Journal of Engineering Science and Technology
Vol. 10, No. 1 (2015) 12 - 24

A RISK STRATIFICATION SYSTEM TO DISCRIMINATE CONGESTIVE HEART FAILURE PATIENTS USING MULTI-VALUED COARSE-GRAINING LEMPEL-ZIV COMPLEXITY

CHANDRAKAR KAMATH

Electronics and Communication Department, Manipal Institute of Technology,
Manipal, 576104, India
E-mail: chandrakar.kamath@gmail.com

Abstract

A risk stratification system to discriminate congestive heart failure (CHF) subjects from healthy subjects is proposed. All the previous research to detect CHF patients using Lempel-Ziv complexity measure had used binary coarse-graining (BLZC). In this work, we show that employing multi-valued coarse-graining Lempel-Ziv complexity (MLZC) improves the performance of classification. This finding is confirmed using receiver operating characteristic (ROC) plots. Compared to BLZC, MLZC with six partitions showed higher diagnostic parameters. The risk stratification system proposed in this paper will be a valuable asset to the clinician in the separation of CHF patients from the healthy group.

Keywords: Congestive heart failure, Multi-valued Lempel-Ziv complexity.

1. Introduction

Congestive heart failure (CHF) remains to be one of the major cardiovascular disorders in the world [1]. Despite recent advances in the understanding of the pathophysiology and management of CHF, the mortality rate has remained high [2]. Heart rate (HR) is the reciprocal of the time interval between two consecutive R peaks in the ECG signal. The fluctuation of the HR from its mean value constitutes heart rate variability (HRV). Several studies have shown that the disturbed HRV is a marker for the presence of cardiac diseases, including heart failure, and the degree of HRV impairment is associated with the severity of the disease [3-5]. Hence HRV has become a popular noninvasive tool in the estimation of cardiac health. As an implication, the development of new methods and measures of mortality risk in CHF, including sudden cardiac death, using HRV

Nomenclatures

$C(N)$	Normalized LZC
$c(N)$	Number of subsequences
d	Number of partitions
i, j	Indices
S_i	Symbolic sequence
x_i	Discrete time series, V
x_{max}	Maximum value of the series x_i, V
x_{mean}	Average of the series x_i, V
x_{min}	Minimum value of the series x_i, V
y_i	Set of unique symbols

is still a major challenge in contemporary cardiology. Conventional linear HRV analyses, including time and frequency domain analyses, have been used as prognostic factors for CHF [6,7]. However, ever since HRV has been found to exhibit complex behavior originating from nonlinear processes and usually with nonstationary properties, the paradigm has shifted to nonlinear dynamics, fractals and chaos theory [8,9].

Quantifying the complexity of HRV series in health and disease has been the focus of considerable attention. Such quantifiers have the potential to assess the dynamical models of biologic control systems as well as bedside diagnostics. A wide class of disease states degrades the physiologic information content thereby bringing down the adaptive capability of the subject. Loss of complexity, therefore, has been proposed as a generic feature of pathologic dynamics [10]. Further, the HR time series has been found to be more complex in healthy subjects than in CHF patients [11]. Several measures of complexity are available for analysis in practice, like approximate entropy, sample entropy, Lempel-Ziv complexity (LZC), correlation dimension and Lyapunov exponent.

In this study we examine the complexity of HRV series in normal and CHF subjects using two variants of LZC and use them in risk stratification of CHF patients. LZC is a non-parametric measure of complexity in a one-dimensional signal related to the number of distinct substrings and the rate of their recurrence. The prime advantages of LZC are: (1) it does not require any parameters for computation; (2) it is easy to implement and computationally very fast to measure the complexity of a signal; (3) it does not require long data segments for its computation; (4) normalized LZC is almost invariant with sequence length; (5) it can capture temporal structure of a sequence; (6) it is model-independent, i.e., only those differences between activity patterns that make a difference to the underlying system itself are accounted, no matter whether the system is dominated by deterministic chaos or stochastic processes [12].

For these reasons LZC may be a better nonlinear method to estimate the complexity of biomedical signals. In the literature the LZC measure and its variants [13] have been extensively used to recognize and quantify irregularity and deterministic complexity in signals [12], [14,15]. In specific, this nonlinear method has been applied to detect lethal cardiac arrhythmias [16], to detect the onset of the epileptic seizures [17-20], to assess EEG background activity in Alzheimer's and schizophrenia patients [21,22], and in estimating the depth of

anaesthesia [12]. LZC is based on a coarse-graining measure of the measurements. That is the range of original measurements is partitioned into a finite number of regions and each region is associated with a specific symbolic value so that each measurement is uniquely mapped to a particular symbol depending on the region into which it falls. A general rule of thumb is that the partitions must be such that the individual occurrence of each symbol is equiprobable with all other symbols or the measurement range covered by each region is equal. This is done to bring out ready differences between random and non-random symbol sequences.

The transformations into symbols have to be chosen context dependent. For this reason, we use complexity measures on the basis of such context-dependent transformations, which have a close connection to physiological phenomena and are relatively easy to interpret. This way the study of dynamics simplifies to the description of symbol sequences. Some detailed information is lost in the process but the coarse and robust properties of the dynamic behavior are preserved and can be analysed [23]. Unfortunately, most of the previous studies on application of LZC have assumed that a binary conversion (L=2) is enough to study the dynamic complexity of a system and accordingly the signal is transformed into a pattern of only two symbols (0 and 1) [21]. The corresponding LZC is designated binary LZC (BLZC). The usage of BLZC, in general, has the following drawback: the low amplitude intervals present in the signal will influence the number of distinct patterns severely, even though irrelevant to the actual information in the signal. To reduce the ill-effects of low amplitude intervals, we recommend a multi-level symbolizing procedure. Hypothesizing that other conversions with more symbols could keep more information from the signal leading to better results, we investigated the effect of multi-valued coarse-graining LZC (MLZC) on the risk stratification of CHF subjects in this study (with L=4 and L=6). Comparing the performance of BLZC and MLZCs we find that MLZCs outperform BLZC.

2. Methods and Materials

2.1. HR database

The interbeat (R-R) interval or HR database used in this study is obtained from normal sinus rhythm (NSR database-nsrdb) and congestive heart failure (CHF database-chf2db) database available at htpp://www.physionet.org [24]. The work involved beat annotation files of long term ECG records of 52 subjects including 24 women (aged 56–73 years) and 28 men (aged 28.5–76 years) from NSR database and beat annotation files of long term ECG records of 29 subjects (aged 34–79 years) from CHF database (NYHA classes I, II, and III). The sampling frequency for both normal sinus rhythm and CHF data is F_s=128 Hz. The beat annotations have been obtained by automated analysis with careful manual review and correction by the experts.

A rhythmic pattern of the heart rate may be destroyed by the presence of non-sinus beats and artifacts which usually appear very early or very late. We preprocess the R-R interval time series of both the normal and CHF I, II, and III groups to remove such potential artifacts, trends, ectopic beats and post-ectopic compensatory pauses. We use annotation filter combined with square filter and a

filter to remove haemo-dynamics for certain types of beats [25-27]. For HRV analysis we use normal beats only as annotated in the PhysioNet database resource. On an average about 10-12% of the R-R intervals are eliminated during R-R interval rejection operation.

2.2. Multi-valued coarse-graining Lempel-Ziv complexity

The Lempel-Ziv complexity (LZC) algorithm was proposed by Lempel and Ziv to evaluate the randomness of finite sequences [13]. It is rather a simple-to-compute nonparametric measure of complexity suitable for finite length one-dimensional signals related to the number of distinct substrings and the rate of their recurrence along the given sequence. Larger values of LZC imply higher complexity data. Since LZC analyses finite symbol-sequences it is essential that the given signal must first be coarse-grained, i.e. the signal to be analysed is transformed into a sequence whose elements are only a few symbols. The most commonly used computation of LZC is based on binary sequence. We hypothesize that the binary sequence cannot well characterize HRV signal and may lose some important information in the signal. As an implication we present in this study, a multi-valued coarse-graining LZC. Since there is a need to compare the performance of LZC based on coarse-graining used, in the following sections we discuss both binary and multi-valued methods.

2.2.1. Binary coarse-graining method

This is the simplest possible coarse-graining involving the division of data range into two partitions (binary partition with L=2, L being the number of partitions) [28]. Those data which are above a cut-off value (usually, either mean or median) are assigned a symbolic value of '1', while those below the cut-off value are assigned a symbolic value of '0'. In case the cut-off value is chosen to be equal to the mean of the data, x_{mean}, the time series x_i is transformed into the symbolic sequence S_i , where $S_i \in \{0, 1\}$, as given below.

$$S_i = \begin{cases} 1 & \text{if } x_i \geq x_{mean} \\ 0 & \text{if } x_i < x_{mean} \end{cases} \quad (1)$$

The Lempel-Ziv algorithm is then applied on the symbolic sequence, S_i. This binary string is scanned from left to right and a complexity counter $c(N)$ is incremented by one unit every time a new subsequence pattern is encountered in the scanning process, and the immediate next symbol is regarded as the beginning of the next subsequence pattern. The corresponding LZC is called binary LZC (BLZC).

2.2.2. Multi-valued coarse-graining method

As hypothesized above the binary coarse-graining method may miss significant information on dynamical systems and hence we employ multi-valued coarse-graining method which is explained below [28].

Let x_i represent the discrete time series with x_{max} and x_{min} as maximum and minimum values, respectively. Then with L (L>2) representing the number of partitions for multi-valued coarse-graining we have,

$$d = (x_{max} - x_{min})/L \quad (2)$$

Let y_j (j=1, 2, …, L) represent the set of unique symbols with each y_j corresponding to a particular partition. The time series x_i is then transformed into the symbolic sequence S_i , where $S_i \in \{y_1, y_2, \ldots, y_L\}$, as given below.

$$S_i = \begin{cases} y_j & \text{for } x_{\min} + (j-1)d \le x_{\min} + jd, (j = 1,2,.....,L) \\ y_L = x_{\max} \end{cases} \quad (3)$$

The Lempel-Ziv algorithm is then applied on the symbolic sequence, S_i. This multi-valued string is scanned from left to right and a complexity counter *c(N)* is incremented by one unit every time a new subsequence pattern is encountered in the scanning process, and the immediate next symbol is regarded as the beginning of the next subsequence pattern. The resulting LZC is designated as multi-valued LZC (MLZC).

2.2.3. Lempel-Ziv complexity

Once the symbolic string is ready the LZC can be estimated using the following algorithm [13]:

1) Let *P* denote the original string sequence, i.e., $P= \{s_1, s_2, s_3, \ldots\}$, with s_i defined as in Eq. (1). This sequence can be parsed to arrive at distinct patterns. Let the string *P* be divided into substrings *P(i, j)* which start at location i (initialized to 1), end at the location j (initialized to 2); that is to say, for $i \le j$, *P(i, j) = s(i) ... s(j)* and for $i > j$, *P(i, j)* = Φ, a null set. Let *V(P)* represent the set of substrings (i.e., the set of distinct patterns) in the sequence *P*, including the null set.

2) The parsing procedure involves a left-to-right scan of the sequence *P*. A substring *P(i, j)* is compared with *V(P(1, j-1))*.
   a. If *P(i, j)* happens to be a member of *V(P(1, j-1))* or in other words, *P(i, j)* $\in$ *V(P(1, j-1))*, then *P(i, j)* and *V(P(1, j-1))* are updated to *P(i, j+1)* and *V(P(1, j))*, respectively.
   b. b. If the substring is not present, then *s(j)* is marked to point to the end of a new distinct pattern. *P(i, j)* and *V(P(1, j-1))* are updated to *P(i+1, j+1)* and *V(P(1, j)) = V(P(1, j-1))* U *P(i, j)*, respectively, where U represents union of left and right strings of the operator.

3) The procedure continues until j = N, where N is the length of the binary/multi-valued coarse-grained sequence, *P*.

Let *c(N)* denotes the number of distinct patterns after parsing the coarse-grained sequence, which obviously corresponds to measure of complexity. For example, consider a binary coarse-grained sequence, P = {1, 0, 1, 1, 1, 0, 1, 0} will be parsed as a sequence = {1.0.11.10.10}, where the '.' is employed to separate the distinct patterns. In this example, *c(N)* = 4. Figure 1 illustrates the parsing procedure for the binary/multi-valued coarse-grained sequence of the R-R interval time series.

To arrive at a measure of complexity independent of sequence length, $c(N)$ must be normalized. If the length of the sequence is n and the number of different symbols is α, it has been shown that the upper bound of $c(N)$ is [29]

$$c(N) < N / ((1-\epsilon_N)\log_\alpha(N)) \quad (4)$$

where ε_N is a small quantity and $\varepsilon_N \to 0$ ($N \to \infty$). In general, $N/\log_\alpha(N)$ is the upper limit of $c(N)$, i.e.,

$$\lim_{N\to\infty} c(N) = b(N) = N / \log_\alpha(N) \quad (5)$$

For a binary conversion $\alpha=2$, $b(N)=N/\log_2(N)$ and the resulting LZC is BLZC. For a multi-valued conversion $\alpha=L$, $b(N)=N/\log_L(N)$ and the resulting LZC gives MLZC.

$c(N)$ can be normalized by $b(N)$ as

$$C(N) = c(N) / b(N) \quad (6)$$

$C(N)$, the normalized LZC, reflects the arising rate of new patterns along with the sequence and thus captures the temporal structure of the sequence. A larger value of LZC means that the chance of generating a new pattern is greater, so the sequence is more complex, and vice versa [21]. In this work we evaluate the evolution of new patterns in HR time series in healthy subjects and in CHF patients of I, II, and III groups.

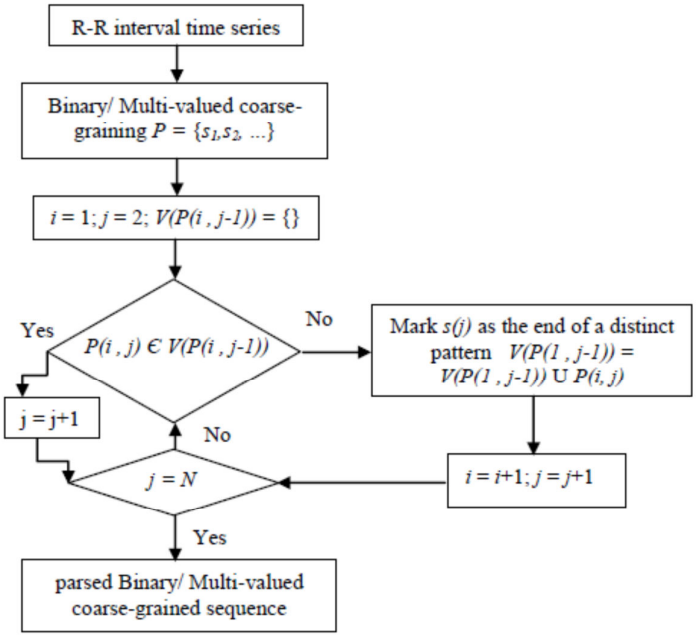

Fig. 1. Flow chart to show the computation of parsed Binary/ Multi-valued coarse-grained sequence (U denotes the union of two strings).

2.3. Statistical analysis

Student's *t*-tests are used to evaluate the statistical significance of the BLZC and MLZC values (with L=4 and L=6) of HR time series in healthy subjects and in CHF patients. Parameters are regarded as statistically significant if $p < 0.01$. If significant differences between groups are found, then the diagnostic ability of the nonlinear analysis method to discriminate between HR time series in healthy group and CHF I, II, and III groups is evaluated using receiver operating characteristic (ROC) plots in terms of area under ROC (AROC). ROC plots are used to gauge the predictive ability of a classifier over a wide range of values [30]. A threshold value is applied such that a feature value below this threshold will be assigned one category while a feature value above the threshold will be assigned other category. ROC curves are obtained by plotting sensitivity values (that represent the proportion of the features of category-1 and test positive) along the y axis against the corresponding (1-specificity) values (which represent the proportion of the correctly identified features of the category-2) for all the available cut-off points along the x axis. Accuracy is a related parameter that quantifies the total number of features (both categories 1 and 2) precisely classified. The AROC measures this discrimination, that is, the ability of the test to correctly classify into categories 1 and 2, and is regarded as an index of diagnostic accuracy. The optimum threshold is the cut-off point in which the highest accuracy (minimal false negative and false positive results) is obtained. This can be determined from the ROC curve as the closet value to the left top point (corresponding to 100% sensitivity and 100% specificity). An AROC value of 0.5 indicates that the test results are better than those obtained by chance, where as a value of 1.0 indicates a perfectly sensitive and specific test. A rough guide to classify the precision of a diagnostic test based on AROC is as follows: If the AROC is between 0.9 and 1.0, then the results are treated to be excellent; If the AROC is between 0.8 and 0.89, then the results are treated to be good; the results are fair for values between 0.7 and 0.79; the results are poor for values between 0.6 and 0.69; If the AROC is between 0.5 and 0.59, then the outcome is treated to be bad.

3. Results and Discussion

We evaluated the ability of the LZC to discriminate healthy and CHF I, II, and III groups with binary coarse-graining (L=2) and multi-valued coarse-graining (L=4 and L=6) methods. We averaged the respective LZC values for each method in all the groups. The results of statistical analysis for healthy and CHF I, II, and III groups with binary and multi-valued coarse-graining methods are tabulated in Table 1. All the values are expressed as mean ± standard deviation. The results of the Kruskal-Wallis test for healthy and CHF I, II, and III groups for different values of L are tabulated in Table 2. A result is significant if the corresponding p-value is less than 0.05. It is found that the binary coarse-graining (L=2) method is statistically not significant while the multi-valued coarse-graining (L=4 and L=6) methods are statistically significant. This implies that for some applications binary coarse-graining may not be sufficient to determine the complexity of a signal. Moreover, the results form Table 1 show that for $L > 2$, CHF patients have significantly lower LZC values compared to normal subjects, irrespective of the method of coarse-graining. This implies that the HRV of CHF patients is more regular and less complex than those of normal subjects. Of course, these findings are in agreement

with the earlier studies [19,20]. In other words, the chance of generating new patterns is greater in the healthy subjects compared to CHF patients.

Table 1. Average BLZC and MLZC values of the HRV time series for healthy and CHF groups. All values are expressed as mean ± SD.

L	Healthy	CHF-I	CHF-II	CHF-III
2	0.4426±0.0675	0.4907±0.1147	0.5109±0.0998	0.3821±0.0876
4	0.3938±0.0548	0.2318±1177	0.2081±0.0933	0.1858±0.0673
6	0.4295±0.0392	0.2496±0.1019	0.2242±0.0774	0.199±0.0653

Table 2. Descriptive results of the Kruskal-Wallis test of the HRV time series for healthy and CHF groups for different values of *L*.

L	Chi-sq	*p*-value
2	0.84	0.8409
4	27.54	4.53×10^{-06}
6	34.63	1.46×10^{-07}

The box plots for LZC values in healthy and CHF groups with multi-valued coarse-graining method (MLZC) with $L = 4$, and $L = 6$, are shown in Figs. 2(a) and 3(a), respectively. The box plots provide a graphical visual summary of the data analysed. From the plots in Fig. 2(a) it is clear that the boxes for healthy and CHF III groups do not overlap, while the boxes for healthy and CHF I, II groups overlap. This indicates that $L = 4$ can readily separate healthy and CHF III subjects, but not lower severity CHF subjects. But, from the plots in Fig. 3(a) it is clear that the boxes for healthy and none of the CHF groups overlap. In other words, $L = 6$ can readily separate healthy and CHF subjects, irrespective of the severity of the disease. It is to be noted that in either method the variability/spread of LZC values in CHF group is decreased compared to the corresponding variability of LZC values in healthy group.

Finally, we compared the diagnostic performance of MLZC methods with $L = 4$ and $L = 6$ using ROC plots. The respective ROC curves are shown in Figs. 2(b) and 3(b). The AROCs at the cut-off points in the respective cases are shown in Table 3. It is evident that in each case of risk stratification MLZC with $L = 6$, outperforms that with $L = 4$. For example, in MZLC approach with $L = 4$, the AROC = 0.7265 for separation between healthy and CHF I group. This indicates that a randomly selected subject from the healthy group has a LZC value larger than that of a randomly chosen subject from the CHF I group in 72.65% of the time. On the other hand, for MZLC approach with $L = 6$, the AROC = 0.8177 which means that a randomly selected subject from the healthy group has a LZC value larger than that of a randomly chosen subject from the CHF I group in 81.77% of the time. Thus MLZC method with $L = 6$ greatly enhances the performance parameters of the diagnosis test and are tabulated in Table 4. This clearly demonstrates the potential of MLZC in discriminating the CHF patients from the normal subjects.

Table 3. Effect of *L* on AROC in risk stratification of CHF subjects.

Parameter, *L*	Normal vs. CHF I	Normal vs. CHF II	Normal vs. CHF III
4	0.7265	0.8556	0.9101
6	0.8177	0.8797	0.9420

Table 4. Performance parameters of MLZC (L=6) analysis in risk stratification.

Parameter, L	Normal vs. CHF I	Normal vs. CHF II	Normal vs. CHF III
Threshold	0.3839	0.3563	0.3394
AROC	0.8177	0.8797	0.9420
Sensitivity%	90.0	81.8	88.9
Specificity%	73.5	79.4	82.4
Predictivity of Positive test%	50.0	56.3	72.7
Predictivity of Negative test%	96.2	93.1	93.3
Accuracy%	77.3	80.0	84.6

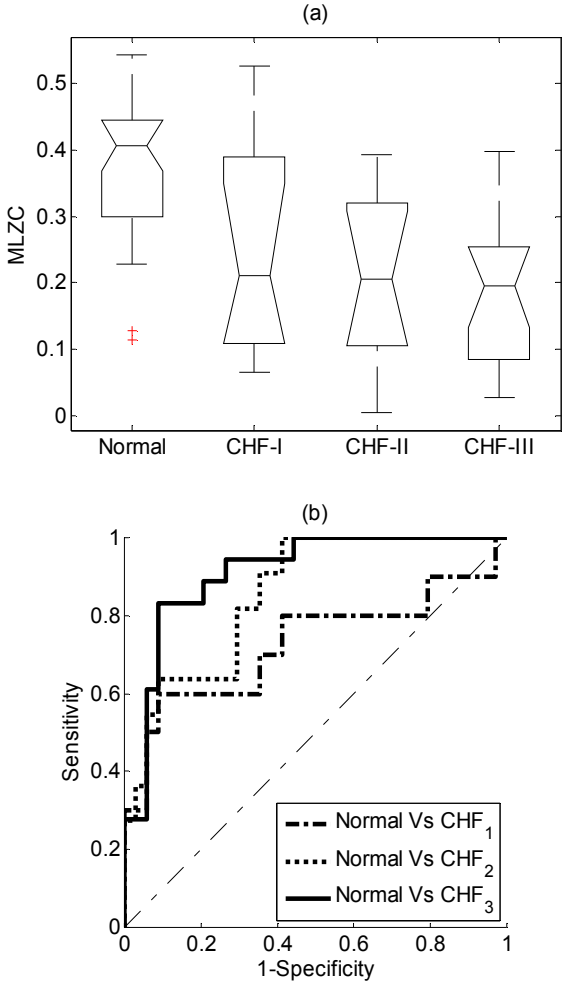

Fig. 2. (a) The distribution of MLZC values using Box-whiskers plots (with outliers) for healthy group and CHF groups with MLZC (L = 4) method and (b) corresponding ROC curves for healthy group and CHF groups.

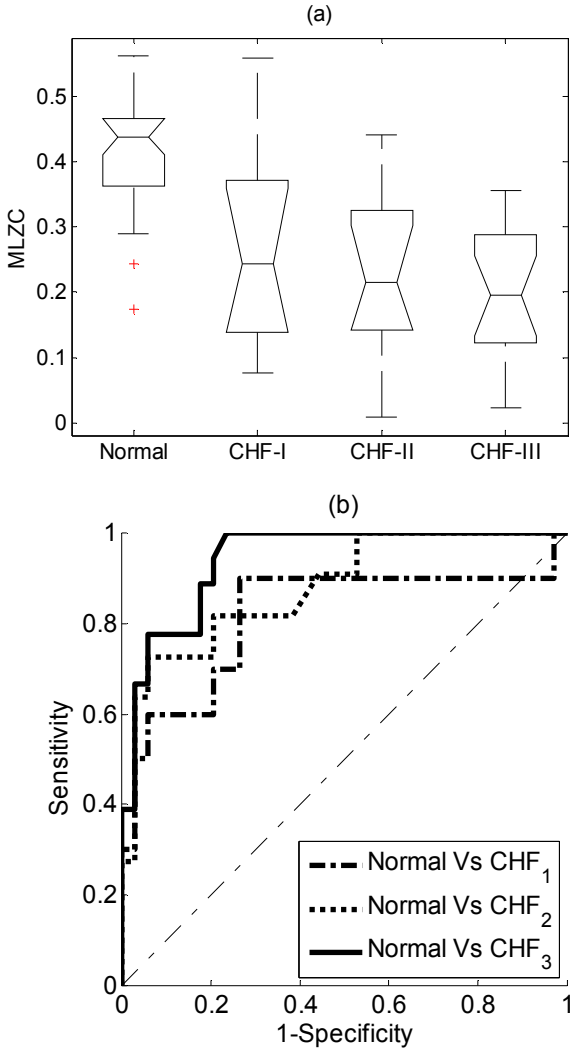

Fig. 3. (a) The distribution of MLZC values using Box-whiskers plots (with outliers) for healthy group and CHF groups with MLZC (L = 6) method and (b) corresponding ROC curves for healthy group and CHF groups.

4. Limitations

The foremost limitation of this study is the small sample size. Although we have reported MLZC to yield a very sensitive measure based on the p-value generated from the t-statistics, factors like high variance, age differences, and slightly differing male-to-female ratios between groups will have an impact on the results when statistical analyses are carried out on small sample sizes. Nevertheless, the results of this study provide sufficient evidence to warrant the execution of larger studies that can provide more statistically robust confirmation of the application of MLZC as a sensitive measure of cardiac health.

5. Conclusion

Since there is no general rule for fixing the number of partitions and the transformation is context dependent, there is a need to experiment to arrive at an optimum number of partitions. In this study it is found that to very well distinguish the healthy from CHF I, II, and III subjects BLZC is not sufficient. Instead, MLZC (with $L = 6$) is necessary. We have found that MLZC greatly enhances sensitivity, specificity, precision, and accuracy of the diagnosis test. This study represents the first step in demonstrating the feasibility of using MLZC for risk stratification in CHF subjects. This risk stratification system will be a valuable tool to the clinician in the discrimination of CHF patients from the healthy group.

References

1. Wang, T.J.; Evans, J.C.; Benjamin, E.J.; Levy, D.; LeRoy, E.C.; and Vasan R.S. (2003). Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation*, 108(8), 977-982.
2. Sandercock G.R.; and Brodie, A.D. (2006). The role of heart rate variability in prognosis for different modes of death in chronic heart failure. *Pacing and Clinical Electrophysiology*, 79(8), 892-904.
3. Saul, J.P.; Arai, Y.; Berger, R.D.; Lilly, L.S.; Colucci, W.S.; Cohen, R.J. (1988). Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *The American Journal of Cardiology*, 61(15), 1292–1299.
4. Casolo, G.; Balli, E.; Taddei, T.; Amuhasi, J.; Gori, C. (1989). Decreased spontaneous heart rate variability in congestive heart failure. *The American Journal of Cardiology*, 64(18), 1162-1167.
5. Szabo, B.M.; Van Veldhuisen, D.J.; Brouwer, J.; Haaksma, J.; Lie, K.I. (1995). Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease. *The American Journal of Cardiology*, 76(10), 713-716.
6. Fauchier, L.; Babuty, D.; Cosnay, P.; Fauchier, J.P. (1999). Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *Journal of the American College of Cardiology*, 33(5), 1203-1207.
7. La Rovere, M.T.; Pinna, G.D.; Maestri, R.; Mortara, A.; Capomolla, S.; Febo, O.; Ferrari, R.; Franchini, M.; Gnemmi, M.; Opasich, C.; Riccardi, P.G.; Traversi, E.; and Cobelli, F. (2003). Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*, 107(4), 565-570.
8. Jagric, T.; Marhl, M.; Stajer, D.; Kocjancic, S.T.; Jagric, T.; Podbregar, M.; and Perc, M. (2007) Irregularity test for very short electrocardiogram (ECG) signals as a method for predicting a successful defibrillation in patients with ventricular fibrillation. *Translational Research*, 149(3), 145-151.
9. Perc, M. (2005). Nonlinear time series analysis of the human electrocardiogram. *European Journal of Physics*, 26(5), 757-768.

10. Pincus, M. (2001). Assessing serial irregularity and its implications for health. *Annals of New York Academy of Science*, 954, 245-267.
11. Doyle, T.L.A.; Dugan, E.L.; Humphries, B.; and Newton, R.U. (2004). Discriminating between elderly and young using a fractal dimension analysis of centre of pressure. *International Journal of Medical Sciences*, 1(1), 11-20.
12. Zhang, X.-S.; Roy, R.J.; Jensen, E.W. (2001). EEG complexity as a measure of depth of anaesthesia for patients. *IEEE Transactions on Biomedical Engineering*, 48(11), 1424-1433.
13. Lempel, A.; and Ziv, J. (1976). On the complexity of finite sequences. *IEEE Transactions on Information Theory*, IT-22(1), 75-81.
14. Nagarajan, R. (2002). Quantifying physiological data with Lempel–Ziv complexity-certain issues. *IEEE Transactions on Biomedical Engineering*, 49(11), 1371-1373.
15. Aboy, M.; Hornero, R.; Abásolo, D.; and Álvarez, D. (2006). Interpretation of the Lempel–Ziv complexity measure in the context of biomedical signal analysis. *IEEE Transactions on Biomedical Engineering*, 53(11), 2282-2288.
16. Chen, S.W. (2007). Complexity-Measure-Based Sequential Hypothesis Testing for Real-Time Detection of Lethal Cardiac Arrhythmias. *EURASIP Journal on Advances in Signal Processing*, Article ID 20957, 8 pages.
17. Akay, M.; Wang, K.; Akay, Y.M.; Dragomir, A.; and Wu. J. (2009). Nonlinear dynamical analysis of carbachol induced hippocampal oscillations in mice. *Acta Pharmacol Sin*, 30 (6), 859-867.
18. Qu, H.; and Gotman, J. (1997). A patient-specific algorithm for the detection of seizure onset in long-term EEG monitoring: Possible use as a warning device. *IEEE Transactions on Biomedical Engineering*, 44(2), 115-122.
19. Radhakrishnan, N.; and Gangadhar, B.N. (1998). Estimating regularity in epileptic seizure time series data - A complexity measure approach. *IEEE Engineering in Medicine and Biology Magazine* , 17(3), 89-94.
20. Hu, J.; Gao J.; and Principe, J. (2006). Analysis of biomedical signals by the Lempel-Ziv complexity: the effect on finite data size. *IEEE Transactions on Biomedical Engineering*, 53(12: Part 2), 2606-2609.
21. Abásolo, D.R.; Hornero, C.; Gómez, M.; and López, G.M. (2006). Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure. *Medical Engineering & Physics*, 28(4), 315-322.
22. Li, Y.; Tong, S.; Liu, D.; Gai, Y.; Wang, X.; Wang, J.; Qiu, Y.; and Zhu, Y. (2008). Abnormal EEG complexity in patients with schizophrenia and depression. *Clin Neurophysiology*, 119(6), 1232-1241.
23. Voss, A.; Kurths, J.; Kleiner, H.J.; Witt, A.; Wessel, N.; Saparin, P.; Osterziel, K.J.; Schurath, R.; and Dietz, R. (1996). The application of methods of nonlinear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovascular Research*, 31(3), 419-433.
24. Goldberger, A.L.; Amaral, L.A.N.; Glass, L.; Hausdorff, J.M.; Ivanov, P.C.; Mark, R.G.; Mietus, J.E.; Moody, G.B.; Peng, C.K.; and Stanley, H.E. (2000). Physiobank, physiotoolkit, and physionet: Components of a new research resource for complex physiologic signals. *Circulation*, 101(23),

e215–e220. Circulation Electronic Pages: http://circ. ahajournals.org/ cgi/content/full/101/23/e215.

25. Thuraisingham, R.A. (2006). Preprocessing R-R interval time series for heart rate variability analysis and estimates of standard deviation of R-R intervals. *Computer Methods and Programs in Biomedicine*, 83(1), 78–82.
26. Piskorski, J.; and Guzik, P. (2005). Filtering Poincaré plots. *Computational methods in science and technology*, 11(1), 39-48.
27. Piskorski, J.; and Guzik, P. (2010). Dynamic decomposition of Poincaré plots for multivariate analysis and visualization of simultaneously recorded physiological time series. *Computational Methods in Science and Technology*, 16(2), 1-6.
28. Zhao, H.; Wang, G.; Xu, C.; and Yu, F. (2011). Voice activity detection method based on multi-valued coarse-graining Lempel-Ziv complexity. *ComSIS*, 8(3), 869-888.
29. Gómez, C.; and Hornero, R. (2010). Entropy and complexity analyses in alzheimer's disease: An MEG study. *The Open Biomedical Engineering Journal*, 4, 223-235.
30. Zweig, M.H.; and Campbell, G. (1993). Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry*, 39(4), 561-577.