presence of echogenic cap	morphology	0.001
degree of stenosis	morphology	2.9×10^{-13}
plaque echo-structure appearance	morphology	1.6×10^{-10}
mean	normalized histogram	0.001
skewness	normalized histogram	0.009
percentile 10	normalized histogram	0.022
percentile 50	normalized histogram	0.047
4^{th} Rayleigh parameter	RMM (envelope RF)	0.010
5^{th} Rayleigh parameter	RMM (envelope RF)	0.010
6^{th} Rayleigh parameter	RMM (envelope RF)	0.010
5^{th} mixture component	RMM (envelope RF)	0.004
6^{th} mixture component	RMM (envelope RF)	0.014
no. mixture components	RMM (envelope RF)	0.016
GLCM homogeneity	speckle	0.016
wavelet decomposition energy	speckle	0.004

Table 1. Significant feature set obtained with MW-test.

2.2 Enhanced activity index

So far the profile of the active plaque has been established. A quantitative diagnostic measure - EAI - is now developed as follows (Fig. 3):

1. A statistical test allows to obtain a relevant feature set (Table 1) for separating plaques with and without symptoms in a cross-sectional study (Fig. 1);
2. Reference values are taken for each feature, f_i, and group (symptomatic, $\omega(S)$, and asymptomatic, $\omega(A)$), considering the mean ($\mu_i(S)$, $\mu_i(A)$) and variance ($\sigma_i^2(S)$, $\sigma_i^2(A)$);
3. The EAI* (re-named for convenience) is computed as:

$$\mathrm{EAI}^* = \frac{\mathrm{R}_S}{\mathrm{R}_A}, \tag{1}$$

where

$$\mathrm{R}_k = \sum_i p(f_i|\omega_k) \approx \mathcal{N}(\mu_i(k), \sigma_i^2(k)), \quad k = \{S, A\} \tag{2}$$

is the sum of the conditional probabilities of each feature belonging, respectively, to the symptomatic or asymptomatic group. For continuous variables, the conditional probabilities in (2) are computed assuming a normal distribution (Fig. 3) whereas the probability associated with each categorial parameter (morphological features, except for degree of stenosis) is given by the ratio between the number of plaques belonging to each class and having each categorial variable and the total number of plaques with each categorial variable. In (1), R_S and R_A represent the likelihoods of each plaque producing symptoms or stabilize, respectively. Hence, when $\mathrm{EAI}^* = 1$, the result is inconclusive while for $\mathrm{EAI}^* < 1$ the plaque will stay harmless with a significant probability which is higher as EAI* decreases. Contrarily, plaques showing a $\mathrm{EAI}^* > 1$ are prone to produce symptoms, being more "dangerous" when EAI increases.

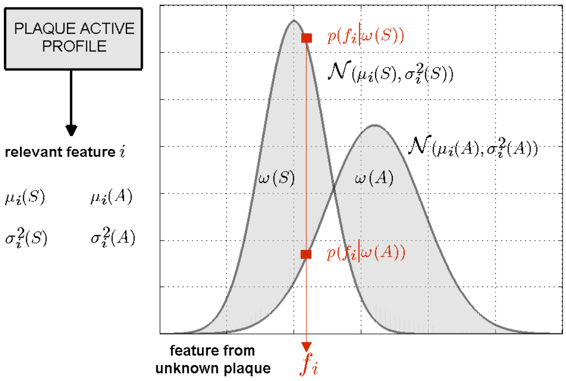

Fig. 3. Illustrative concept of conditional probabilities for a particular plaque feature f_i used to compute EAI.

4. The EAI* is re-scaled using a sigmoid mapping function which places the EAI onto a 0-100 scale. This function is defined as:

$$\text{EAI} = \frac{100}{1 + \exp\left(1 - \text{EAI}^*\right)}. \tag{3}$$

This mapping technique is useful to make the predictive power of the proposed EAI method comparable to AI [6] and DS [4].

3 Experimental Results

We have provided a description of the ultrasound profile of the active plaque and consequently designed a score for predicting the occurrence of neurological complications. Here, the diagnostic power of EAI is evaluated on a group of 112 asymptomatic plaques, acquired from 112 patients. B-mode ultrasound images were collected from the ACSRS (Asymptomatic Carotid Stenosis and Risk Study) [5], consisting of a multicentre natural history study of patients with asymptomatic internal carotid diameter stenosis greater than 50%. The degree of stenosis was graded using multiple established ultrasonic duplex criteria. Patients were followed for possible occurrence of symptoms for a mean time interval of 37.1 weeks. At the end of the study, 13 out of 112 patients (11.6%) had developed symptoms.

To make this study more feasible, we compare it with other strategies of plaque risk prediction, including the AI and DS, using ROC (Receiver Operating Characteristic) curve analysis (Fig. 4). In a ROC curve, the TP rate (Sensitivity) is plotted as function of the FP rate (100-Specificity) for different cut-off points. Each point of the ROC plot represents a sensitivity/specificity pair corresponding to a particular decision threshold. Moreover, the area under the ROC

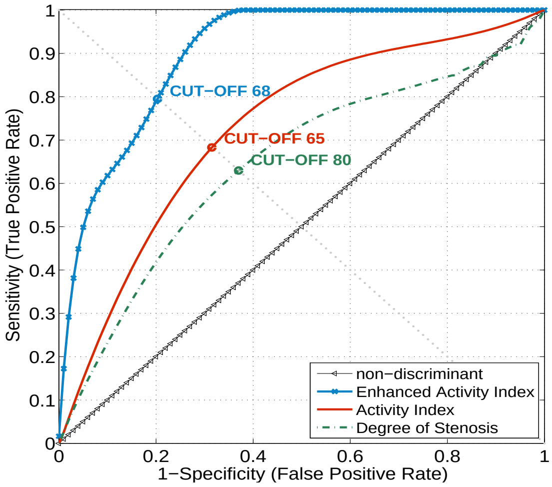

Fig. 4. ROC curves of degree of stenosis (DS), AI and EAI.

		Ground truth					
		P			N		
		Sten	AI	EAI	Sten	AI	EAI
Predicted value	P'	12	11	**13**	68	49	**29**
	N'	1	2	**0**	31	50	**70**

Table 2. Confusion matrix with prediction outcome of DS, AI and EAI.

curve (ROC AUC) statistic is often used for model comparison. This measure indicates that a predictive method is more accurate as higher is the ROC AUC. Moreover, the intercept of the ROC curve with the line at 90 degrees to the no-discrimination line is also considered as an heuristic method to investigate the cut-off providing the best discriminative power for each method (Fig. 4). The ROC AUCs are 0.6496 (64.96%), 0.7329 (73.29%) and 0.9057 (90.57%) for DS, AI and EAI, respectively. These results show that the EAI technique outperforms the other methods, which could be explained by the fact that it considers ultrasound parameters used in AI, besides the DS.

Moreover, the predictive analysis of EAI, AI and DS is evaluated from a different viewpoint, using a table of confusion (Table 2). The EAI method is able to identify the 13 patients that had developed symptoms by the end of the follow-up (longitudinal) study, whereas DS and AI methods were unable to identify, respectively 1 and 2 patients that developed neurological complications later. Moreover, as far as the false positive number is concerned, the EAI method yields 29 FP, which is significantly lower than other state-of-the-art methods. This means that if the decision of surgery for plaque removal was based in the former method only 29 patients were unnecessarily operated, suggesting that EAI is the most cost-effective method. Thus, the EAI technique demonstrates to provide the most accurate selection of patients at high risk within a population of asymptomatic subjects.

4 Conclusions

Carotid plaques are the commonest cause of neurological symptoms, however the early detection of plaques at high risk based on the degree of stenosis is neither optimal nor cost-effective. This paper proposes an Enhanced Activity Index technique which quantifies the likelihood of a stable plaque to becoming symptomatic. This method consists of a two-step method including the identification of an ultrasound profile of the active plaque and the computation of a risk score. The proposed prediction method provides an effective selection of a subgroup of plaques at high risk of developing symptoms.

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