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Reduced Data Dualscale Entropy Analysis of HRV Signals for Improved Congestive Heart Failure Detection

[1]Srinivas Kuntamalla, [2]Ram Gopal Reddy Lekkala

Department of Physics, National Institute of Technology, Warangal-506004, INDIA,
[1]ksvchary@gmail.com, [2]lrgreddy@gmail.com

Heart rate variability (HRV) is an important dynamic variable of the cardiovascular system, which operates on multiple time scales. In this study, Multiscale entropy (MSE) analysis is applied to HRV signals taken from Physiobank to discriminate Congestive Heart Failure (CHF) patients from healthy young and elderly subjects. The discrimination power of the MSE method is decreased as the amount of the data reduces and the lowest amount of the data at which there is a clear discrimination between CHF and normal subjects is found to be 4000 samples. Further, this method failed to discriminate CHF from healthy elderly subjects. In view of this, the Reduced Data Dualscale Entropy Analysis method is proposed to reduce the data size required (as low as 500 samples) for clearly discriminating the CHF patients from young and elderly subjects with only two scales. Further, an easy to interpret index is derived using this new approach for the diagnosis of CHF. This index shows 100 % accuracy and correlates well with the pathophysiology of heart failure.

Keywords: Multiscale entropy analysis, empirical mode decomposition, heart rate variability, congestive heart failure.

1. INTRODUCTION

MULTISCALE SYSTEMS possess complicated nonlinear interactions and consist of multiple subsystems. A cardiovascular system is the best example of multiscale system and heart rate variability (HRV) is an important dynamical variable of it, which refers to the beat-to-beat alterations in the heart rate. The important feature of HRV is that a variable heart rate is a normal physiological feature. Even under constant environmental parameters and without any perturbing influences the HRV shows spontaneous fluctuations.

In healthy subjects, the sinus node of heart spontaneously depolarizes approximately at a rate of 100 beats/min in the absence of sympathetic and parasympathetic inputs and is called intrinsic heart rate. Heart rate decreases on the release of acetylcholine from efferent vagal nerve endings (parasympathetic activation), whereas heart rate increases on the circulation of epinephrine or neural release of norepinephrine (sympathetic activation). As the sympathetic and parasympathetic inputs are generally antagonistic in nature in a stable physiological state the dominant level of activity determines the actual heart rate at that state. Based on the physiological state, the heart rate consistently responds in an expected direction (sympathetic and parasympathetic stimulation or blockade). Usually the R peaks of electrocardiogram (ECG) are taken as heart beat instants and consequently the inter beat intervals are obtained as the time interval from one R peak to the next one. When these R-R intervals are plotted against their beat number, it shows the alterations in the heart rate over a period of time (i.e., HRV) and is called a tachogram (Fig.1.). Therefore, the balance between sympathetic and parasympathetic activities can be assessed using the HRV analysis [1].

In 1996, the Taskforce of the ESC/NASPE [2] published standards in HRV analysis and proposed several time and frequency parameters based on short-term (5-min) and long-term (24-h) HRV data, which are broadly classified into time domain and frequency domain methods. However, nonlinear analysis methods are more appropriate means to get accurate information about the heart rate variability as the dynamics of heart rate is nonlinear in nature. 1/f scaling of Fourier spectra, H scaling exponent, Coarse graining spectral analysis, Poincare plots, and Correlation dimension are some of the emerging nonlinear analysis methods of HRV [2].

As Physiological systems are governed by mechanisms which are operating over multiple time scales, many methods, such as Scale dependent Lyapunov exponent(SDLE) [3, 4], Multifractal Analysis (MFA) [5–7] and Entropy analysis [8, 9] have been developed in the last few years for the analysis of these complex physiological signals. By analyzing the degree of complexity, a greater understanding can be achieved on the fundamental mechanisms and their underlying dynamics of physiological systems. This can be only obtained by studying such systems on multiple time scales. In a recent study, Multiscale Entropy (MSE) analysis approach [10, 11] has been applied to 24 hour ECG recordings to analyze heart rate dynamics.

Although HRV has been the subject of many clinical studies investigating a wide spectrum of cardiological and non-cardiological diseases and clinical conditions, a general consensus of the practical use of HRV in medicine has been reached only in two clinical scenarios: depressed HRV can be used as a predictor of risk after acute myocardial infarction, and as an early warning sign of diabetic neuropathy [2].

Depressed HRV has also been observed in patients suffering from dilated cardiomyopathy and congestive heart failure (CHF) [12]. Heart failure is characterized by increased sympathetic activity, which decreases the heart rate variability. The ability of the heart to fill itself with

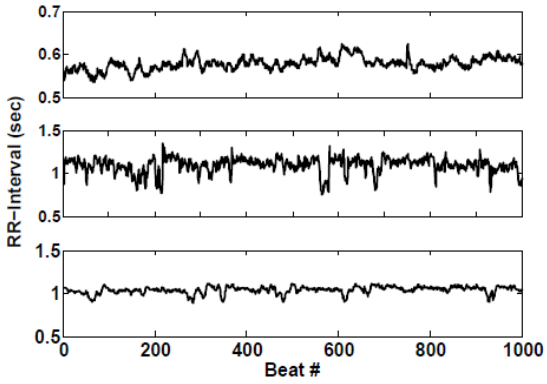

Fig.1. Tachogram of a) CHF patient b) young healthy subject c) old healthy subject.

blood or empty the blood will be decreased in heart failure. Accumulation of fluid in various parts of the body is usually found in heart failure patients, and hence, it is called as congestive heart failure.

The HRV linear and nonlinear measures are used as prognostic values of CHF for predicting the risk of mortality in most of the research studies [12–19]. Only a few researchers focused on diagnosis of CHF using HRV parameters. Isler and Kuntalp [20] reported 100 % sensitivity and 94.74 % specificity by using short-term time and frequency domain measures of HRV, including nonlinear measure wavelet entropy to discriminate CHF patients from Normal subjects. Further, they used Genetic algorithm (GA) in their study to get a better performance. The same authors in another study [21] reported 100 % specificity and only 82.76 % sensitivity. This increase in specificity is achieved by employing heart rate normalization in addition to K-nearest neighbor classifier and genetic algorithm for feature selection. Pecchia et al. [22] developed a classifier using Classification and Regression Tree (CART) to study the discrimination power of identified HRV standard measures and achieved a specificity of 79.31 % and sensitivity of 100 %. They also reported an increased specificity of 89.7 % by taking two non-standard long-term HRV measures into consideration. Sung-Nien Yu and Ming-Yuan Lee [23, 24] proposed two different classification algorithms to recognize CHF patients using HRV based on feature selection. One algorithm uses the conditional mutual information feature selector with uniform distribution (UCMIFS) and the other uses a GA feature selector. With UCMIFS an accuracy of 97.59 % was obtained in recognizing CHF patients by using 15 features derived from personal, time-domain, frequency-domain, Poincare and bispectral categories. GA feature selector uses features from bispectral analysis and recognized CHF patients with an accuracy of 98.79 %. Jing Hu et al. [25] proposed SDLE as a multiscale complexity measure to distinguish between CHF and healthy subjects. They achieved 100 % accuracy with false positive rate percentage of $\leq$ 5 %. In all these studies, there is no report on the discrimination between CHF patients and healthy elderly subjects having more than 70 years of age and all these methods require huge data and lack the simplicity of screening CHF patients by using short-term data of as little as 500 samples.

The present study aims for the development of an easy to interpret measure for the diagnosis of CHF, in particular, for screening large populations, without any complex classifiers or genetic algorithms and many other variables. This study also aims for diagnosis using short-term data comprising of only 300 to 500 RR intervals. In this paper, we proposed the Reduced Data Dualscale Entropy (RDDE) analysis method which can be successfully used to short-term HRV recordings to discriminate CHF patients from normal subjects.

2. METHODS & DATA

A. Data.

This study is based on the data obtained from Physionet data bank [26], the MIT/BIH Normal database [26] and BIDMC congestive heart failure database [27]. The MIT/BIH normal database includes 18 long term ECG recordings of 5 men and 13 women having the age between 20 and 50 years, referred to the Arrhythmia Laboratory at Boston's Beth Israel Hospital. Further, these subjects were found to have no significant arrhythmias. The recordings were digitized at 128 samples per second. The BIDMC congestive heart failure database includes long-term ECG recordings of 15 subjects (11 men, aged 22-71 years and 4 women, aged 54-63 years) with severe congestive heart failure (NYHA class 3-4). This group of subjects was part of a larger study group receiving conventional medical therapy prior to receiving the oral inotropic agent, mirinone. The individual recordings were sampled at 250 samples per second and were 20 hours in duration. Heart beat annotation files for these long-term ECG recordings obtained using automated analysis software with manual inspection and correction were also available in these databases.

Another database used in this study is publicly available FANTASIA [28] database from the Physionet website. This database contains rigorously-screened twenty young healthy subjects between 21-34 years of age and twenty healthy elderly subjects (aged 68-85 years) ECG, and respiration signals of 120 minutes duration. Each group of subjects includes equal numbers of men and women. All the subjects are made to watch the movie Fantasia (Disney, 1940) in a resting position to maintain wakefulness. The signals were digitized at a rate of 250 Hz. Heart beat instances annotated using an automated arrhythmia detection algorithm and verified by visual inspection are provided in this database for all the signals. In this study, nineteen records from young group and nineteen records from elderly group are considered, because the two records f2o08 and f2y09 are of poor quality having lot of ectopic beats.

B. Multiscale Entropy analysis.

In this section, we briefly describe the multiscale entropy analysis. To determine the complexity of finite length time series, Costa et al. [10, 11] introduced a new method called Multiscale Entropy (MSE) analysis, which is based on calculating the entropy on multiple time scales. The entropy which is used to quantify the regularity of the time series in MSE analysis is Sample Entropy (*SampEn*). In this paper, a

modified MSE method is used for the diagnosis of congestive heart failure. Entropy characterizes the rate of creation of information in dynamical systems and is one of the mostly used complexity measures for biomedical signal analysis. The potential application of complexity related metrics is to discriminate signals generated either by the system under different conditions or by different systems. Traditional entropy based measures quantify the degree of regularity by evaluating the appearance of repetitive patterns in the time series on a single scale only. Complexity incorporates correlations over multiple spatial and temporal scales, and exhibits relatively higher regularity compared to random phenomena. Complexity is associated with meaningful structural richness [10, 11]. Further, it is observed that single scale entropy estimates tend to show lower entropy value in physiological time series than in surrogate series. This is misleading as original series is more complex than the surrogate; the original data contains correlations at multiple time scales, whereas the surrogate data destroys the correlations [10, 11]. According to Costa et al., traditional entropy based measures assign higher entropy values to certain pathologic cardiac rhythms that generate erratic outputs than to healthy cardiac rhythms that are exquisitely regulated by multiple interacting control mechanisms [10, 11].

Consider a single-dimensional discrete time series consisting of N samples,

$$\{x_1,\ldots..,\ x_i,\ldots..,\ x_N\},$$

The consecutive coarse-grained time series, $\{y^{(\tau)}\}$, determined by the scale factor, τ , is to be constructed according to the equation:

$$y_j^{\tau} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i$$

where τ represents the scale factor and $1 \le j \le N/\tau$

The length of each coarse-grained time series is N/τ. For scale one, the coarse-grained time series is simply the original time series. Next, *SampEn* for each scale using the following method is calculated.

$\{X_i\} = \{x_1,\ldots x_i,\ldots x_N\}$, be a time series of length N

$u_m(i) = \{x_i, x_{i+1}, \ldots\ldots x_{i+m-1}\}, \quad 1 \le i \le N-m-1$ be

vectors of length m

Let $n_m(r)$ represent the number of vectors $u_m(j)$ within distance r of $u_m(i)$ where i, j ranges from 1 to $(N-m)$ and $j \neq i$ to exclude the self matches.

The probability that any $u_m(j)$ is within the distance r of $u_m(i)$ is given by

$$C_i^m(r) = \frac{n_m(r)}{(N-m-1)}$$

We then define

$$U^m(r) = \frac{1}{(N-m)} \sum_{i=1}^{N-m} \ln C_i^m(r)$$

For finite length N the Sample Entropy is estimated by the statistics

$$SampEn(m,r,N) = -\ln \frac{U^{m+1}(r)}{U^m(r)}$$

Sample Entropy is less dependent on time series length and is relatively consistent over broad range of possible r, m and N values [11].

We have calculated *SampEn* for all the studied data sets with the parameters m=2 and r=0.15x SD (SD is the standard deviation of the original time series). Fig.2. shows the average sample entropy values of the Normal and CHF datasets for a template length of m=1 to m=5 on the segments of data comprising of 20,000 samples. The values are almost constant from m=2 to m=5.

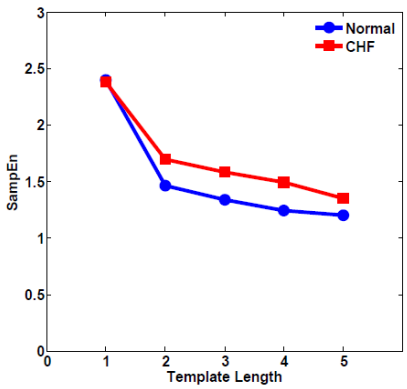

Fig.2. Average *SampEn* value of HRV signals on BIDMC CHF dataset (n=15) and MIT/BIH normal dataset (n=18) for different template lengths.

We consider the application of MSE analysis to the RR interval records of Normal and BIDMC congestive heart failure databases of MIT/BIH database of the Physionet data bank. From each long-term data record we randomly extracted data segments of varying lengths (N=1200, 2000, 3000, 4000, 6000, 8000, 10000 and 20,000 RR intervals) and the MSE analysis was carried out on each realization with the scale factor τ =20. We report in Fig.3. averaged *SampEn* with standard deviation of all the records of Normal as well as CHF databases versus scale factor for eight values of N. These results are encouraging and coincide with the previous studies that MSE analysis can be applied to short-term data and there is a clear discrimination between the two groups in some of the intermediate scales [29-30]. Further, we have applied the MSE analysis on the HRV data of elderly healthy subjects of age greater than 70 years (data taken from FANATASIA database of the Physionet data bank) with N=4000 and compared with the MSE values of CHF patients. The results, depicted in Fig.4., show no discrimination between the aged people and CHF patients.

However, RDDE analysis resulted in excellent discrimination between healthy subjects and the CHF patients and it is described in the section 2(D).

C. Empirical mode decomposition.

Empirical Mode Decomposition (EMD) is a signal processing technique used in combination with Hilbert Transform to analyze non-stationary, nonlinear multi-component signals [31]. EMD decomposes a complex time series into a number of components called intrinsic mode functions (IMFs) based on a posteriori basis that is data dependent. By definition, an Intrinsic Mode Function (IMF) should satisfy the following two conditions.

a) The number of extrema and the number of zero crossings must be equal or may differ at most by one.

b) The local mean, defined by the average of the upper and lower envelopes, is zero everywhere.

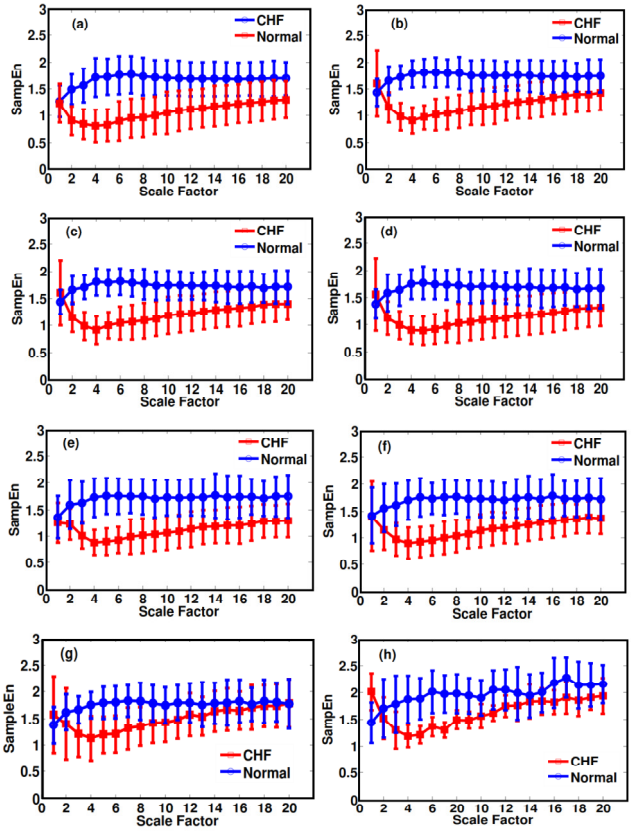

Fig.3. Multiscale entropy analysis of HRV signals on BIDMC CHF dataset (n=15) and MIT/BIH normal dataset (n=18) for different time series lengths a) 20000 samples b) 10000 samples c) 8000 samples d) 6000 samples e) 4000 samples f) 3000 samples g) 2000 samples h) 1200 samples.

The process of extracting IMFs is called sifting process and for a given signal $f(t)$, $t = 1,..., T$; it can be implemented by the following procedure:

1. First all the maxima and minima of $f(t)$ are to be identified,

2. Through cubic spline interpolation, all maxima are connected to generate the signal's upper envelope, $F_u(t)$ and similarly lower envelope $F_l(t)$ is generated,

3. Determine the local average (i.e., on point-by-point basis) from the upper and lower envelopes, by using

$$m_1(t) = (F_u(t) + F_l(t))/2,$$

4. The first proto-IMF is extracted by subtracting the local mean from the signal, $h_1(t) = f(t) - m_1(t)$,

5. a) If $h_1(t)$ satisfies the two conditions of IMF definition, then the first IMF is extracted, $c_1(t) = h_1(t)$ and $f(t)$ is replaced with the residue $r_1(t) = f(t) - c_1(t)$; and the steps 1 to 5 (sifting process) are repeated to extract the second IMF, $c_2(t)$,

b) If $h_1(t)$ is not an IMF, $f(t)$ is replaced with $h_1(t)$, and the sifting process is repeated until the first IMF, $c_1(t)$ is extracted.

This process is repeated until the residue is a monotonic, a constant or a single maximum or minimum. In practice, the second condition for IMF is only approximately satisfied and a function is accepted as an IMF, whenever the mean squared error between two consecutive proto-IMFs, $h_{k-1}(t)$ and $h_k(t)$ is smaller than a pre-specified threshold, which is very small.

At the end of this process, the signal $f(t)$ can be expressed as follows:

$$f(t) = \sum_{n=1}^{N} c_n(t) + r_N(t)$$

where N is the number of intrinsic mode functions,

$r_N(t)$ denotes the final residue, which can be interpreted as the DC component of the signal,

$c_n(t)$ are the intrinsic modes, orthogonal to each other and all have zero means.

EMD of a typical RR interval time series for N=500 is shown in Fig.5.

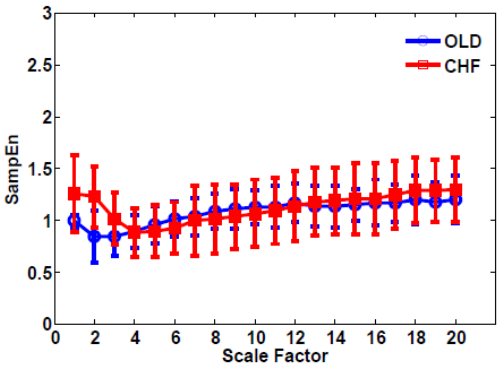

Fig.4. Multiscale entropy analysis of HRV signals on BIDMC CHF dataset (n=15) and old healthy subjects of FANATASIA dataset, older than 70 years of age (n=5) for a data length of 4000 samples.

D. Reduced data dualscale entropy analysis.

The application of the EMD method to a signal results in producing N IMFs and a residue signal. If we consider $c_n(t)$ as the nth-order IMF then, the lower-order IMFs are high frequency components, while higher-order IMFs represent low frequency components. In this paper, the EMD is

considered as a time-scale analysis method, the increasing order of IMFs corresponding to the fine to coarse scaling of the signal.

We replaced the coarse graining procedure for scaling the original time series in MSE analysis with the EMD. The advantage of using EMD for scaling is that all the scaled series are of the same length as the original time series. The MSE analysis is carried on all the IMFs generated for both the normal and CHF data sets taking N=1000 and is depicted in Fig.6. The circled portion of Fig.6. is interesting and encourages the authors to modify the method further. Now, as a further modification, the *SampEn* is calculated for two scales only. The IMF1 is taken as first scaled time series, IMF2 and IMF3 are added to make second scaled time series. The selection of only first three IMFs as scaled time series and their physiological correlation needs to be clarified and is described in the Discussion section. These modifications are primarily made to the original MSE analysis to obtain a clear index to separate out CHF patients from healthy population, irrespective of their age, by taking only two scales and very short data segments of only 10 minute duration or 500 RR intervals.

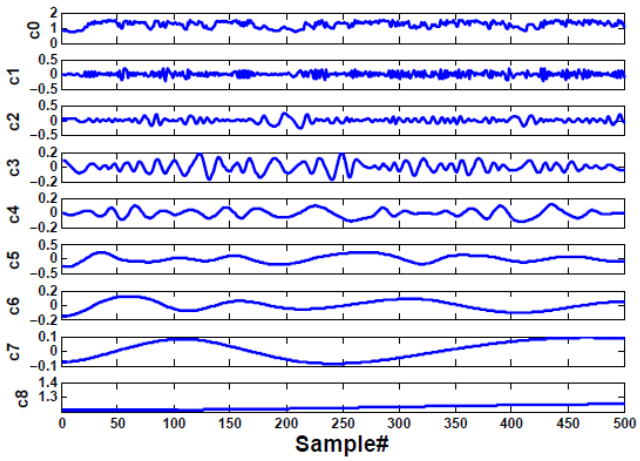

Fig.5. Empirical mode decomposition of HRV signal showing all the extracted intrinsic mode functions (c_1 to c_8) for a data length of 500 samples.

3. Results

In Fig.2. we showed the sample entropy values for different template lengths for a HRV time series. A large deviation can be observed in the *SampEn* value from m=1 to m=2 for both CHF group and Normal group. It is also obvious that the entropy value of CHF group is larger than the Normal people. The entropy value remained almost the same for m=2 to m=5. This is a misleading result, as depicted by Costa et al. [11], single scale based entropy measures assign higher entropy values to certain pathologic cardiac rhythms that generate erratic outputs than to healthy cardiac rhythms that are exquisitely regulated by multiple interacting control mechanisms. In Fig.3., the entropy values for HRV data of CHF patients are lower than the healthy people from $\tau = 2$ onwards. The discrimination is very good for $\tau = 2$ to 9 for 20,000 data points and as the data size reducing the discrimination capability decreased. A data segment of length 4000 is an optimum choice to have a clear discrimination at $\tau = 4$ to 6. Beyond this value, if the data size is reduced the discrimination power of MSE will be lost. In Fig.4., MSE analysis of CHF group is compared with elderly healthy subjects of age 70 years and above. It is clear that the MSE method could not resolve the groups. The EMD based MSE analysis is shown in Fig.6. An interesting result is found in the circled portion of Fig.6. The entropy value of the normal group is more than the CHF group in the first scale (IMF1) and the entropy value of the CHF group is more than the normal in second scale (IMF2). This crossover of entropy values for the first two IMFs gave an excellent discrimination of CHF and Normal groups, irrespective of age. The results are shown in Fig.7. As we are going from the first IMF to the second IMF, the entropy is increased for the CHF group and contrastingly it decreased for the Normal group. From Fig.7. it is obvious that all the ages of healthy people have a negative slope indicating a decrease in entropy from IMF1 to IMF2 while the CHF patients have a positive slope indicating an increase in entropy from IMF1 to IMF2. The second coarse grained series is taken as IMF2+IMF3 instead of just IMF2 and is discussed in the next section. The slopes of all the lines in Fig.7. corresponding to Normal dataset, CHF dataset, Old healthy dataset and Young healthy dataset are given in Fig.8. There is 100 % accuracy found in distinguishing the CHF patients from normal subjects of young and aged group.

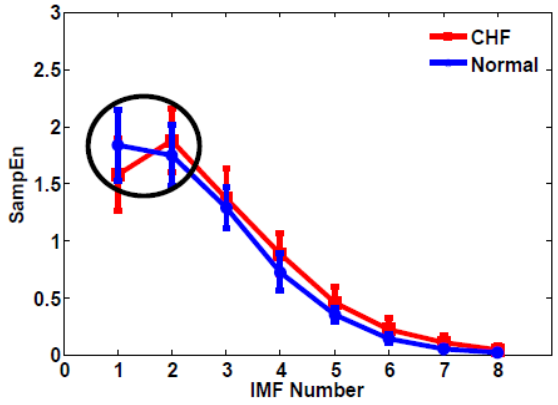

Fig.6. EMD based MSE analysis on BIDMC CHF dataset (n=15) and MIT/BIH normal dataset (n=18) for a data length of 500 samples.

4. Discussion

In this paper we have presented EMD based MSE analysis to discriminate CHF patients from young, middle aged and elderly healthy population. We have shown that the MSE analysis of Costa et al. [10] can be applied to short-term time series of length about 4000 data points to discriminate between the CHF and Normal group consisting of only young and middle aged. It is also observed that as the data size is reduced the discrimination power of MSE decreases and it cannot resolve the CHF and Normal subjects for a data size of 2000 and below. The separating capability is observed to be high for τ values of 4, 5 and 6. We have found that the MSE could not discriminate the CHF from

elderly healthy subjects of age 70 years and above (Fig.4.). Wessel [32], Thuraisingham [33] and Huang XiaoLin [30] have also reported that the CHF patients and elder subjects cannot be discriminated using the MSE analysis.

To be able to reduce the data size to a smaller interval of 10 minutes (around 500 RR intervals) and effectively separate the old people from CHF group, we have successfully introduced EMD into the MSE analysis. Coarse graining procedure of MSE analysis is replaced with EMD to divide the original RR interval time series into different intrinsic mode functions. Each IMF is a scaled component of the original signal and MSE can be applied to all the IMFs. This reduces the number of scales to be considered and each IMF will have the same size of the original signal. For a simple MSE analysis, the 20th scale component will consist of 1000 data points for a signal of 20,000 data points whereas a 1000 data point signal's last IMF (coarsely grained) or first IMF (fine grained) will have the same length of 1000 data points which leads to an accurate calculation of *SampEn*. Isler and Kuntalp also studied the short term heart rate variability to discriminate the CHF patients from normal subjects. Their study involved many features of heart rate variability which makes complex feature selection and classification algorithms necessary to discriminate the people [21]. This study is the first of its kind to discriminate elderly people from CHF patients. We have found that, as we go from the first IMF to the second IMF, entropy increased for the CHF group and it also decreased for the Normal group. From Fig.7. it is obvious that all the ages of healthy people have a negative slope indicating a decrease in entropy from IMF1 to IMF2 while the CHF patients have a positive slope indicating an increase in entropy from IMF1 to IMF2. The second coarse grained series is taken as IMF2 +IMF3 instead of just IMF2 due to a striking agreement found by E.P. Souza Neto et al. [34] between the LF and HF structure of the signal and the first three IMFs. E.P. Souza Neto et al. [34] showed that HF component of RR intervals in time frequency domain is identified as IMF1 of the EMD and LF component of RR intervals in time frequency domain is identified as IMF2+IMF3 of the EMD. Now it has become possible to separate out the LF and HF components and process them independently. From Fig.7. it implies that the entropy in LF component is more than the entropy in HF component for the CHF group and the entropy in HF component is more than the entropy in LF component for the Normal group including elderly people. It is widely accepted that heart failure patients had high sympathetic and low parasympathetic outflows and healthy subjects had low sympathetic and high parasympathetic outflows [35]. Most of the studies attribute LF component of HRV to sympathetic activity and HF to parasympathetic activity. This may be a reason for what we observed in Fig.7. The slope of the line joining the *SampEn* value of scale 1 series (IMF1) and *SampEn* value of scale 2 series (IMF2+IMF3) is found to be an excellent discriminator of CHF and healthy subjects, as shown in Fig.8. The result can be interpreted just as *'Positive slope'* or *'Negative slope'*. *Positive slope* indicates CHF, *Negative slope* indicates Normal.

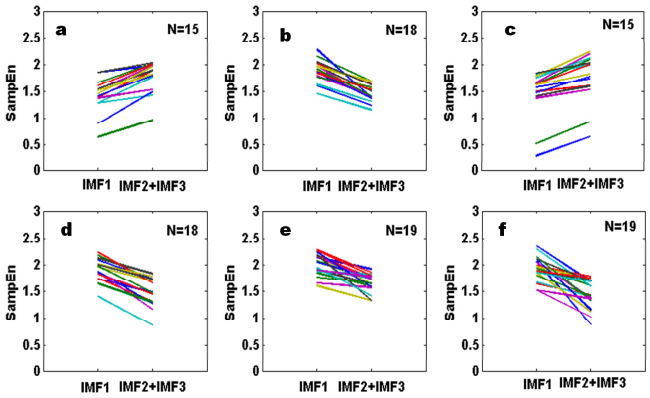

Fig.7. Entropy analysis for two scales (scale1: IMF1, scale2: (IMF2+IMF3)) on a) BIDMC CHF dataset for data length of 1000 samples b) MIT/BIH normal dataset for data length of 1000 samples c) BIDMC CHF dataset for data length of 500 samples d) MIT/BIH normal dataset for data length of 500 samples e) Young healthy dataset of FANATASIA dataset for data length of 500 samples f) Elderly healthy dataset of FANATASIA dataset for data length of 500 samples.

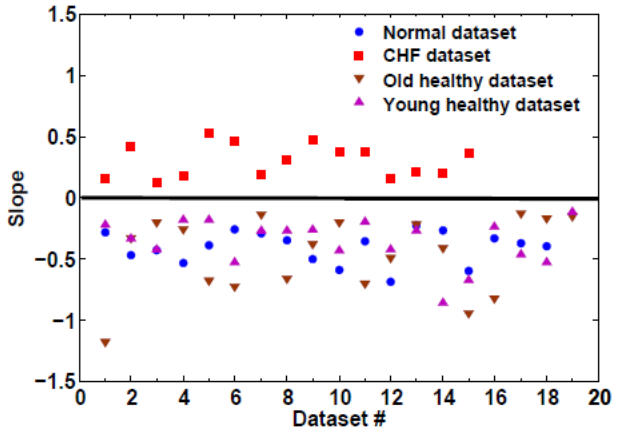

Fig.8. The slope values of all the lines in Fig.7., as a measure of discrimination of CHF patients from normal.

7. Conclusion

Modified MSE analysis is carried out successfully on the HRV signals pertaining to the datasets of normal subjects, CHF patients, and young healthy and old healthy subjects taken from the Physiobank website. We have suggested an easy to interpret single measure to distinguish CHF patients from healthy people. This study finds a way to diagnose CHF especially while screening large populations by using short-term data. The HRV data of size 500 samples is sufficient for this method, which corresponds to only a 10 minute ECG recording. Further, we are working on developing a standalone system using a Photoplethysmographic signal to derive HRV and identify CHF based on this modified method.

REFERENCES

[1] Lahiri, M.K., Kannankeril, P.J., Goldberger, J.J. (2008). Assessment of autonomic function in cardiovascular disease. *Journal of the American College of Cardiology*, 51, 1725-1733.

[2] Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards of measurements, physiological interpretation, and clinical use. *European Heart Journal*, 17, 354-381.

[3] Gao, J., Hu, J., Tung, W.W., Blasch, E. (2012). Multiscale analysis of biological data by scale-dependent Lyapunov exponent. *Frontiers in Physiology*, 2, 1-13.

[4] Hu, J., Gao, J., Tung, W.W. (2009). Characterizing heart rate variability by scale dependent Lyapunov exponent. *Chaos*, 19, 028506.

[5] Ivanov, P.Ch., Amaral, L.A.N., Goldberger, A.L., Havlin, S., Rosenblum, M.G., Struzik, Z.R., Stanley H.E. (1999). Multifractality in human heart beat dynamics. *Nature*, 39, 461-465.

[6] Meyer, M., Stiedl, O. (2003). Self–affine fractal variability of human heart beat interval dynamics in health and disease. *European Journal of Applied Physiology*, 90, 305-316.

[7] Sassi, R., Signorini, M.G., Cerutti, S. (2009). Multifractality and heart rate variability. *Chaos*, 19, 028507.

[8] Gao, J., Hu, J., Tung, W.W. (2012). Entropy measures for biological signal analyses. *Nonlinear Dyn*, 68, 431-434.

[9] Richman, J.S., Moorman, J.R., (2000). Physiological time series analysis using approximate entropy and sample entropy. *American Journal of Physiology - Heart and Circulatory Physiology*, 278, H2039-H2049.

[10] Costa, M., Goldberger, A.L., Peng, C.K. (2002.) Multiscale entropy analysis of physiological time series. *Physical Review Letters*, 89 (6), 068102.

[11] Costa, M., Goldberger, A.L., Peng, C.K. (2005). Multiscale entropy analysis of biological signals. *Physical Review E*, 71, 021906.

[12] Ponikowski, P., Anker, S.D., Chau, T.P., Szelemei, R., Piepoli, M., Adamopoulos, S., Webb-Peploe, K., Harrington, D., Banasiak, W., Wrabec, K., Coats, A.J. (1997). Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dialeted cardiomyopathy. *American Journal of Cardiology*, 79, 1645-1650.

[13] Arbolishvili, G.N., Mareev, V.Y., Orlova, Y.A., Belenkov, Y.N. (2006). Heart rate variability in chronic heart failure and its role in prognosis of the disease. *Kardiologiia*, 46 (12), 4-11.

[14] Ho Y.L., Lin, C., Lin, Y.H., Lo, M.T. (2011.) The prognostic value of non-linear analysis of heart rate variability in patients with congestive heart failure: A pilot study of multiscale entropy. *PLoS ONE*, 6 (4), e18699.

[15] Kikuya, M., Ohkubo, T., Metoki, H., Asayama, K., Hara, A., Obera, T., Inoue, R., Hoshi, H., Hashimoto, J., Totsune, K., Satoh, H., Imai, Y. (2008). Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: The Ohasama Study. *Hypertension*, 52 (6), 1045-1050.

[16] Rovere, M.T.L., Pinna, G.D., Maestri, R., Mortara, S., Capomolla, A., Febo, O., Ferrai, R., Franchini, M., Gnemmi, M., Opasich, C., Riccardi, P.G., Travesri, E., Cobelli, E. (2003). Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*, 107 (4), 565-570.

[17] Lucreziotti, S., Gavazzi, A., Scelsi, L., Inserra, C., Klersy, C., Campana, C., Ghio, S., Vanoliand, E., Tavazzi, L. (2000). Five-minute recording of heart rate variability in severe chronic heart failure: Correlates with right ventricular function and prognostic implications. *American Heart Journal*, 139 (6), 1088-1095.

[18] Villegas, J.F.R., Espinosa, E.L., Moreno, D.F.R., Echeverry, P.C.C., Rodriguez, W.A. (2011). Heart rate variability dynamics for the prognosis of cardiovascular risk. *PLoS ONE*, 6 (2), e17060.

[19] Smilde, T.D.J, Veldhuisen, D.J.V., Berg, M.P.V.D. (2009.) Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clinical Research in Cardiology*, 98 (4), 233-239.

[20] Isler, Y., Kuntalp, M. (2007). Combining classical HRV indices with wavelet entropy measures improves to performance in diagnosing congestive heart failure. *Computers in Biology and Medicine*, 37, 1502-1510.

[21] Isler, Y., Kuntalp, M. (2010). Heart rate normalization in the analysis of heart rate variability in congestive heart failure. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 224 (3), 453-463.

[22] Pecchia, L., Melillo, P., Sansone, M., Bracale, M. (2011). Discrimination power of short-term heart rate variability measures for CHF assessment. *IEEE Transactions on Information Technology in Biomedicine*, 15 (1), 40-46.

[23] Yu, S.N., Lee, M.Y. (2012). Conditional mutual information based selection for congestive heart failure recognition using heart rate variability. *Computer Methods and Programs in Biomedicine*, 108, 299-309.

[24] Yu, S.N., Lee, M.Y. (2012). Bispectral analysis and genetic algorithm for congestive heart failure recognition based on heart rate variability. *Computers in Biology and Medicine*, 42, 816-825.

[25] Hu, J., Gao, J., Tung, W.W., Cao, Y. (2010). Multiscale analysis of heart rate variability: A comparison of different complexity measures. *Annals of Biomedical Engineering*, 38, 854-864.

[26] Goldberger, A.L., Amaral, L.A.N., Glass, L., Hausdorff, J.M., Ivanov, P.Ch., Mark, R.G., Mietus, J.E., Moody, G.B., Peng, C.K. Stanley, H.E., (2000). PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals. *Circulation*, 101 (23), e215-e220.

[27] Baim, D.S., Colucci, W.S., Monrad, E.S., Smith, H.S., Wright, R.F., Lanoue, A., Gauthier, D.F., Ransil, B.J., Grossman, W., Braunwald, E. (1986). Survival of patients with severe congestive heart failure treated with oral milrinone. *Journal of the American College of Cardiology*, 7 (3), 661-670.

[28] Iyengar, N., Peng, C.K., Morin, R., Goldberger, A.L., Lipsitz, L.A. (1996). Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *American Journal of Physiology*, 271, 1078-1084.

[29] Angelini, L., Maestri, R., Marinazzo, D., Nitti, L., Pellicoro, M., Pinna, G.D., Stramaglia, S., Tupputi, S.A. (2007). Multiscale analysis of short term heart beat interval, arterial blood pressure and instantaneous lung volume time series. *Artificial Intelligence in Medicine*, 41, 237-250.

[30] Huang, X.L., Bao, N.X., Long, W.X. (2009). Multiscale analysis of heart beat interval increment series and its clinical significance. *Chinese Science Bulletin*, 54, 3784-3789.

[31] Huang, N.E., Shen, Z., Long, S.R., Wu, M.C., Shih, H.H., Zheng, Q., Tung, C.C., Liu, H.H. (1998). The Empirical mode decomposition and Hilbert spectrum for nonlinear and nonstationary time series analysis. *Proceedings of the Royal Society A*, 454, 903-995.

[32] Wessel, N., Schirdewin, A., Kurths, J. (2003). Intermittently decreased beat to beat variability in congestive heart failure. *Physical Review Letters*, 91, 11980.

[33] Thuraisingham, R.A., Gottwald, G.A. (2006). On the entropy analysis of physiological data. *Physica A*, 366, 323-332.

[34] Neto, E.P.S., Custaud, M.A., Cejka, J.C., Abry, P., Frutoso, J., Gharib, C., Flandrin, P. (2004). Assessment of cardiovascular autonomic control by empirical mode decomposition. *Methods of Information in Medicine*, 43, 60-65.

[35] Porter, T.R., Eckberg, D.L., Fritsch, J.M., Rea, R.F., Beightol, L.A., Schmedtje Jr, J.F., Mohanty, P.K. (1990). Autonomic Pathophysiology in heart failure patients. *The Journal of Clinical Investigation*, 85, 1362-1371.

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