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► **To cite this version:**

Maroun Geryes, Sébastien Ménigot, Walid Hassan, Ali Mcheick, Jamal Charara, et al.. Detection of Doppler Microembolic Signals Using High Order Statistics. Computational and Mathematical Methods in Medicine, 2016, 2016, pp.3243290. 10.1155/2016/3243290 . hal-01407735

**HAL Id: hal-01407735**

**<https://hal.science/hal-01407735>**

Submitted on 20 Dec 2016

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# Detection of Doppler Micro-Embolic Signals using High Order Statistics

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## Abstract

Robust detection of the smallest circulating cerebral micro-emboli is an efficient way of preventing strokes, which is second cause of mortality worldwide. Transcranial Doppler ultrasound is widely considered the most convenient system for the detection of micro-emboli. The most common standard detection is achieved through the Doppler energy signal and depends on an empirically set constant threshold. On the other hand, in the past few years, higher order statistics have been an extensive field of research as they represent descriptive statistics that can be used to detect signal outliers. In this study, we propose new types of micro-embolic detectors based on the windowed calculation of the third moment skewness and fourth moment kurtosis of the energy signal. During energy embolus-free periods the distribution of the energy is not altered and the skewness and kurtosis signals do not exhibit any peak values. In the presence of emboli, the energy distribution is distorted and the skewness and kurtosis signals exhibit peaks, corresponding to the latter emboli. Applied on real signals, the detection of micro-emboli through the skewness and kurtosis signals outperformed the detection through standard methods. The sensitivities and specificities reached 78% and 91%, and 80% and 90% for the skewness and kurtosis detectors respectively.

Index Terms – Signal processing, micro-embolic detection, standard detection, skewness, kurtosis.<sup>1</sup>

## 1 Introduction

Sudden intensity increases in the Transcranial Doppler (TCD) signal are majorly interpreted as signatures resulting from cerebral emboli. The passage of cerebral emboli through blood ves-

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<sup>1</sup>Article published in Computational and Mathematical Methods in Medicine Volume 2016 (2016), Article ID 3243290, 8 pages.

DOI: 10.1155/2016/3243290

sels feeding the brain could result in blockage of these vessels and consequently lead to Stroke; the second cause of mortality worldwide. Embolic strokes constitute up to 14% of all strokes [1]. Therefore, embolic strokes represent a major death threat and thus the early detection of the smallest micro-emboli is an important issue for which robust solutions must be found. This early detection would be a basis for early stroke diagnosis and thus avoiding its occurrence. Nowadays, TCD is considered the most effective embolic stroke diagnosis system.

Although the characteristics and physical nature of embolic signals, in the TCD signal, have been well defined, the task of detecting embolic and particularly small micro-embolic signals still poses a tough challenge. The gold standard method of detecting the passage of emboli is the audible detection of the sudden 'chirp' or 'moan' produced by emboli as well as the visual detection of the time-frequency representation (spectrogram) generated on the TCD screen. A main limitation of the gold standard is the inability to audibly detect micro-embolic signals located at the systolic phase due to temporal and frequency masking effects in audio files.

The standard signal processing method of detecting embolic signals, is based on calculating the energy from the spectrogram and applying constant thresholds to pick up the emboli which, according to Rayleigh theory [2], backscatter ultrasound energy higher than that backscattered by the surrounding blood. The major limitations in standard techniques reside in the inability of detecting small micro-embolic signals having lower intensities than the surrounding background blood mainly at the systolic peak.

As a purpose to detect the smallest micro-emboli, many research works have been carried out. We list some of the most punctual methods. Frequency filtering methods were introduced in [3] and [4]. The study reported high detection sensitivity and specificity rates. Subsequently, an online automated embolic signal detection algorithm based on frequency filtering was developed in [5] and [6]. The latter system showed high performances in terms of sensitivity and specificity for particular cases (post carotid endarterectomy). However, in other conditions (Arterial Fibrillation) the system's sensitivity and specificity severely decreased. Moreover, the system's performance in the detection of low energy micro-embolic signals was arguably less efficient with much lower sensitivity and specificity. Methods based on detection of sudden changes were introduced in [7]. Non-parametric detection methods mainly the Fourier, WignerVille and wavelet approaches were compared to parametric auto-regressive methods. The new parametric methods were proven to be highly performant and efficient in the detection of small micro-emboli. However, the methods were tested on synthetic simulated Doppler signals and never on a set of real signals. Another highly productive wavelet-based system was established in [8]. The system achieved a high combination of sensitivity and specificity. However, the system's rates decreased in the case of low energy micro-embolic signals. A remarkable offline detection was proposed in [9]. The system had excellent performance for emboli having high intensities relative to background blood clutter. However, to be noticed that the study did not take into consideration the detection of weak embolic signals. The authors in [10] introduced another highly achieving detection procedure based on the discrete wavelet transform (DWT). DWT allowed major increases in specificity and sensitivity. Nonetheless, a major deficiency of the DWT implementation was the reduced frequency resolution at low frequency scales, in which embolic signals are mostly found. In [11], the authors proposed embolic detection using the adaptive wavelet packet basis and neurofuzzy classification. The ad-

aptive wavelet packet basis was used to make a sparse representation of Doppler ultrasound blood flow signals. The method produced highly accurate and robust performances. However when compared to other methods only the sensitivity was taken into account and the correlated specificity was not calculated. The study submitted in [12] requested the use of Fractional Fourier Transform rather than the Short Time Fourier Transform; the standard method of detection in TCD systems. The results showed that discriminating parameters based on the Fractional Fourier Transform help easier analysis and detection of embolic signals. Despite of its simplicity and acceptable results, this method was not proven reliably decent for the detection of the smallest micro-emboli. The method proposed in [13], achieved very high sensitivity and specificity but large detection errors occurred due to small gaseous emboli exhibiting small reflected signals.

In most articles previously introduced, the main limitation lies in the fact that the information on which the detection takes place is time-varying while the threshold used is constant. To match between the time-varying information and the threshold, two solutions can be proposed. The first is proposing a time-varying threshold as in [14, 15] that matches with the time-varying trend of the decision information. Second is proposing a constant threshold that matches with the decision information for which the time-varying trend is removed.

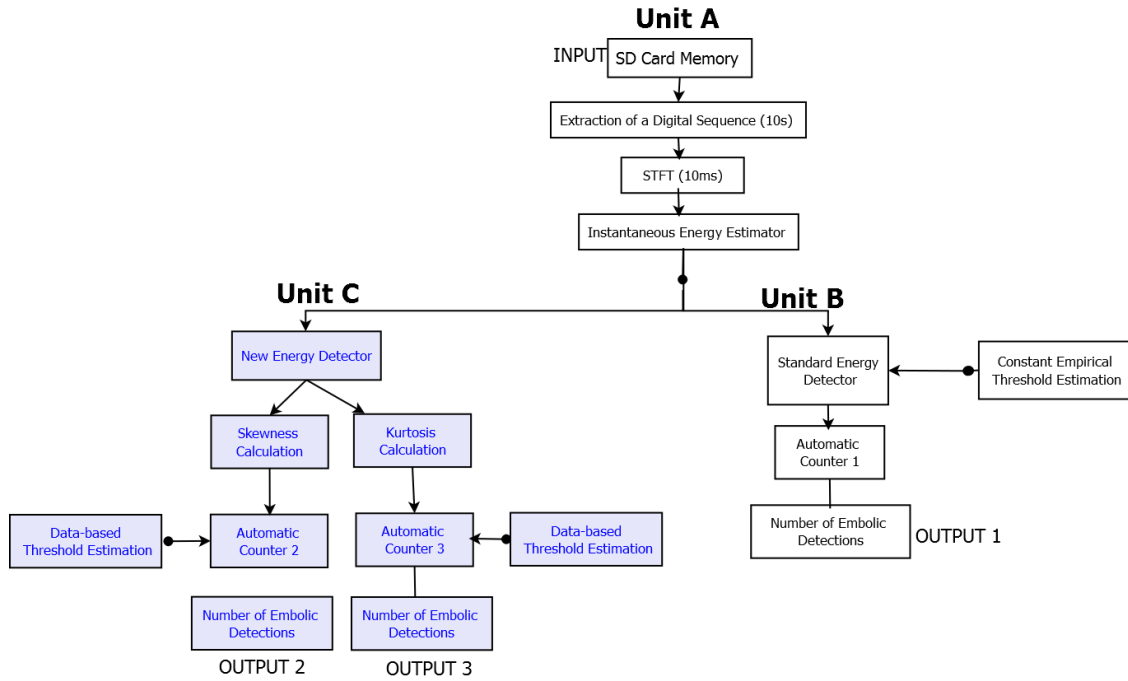
In this work, the methods we proposed of matching between a constant threshold and an energy free of its time varying trend are based on the use of high order statistic (HOS) of windowed Doppler energy signal. We tend to prove the skewness and kurtosis as two solid means to detect micro-embolic signals when asymptomatic caroid artery patients are monitored with a Holter TCD.

## **2 The Offline Micro-Embolic Detection Unit**

As previously mentioned, our objective is to perceive a micro-emboli detector more sensitive and robust regarding most standard detectors.

In this study, the typical off-line signal processing unit is decomposed into 3 units:

- Unit A, allocated for loading the wave file, 10-second signal segmentation, Short Time Fourier Transform (STFT) calculation and instantaneous energy calculation from the STFT;
- Unit B, allocated for standard energy detection on the energy signal obtained in Unit A;
- Unit C, allocated for the new energy detection techniques based on skewness and kurtosis calculation of the energy signal obtained in Unit A ;



$h!][h!]$

## 2.1 Unit A: Doppler signal extraction, STFT and instantaneous energy calculation

The different systems that we want to test, depicted in Figure ??, share a common structure. From the SD card plugged out from the Holter system and plugged into the personal computer, the Doppler signal is picked up and put in memory. From this Doppler digital signal, the short time Fourier transform is calculated, first to display the spectrogram and second to estimate instantaneously the Doppler energy. Calculations of the STFT and the instantaneous energy are carried out repetitively on 10 second segments extracted from the Doppler signal.

Most commercial TCD ultrasound systems are based on the Short Time Fourier Transform. The Short Time Fourier Transform is an adapted form of the Fourier transform that analyzes only a small segment of the signal at a time; a technique called windowing of the signal or also Windowed Fourier Transform (WFT). Short Time Fourier Transform is used when the Doppler signal within the analyzing window is stationary. In reality, transforming data into the frequency domain results in loss of time information. By applying the Fourier transform of a signal, it is impossible to identify when a particular event takes place. The STFT was thus proposed to correct this deficiency. The STFT maps a signal into a two-dimensional function of time and frequency. This representation is known as the spectrogram.

The STFT frequency estimator with a sliding window can be formally written as:

$$S(t, f) = \left| \int x(\tau) w^*(t - \tau) \exp^{-j2\pi f t} d\tau \right|^2, \quad (1)$$

where  $x(t)$  is the analyzed Doppler signal,  $w(t)$  is a sliding window and  $*$  stands for complex conjugation.

When using the STFT to process embolic signals, it is of great importance that the STFT parameters are optimized. The three processing parameters are the window size, the window type and the overlap ratio. Despite the fact that setting the parameters significantly affects the embolus detection system based on STFT calculations, little work on the effect of the different parameters has been reported. A fundamental work was reported in [16]. The authors evaluated the effect of varying the three parameters on embolic signal temporal and frequency resolutions, time of embolic signal onset and on the power of the embolus at the frequency with maximum power relative to the average power of the background intensity. Based on [16] and after a preliminary stage of experimental optimization of the STFT parameters, the STFT in this study is performed using a 14.6 milliseconds Hamming window with an overlap of 65%.

The instantaneous energy at a fixed time  $t$  can be obtained from STFT frequency estimators in equation (1) by:

$$e(t) = \int S(t, f) df, \quad (2)$$

Note that the energy returned by a microembolus would be greater than that returned by billions of red blood cells (RBCs), since a microembolus is often larger than RBCs. Hence, the backscattered energy would function as a solid indicator from which the presence of embolic and micro-embolic signatures could be detected. This justifies why most detectors are chosen to be mainly based on energy criteria.

## 2.2 Unit B: Standard micro-embolic detection

The standard detection methods, to which we compare the new proposed methods, are based on a direct detection of the embolic signatures in the energy signal. An empirical threshold is commonly used. This constant threshold can be fixed empirically by the trained user for the entire examination. It is patient-, operator-, and device-dependent. This threshold is set above the maximal background energy of the Doppler signal when no embolus is present [17] ; i.e. the systolic peak. The micro-embolic standard detection based on a constant threshold is represented in Figure 1 a).

The main limitation of using such method resides in comparing the energy which is time-varying, to a constant threshold. To match between the time-varying trend of the energy and the threshold, two solutions can be proposed: either a time-varying threshold as in [15, 18, 14] that matches with the time-varying trend of the decision information or a constant threshold that matches with the energy while removing the time-varying trend.

### 2.3 Unit C: Skewness and kurtosis-based micro-embolic detection

As previously mentioned, it is a threshold-oriented detection. As shown in Fig. 1 weak embolic events are impossible to detect with a constant threshold. One way to overcome this issue is to remove the time-varying trend in the instantaneous Doppler energy. To prove that high order statistic such as the skewness and the kurtosis are suitable candidates to overcome this limitation, consider a Doppler signal free of micro-embolic events and assume that the statistical distribution remains unchanged whatever the time position is even if the mean  $\mu_i(t)$  and the variance  $\sigma_i^2(t)$  vary with time. Suppose there exists two Gaussian random variables  $X(t_2) = N(\mu_1(t_2), \sigma_1(t_2))$  and  $X(t_3) = N(\mu_2(t_3), \sigma_2(t_3))$ . It can be shown for the skewness S that  $S(t_2) = S(X(t_2)) = S(X(t_3)) = 0$  and for the kurtosis K that  $K(t_2) = K(X(t_2)) = K(X(t_3)) = 3$ . In this example the skewness and the kurtosis are stationary since  $S(t) = 0$  and  $K(t) = 3$  for all t. This outcome can be verified whatever the distribution form while it remains unchanged over all time values. The only change occurs in the value of the skewness and the kurtosis but not in their stationarity. Consequently, when a micro-embolic event occurs at a time position  $t_1$ , the distribution changes. The direct consequence is  $S(t_1) \neq S(t_2)$  and  $K(t_1) \neq K(t_2)$ .

Therefore, we can propose a new detector based on calculating the skewness and kurtosis from the energy signal. The calculations are performed using a sliding window  $g(t)$  where the optimal window length and overlap ratio are set during a training phase (see Results section).

The skewness is the third order standardized moment. When calculated instantaneously (by the sliding window) on the energy it is given by the following equation:

$$S(t) = \frac{E[e(t) - \mu_e(t)]^3}{\sigma_e(t)^3}. \quad (3)$$

The kurtosis is the fourth order standardized moment. When calculated instantaneously on the energy it is given by the following equation:

$$K(t) = \frac{E[e(t) - \mu_e(t)]^4}{\sigma_e(t)^4}, \quad (4)$$

where  $\mu_e(t)$  and  $\sigma_e(t)$  are the instantaneous mean and standard deviation of the energy while  $E[\ ]$  denotes the expected value.

The micro-embolic detection based on the skewness and kurtosis signals is represented in Figure 1 b) and c).

In order to complete the detection on the skewness and kurtosis signals, a threshold has to be set in order to pick up the peak signals. We decided to establish a data-based threshold for the skewness and kurtosis signals from their respective means  $\mu_s$  and  $\mu_k$  and respective standard deviations  $\sigma_s$  and  $\sigma_k$ . This threshold is defined as  $\lambda_s = \mu_s + m\sigma_s$  for skewness and  $\lambda_k = \mu_k + m\sigma_k$  for kurtosis, where m is a parameter whose value is adjusted using an optimization training phase in a manner that increases the system's sensitivity and specificity (refer to Results section). The thresholds are represented in Figure 1 b) and c).

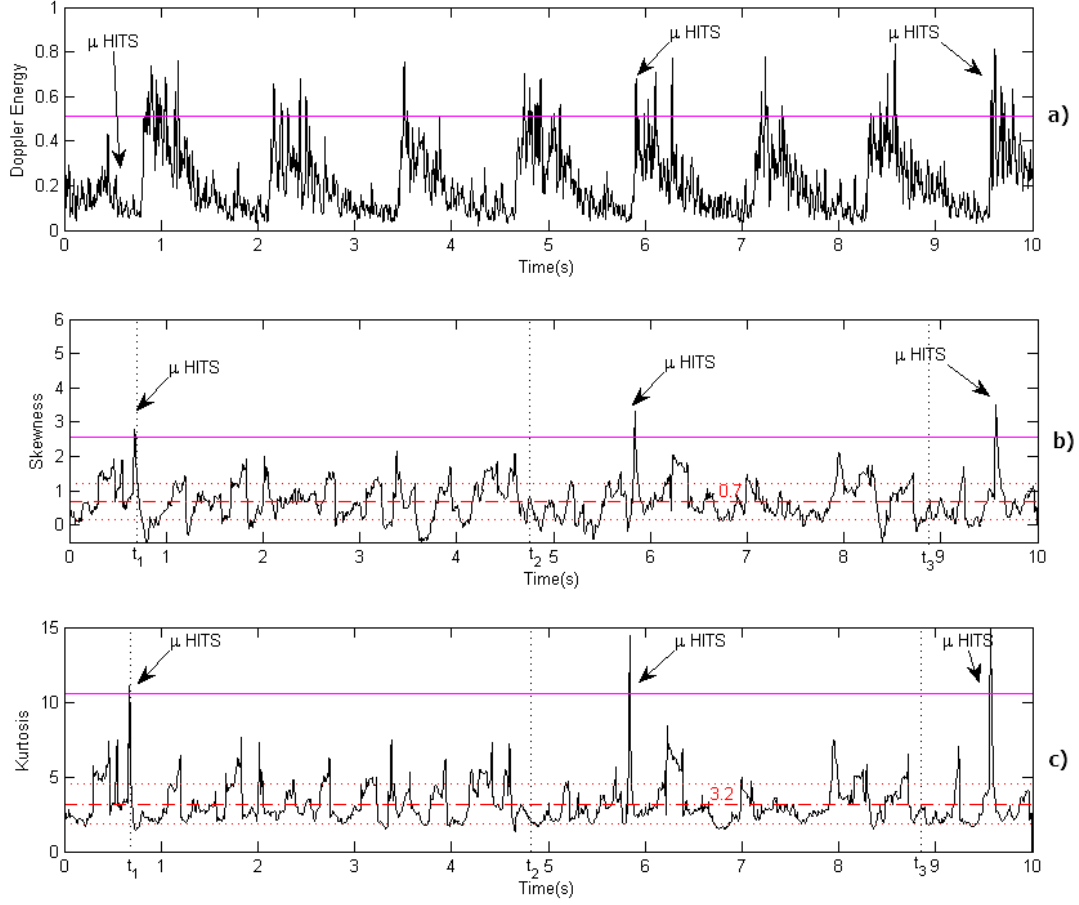


Figure 1: a) The Doppler energy signal. An empirical threshold is applied to obtain the micro-embolic standard detection. b) Skewness signal calculated from the windowed energy signal. A data-based threshold is applied to complete the micro-embolic detection. The mean value of the skewness signal is 0.7 c) Kurtosis signal calculated from the windowed energy signal. A data-based threshold is applied to complete the micro-embolic detection. The mean value of the kurtosis signal is 3.2. Moreover, we choose in b) and c) three time positions:  $t_1 = 0.72s$  during which an embolus is present, and  $t_2 = 4.7s$  and  $t_3 = 8.8s$  when no embolus is present. We detect in the case of absence of embolus:  $S(t_2) \approx S(t_3) \approx 0.7$  and  $K(t_2) \approx K(t_3) \approx 3.2$  while in the presence of embolus:  $S(t_1) = 2.8 \neq S(t_3) \approx 0.7$  and  $K(t_1) = 11 \neq K(t_3) \approx 3.2$

### 3 The Holter system and the Protocol

TCD is a non-invasive, non-ionizing, inexpensive, portable and safe technique, which renders it as a convenient tool for the detection of cerebral micro-emboli. Long time probe positioning and the short effective examination duration are the main limitations of traditional TCD systems. The



Transcranial Holter (TCD-X, Atys Medical, Soucieu en Jarrest, France) shown in Figure 2 allows prolonged patient monitoring (higher than 5 hours) with the patient no longer attached to a TCD and does not need to be laying on a bed, but rather can be monitored under naturalistic conditions. The Holter is equipped with a robotized automatic probe that helps find the best TCD signal and tracks it automatically during the whole recording.

A database obtained from the Centre Hospitalier Régionale Universitaire (CHRU) de Lille (2 Avenue Oscar Lambret, 59000 Lille, France) is used. Informed consent for Holter monitoring was obtained from all monitored patients. The recordings were acquired from the middle cerebral artery of the patients. The ultrasonic wave frequency was  $1.5\text{ MHz}$ , the pulse repetition frequency (PRF) was  $6.4\text{ kHz}$  and the ultrasound power was  $50\text{ mW/cm}^2$ .

After the clinical examination, an analogous conversion is performed on the Doppler digital signal and then the Doppler signal is sent to a loudspeaker. From the audible Doppler signal and from the spectrogram displayed on a screen, we detect and count manually the number of micro-embolic events in order to constitute our gold standard of detection. The gold standard is subject to inter agreement between three experts of our laboratory. Then, the positions in time of audibly and visually agreed-on micro-embolic events are noted. This gold standard is used to assess the results of the different detectors used and validate their performances. Although, the gold standard detections obtained from experts and non-experts might be the same as stated in [19], the experience of the latter experts was useful to distinguish between micro-embolic signals and artifact signals discussed next. We should also point out that listening to the audio files is made at the normal playing speed and another time at half the normal speed which allows us to detect micro-emboli previously inaudible due to the well-known temporal and frequency masking effects in audio files.

## 4 Results

The different detectors are tested through algorithms we developed using the numerical calculation software Matlab (Mathworks, Natick, MA, USA). Our database is composed of 18 recorded signals divided into two categories. The first is the training phase (8 signals) dedicated to determine the best settings of the detectors used. The second is the testing phase (10 signals) dedicated to assess the performances of the detectors used under the optimal settings determined in the training phase.

Two parameters are used to evaluate the detectors:

- Sensitivity or (Detection Rate) calculated as the number of true positive detections / the number of gold standard detections. True positive detection refers to the detection of an embolus recorded in the gold standard.
- Specificity calculated as  $1 - \text{False Alarm Rate (FAR)}$  the latter FAR being the number of false positive detections / the total number of detections. False positive detection refers to the detection of an embolus not recorded in the gold standard or in other words an embolus which has not crossed the sample volume.

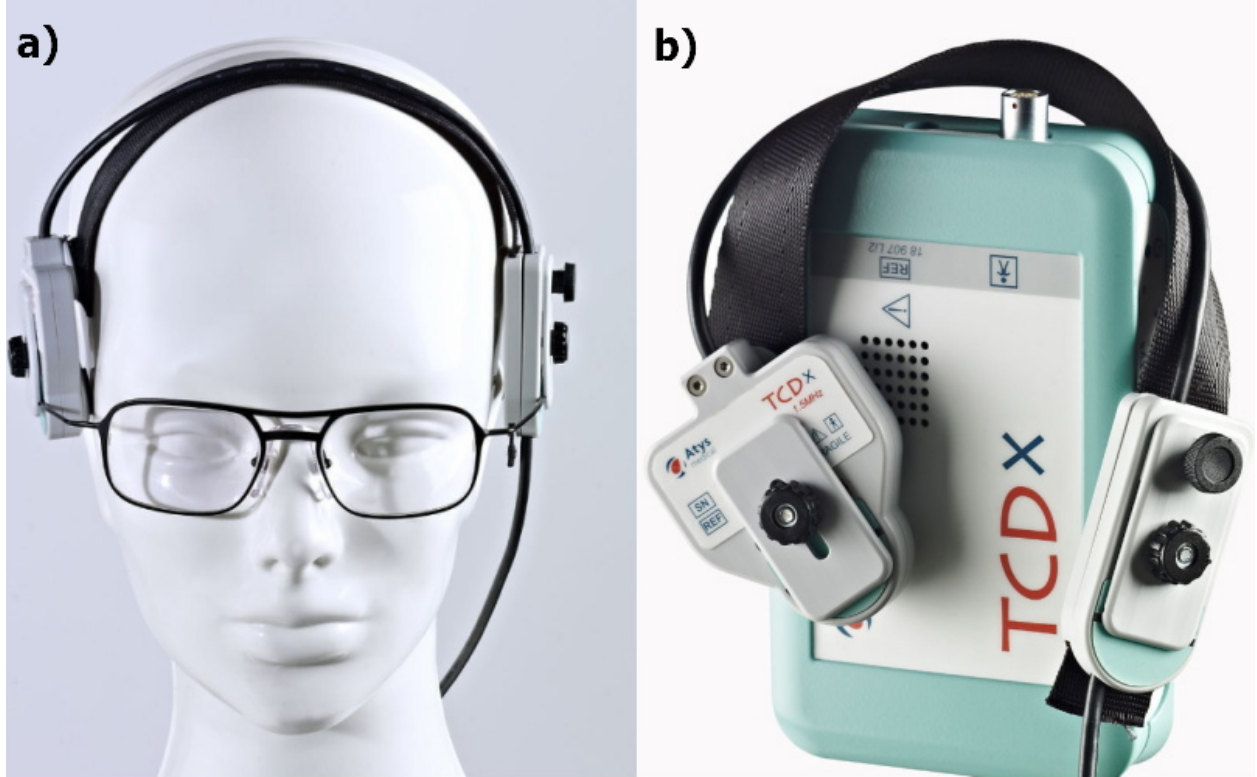


Figure 2: a) Robot probe and b) Holter Transcranial Doppler System (TCD-X, Atys Medical, Soucieu en Jarrest, France)

#### 4.1 Training phase results

Since the threshold applied on the energy signal to achieve the standard detection, is empirically set through the choice of the user, different micro-embolic detections could be obtained. To overcome this we initialize a training phase to pre-set the best empirical threshold to be used in the testing phase. 3 to 9  $dB$  values are used. Table 1 shows the empirical threshold that best maximizes the sensitivity and specificity.

Moreover, since the skewness and kurtosis calculations are performed using a sliding window  $g(t)$  on the energy signal, an experimental test on the training phase signals is initialized to determine the optimal length of the window  $g(t)$  and the optimal overlap ratio. The optimal temporal window length is 7.3 milliseconds and the optimal overlap used is 95%. Also, using these settings we test in the training phase the best data-based threshold  $\lambda_s = \mu_s + m\sigma_s$  and  $\lambda_k = \mu_k + m\sigma_k$  for the skewness and kurtosis signals respectively. Values of  $m$  ranging between 3 and 7 are tested. Table 1 shows the data-based threshold for the skewness and kurtosis signals that best maximizes the sensitivity and specificity.

Table 1: Training phase results of the optimal thresholds that best maximize the sensitivity and specificity for the standard energy detector, and skewness and kurtosis based detectors.

	Optimal Threshold that maximizes the sensitivity and specificity	Sensitivity (%)	Specificity (%)
Standard Energy Detector	5 dB	67%	58%
Skewness Detector	$\lambda_s = \mu_s + 4\sigma_s$	76%	91%
Kurtosis Detector	$\lambda_k = \mu_k + 5\sigma_k$	77%	91%

## 4.2 Testing phase results

Table 2 represents the testing phase results for the three different energy detectors. For the standard energy detector with empirical threshold, the sensitivity is 65% and the specificity is 60%. For the energy detector based on skewness calculation the sensitivity is 78% and the specificity is 91%. For the energy detector based on kurtosis calculation the sensitivity is 80% and the specificity is 90%.

The results presented, show that the new detectors are able to significantly increase the specificity compared to standard detection (more than 30%). Moreover, the sensitivity achieved by the new detectors is increased by 13 % for the skewness detector and 15% for the kurtosis detector compared to that achieved by standard detectors. These results assert the accuracy and superiority of the detection based on skewness and kurtosis calculation of the Doppler energy signal over the standard detection applied directly on the Doppler energy signal.

## 5 Discussion

The results obtained were clear. The methods based on HOS over-passed by far the standard method based on the second order statistics. The reason explaining such superiority lies in the HOS sensitivity in modifying the distribution form. Knowing, that the occurrence of a micro-embolus superimposed on the Doppler energy signal imposes changes in the distribution of this signal, we propose to use the skewness and kurtosis as new tools for micro-embolus detection. During embolus-free periods the Doppler energy signals' distribution is fixed and its skewness and kurtosis are never altered. They do not show any variations. However, in the presence of a micro-embolus superimposed on the energy signal, the skewness and kurtosis signals are altered and the embolus is attributed with a peak whose peakedness level is higher than all the other points of the signal. This detection can outperform standard methods. After being tested on a set of real signals,

Table 2: Results (Sensitivity and Specificity) for the standard energy detector and the new detectors based on skewness and kurtosis calculations of the Doppler energy signal.

Detector Type	True Positive	False Positive	Sensitivity (%)	Specificity (%)
Gold Standard Detections=136				
Standard Detection	88	58	65	60
Skewness Detection	106	10	78	91
Kurtosis Detection	109	12	80	90

the skewness and kurtosis-based detection offered significant improvements including very high specificity reaching up to 91% and 90% respectively compared to 60% achieved by the standard method. In addition, the sensitivity is increased from 65% for standard methods to 78% and 80% for skewness and kurtosis-based detectors respectively.

Consequently, we can affirm that skewness and kurtosis can offer a robust and more reliable detection than standard detection methods and thus can be considered as new techniques for enhancing micro-embolic detection systems.

In view of the fact that we have proposed 2 detectors, one based on skewness detection and the other on kurtosis detection, it is convenient to give note that the two detectors perform very similarly and yield very close results. The only difference that could be observed is that the kurtosis signal displays small fluctuations around the embolic peak detected while the skewness signal fluctuates more strongly around the embolic peaks. This provides the kurtosis detection with a small advantage in terms of the detection threshold which can be more easily and robustly set.

## 6 Conclusion

In this research study, we propose two detectors based on the calculation of the skewness and kurtosis of the Doppler energy signal, as a tool for an enhanced cerebral micro-embolus detection. Compared to the standard detector where the detection is performed directly on the energy signal, the skewness and kurtosis-based detectors allow increasing both the sensitivity and the specificity.

This study emphasizes that standard micro-embolic energy detectors with empirical threshold still pose serious difficulties for the robust detection of micro-emboli. It also shows that detectors incorporating detection based on skewness and kurtosis calculation from the energy allow a much advanced detection of micro-emboli, precursors of coming large emboli with strong stroke risks. Thus using these simple and straightforward detectors would be an additional facility boosting the efforts to reduce the occurrence of strokes.

The upcoming step would be attempting to increase the overall performance of the techniques particularly in terms of sensitivity and validating the developed algorithms on a larger database. Moreover, we are on course of including in the whole detection system, automatic artifact rejection techniques rather than using manual techniques.

## Acknowledgments

This research was financially supported by the Doctoral School of Sciences and Technology, Lebanese University, Lebanon, the National Council for Scientific Research CNRS, Lebanon and the French Institute of Health and Medical Research INSERM, France.

The authors would like to sincerely thank Marilys Almar and Benoit Guibert for the Holter TCD equipment. They also acknowledge Corinne Gautier for the Holter Doppler recordings.

## Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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