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# CLASSIFICATION OF HEART RATE SIGNALS OF HEALTHY AND PATHOLOGICAL SUBJECTS USING THRESHOLD BASED SYMBOLIC ENTROPY

Wajid Aziz,[1] M. Rafique,[2]* I. Ahmad,[3] M. Arif,[4]
Nazneen Habib[5] and M. S. A. Nadeem[1]

[1]Department of Computer Sciences and Information Technology, University of Azad Kashmir 13100, Azad Kashmir, Pakistan
[2]Department of Physics, University of Azad Jammu and Kashmir Muzaffarbad, 13100, Azad Kashmir, Pakistan
[3]Department of Mathematics, University of Azad Jammu and Kashmir Muzaffarbad, 13100, Azad Kashmir, Pakistan
[4]College of Computer and Information System, Al-Abidiyya Building, Um-Alqura University, P.O. Box 715 Makkah, Saudi Arabia
[5]Department of Sociology and Rural Development, University of Azad Jammu and Kashmir Muzaffarbad, 13100, Azad Kashmir, Pakistan

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The dynamical fluctuations of biological signals provide a unique window to construe the underlying mechanism of the biological systems in health and disease. Recent research evidences suggest that a wide class of diseases appear to degrade the biological complexity and adaptive capacity of the system. Heart rate signals are one of the most important biological signals that have widely been investigated during the last two and half decades. Recent studies suggested that heart rate signals fluctuate in a complex manner. Various entropy based complexity analysis measures have been developed for quantifying the valuable information that may be helpful for clinical monitoring and for early intervention. This study is focused on determining HRV dynamics to distinguish healthy subjects from patients with certain cardiac problems using symbolic time series analysis technique. For that purpose, we have employed recently developed threshold based symbolic entropy to cardiac inter-beat interval time series of healthy, congestive heart failure and atrial fibrillation subjects. Normalized Corrected Shannon Entropy (NCSE) was used to quantify the dynamics of heart rate signals by continuously varying threshold values. A rule based classifier was implemented for classification of different groups by selecting threshold values for the optimal separation. The findings indicated that there is reduction in the complexity of pathological subjects as compared to healthy ones at wide range of threshold values. The results also demonstrated that complexity decreased with disease severity.

*Keywords:* HRV analysis – biological signals – complexity – optimal variability

## INTRODUCTION

The temporal fluctuation of complex biological signals such as heart rate, respiratory rate and brain signals manifest dynamic process [18]. Complex dynamics enable a physiological control system to respond to internal and external fluctuations. The

*Corresponding author; e-mail addresses: rafi_722002@yahoo.com; mrafique@gmail.com; mrafique@ajku.edu.pk

changes that occur with aging and disease are associated with the loss of complexity in the dynamics of integrated processes [12]. The complexity analysis of physiological signals originated with the examination of cardiovascular dynamics of elderly and pathological subjects suffering from different cardiovascular diseases.

Heart rate variability (HRV) is an important dynamical variable of the cardiovascular system, which refers to the beat-to-beat alterations in heart rate [19]. It has become a valuable non-invasive tool for describing the role of sympathetic and parasympathetic branches of autonomic nervous system (ANS) in the cardio-circulatory system regulation [19]. Numerous studies have been performed in connection with HRV related cardiac issues. A reduction of HRV has been associated with increased risk of sudden cardiac death in post-infarction patients [1, 19] and risk of development of coronary artery disease in the growth restricted children in later life [3–5].

Kaplan and his coworkers [10] were the pioneers who directly examined the complexity of the heart beat intervals and systolic blood pressure from radial artery in young and elderly subjects in metronome and quiet breathing conditions. The authors found reduction in the system complexity in both metronome and free breathing condition for elderly subjects as compared to healthy young subjects.

Costa and co-authors proposed multiscale entropy (MSE), a novel technique, to measure complexity over multiple scales [6, 7] by quantifying the regularity of the finite length time series using sample entropy [17], a modification of approximate entropy algorithm [15]. They employed MSE method to cardiac inter beat interval time series of healthy and pathological (AF and CHF) subjects. They investigated that for scale one, which is the only scale considered by traditional entropy based algorithms, the entropy of heartbeat time series of healthy subjects was smaller than entropy of time series of AF and CHF subjects. In contrast, for sufficiently large time scale, the entropy of time series of healthy subjects is assigned higher entropy values than time series of both pathological groups. The MSE method focuses on quantifying the information expressed by the physiological dynamics over multiple scales.

Analysis of symbolic sequences generated from biological signals appears to be a valuable tool to consistently characterize the dynamics of biological systems [11, 14, 20]. Kurths et al. (1995) used both static and dynamic transformations to characterize heart rate variability and found that cardiac risk patients exhibit more ordered patterns [11]. Park and Yi (2004) used symbolic entropy to examine the complexity of heartbeat signals at different threshold values [14]. They calculated Corrected Shannon Entropy (CSE) and Corrected Conditional Entropy (CCE) of symbolic sequences extracted from heartbeat time series at various threshold values for classifying healthy and pathological subjects.

In our previous study we have used threshold based symbolic entropy to explore the complex dynamics of stride interval time series of healthy and neurodegenerative disease subjects [2]. NCSE was used to quantify the dynamics of these subjects at different threshold values. The findings revealed that mean value of NCSE for healthy subjects was greater than that of diseased subjects. Decrease in NCSE with advanced disease was also observed [2]. In this study, we have examined the complexity of heartbeat interval time series of healthy and pathological (CHF and AF) subjects. Our

approach focused on quantifying the information expressed by cardiac dynamics at different threshold values by using symbolic entropy and then using this information to implement a rule based classifier for classification of healthy and pathological subjects.

## MATERIALS AND METHODS

The symbolic treatment of the time series involves the transformation of original measurements into temporal patterns consisting of few symbols [11, 20]. In doing so some detailed information is lost but invariant robust dynamics are preserved and can be analyzed. Various data symbolization procedures have been used [2, 11, 20]. In the present study, following procedure was used for transforming the RR interval time series into symbol sequences and for quantifying heart rate dynamics.

Given a RR interval time series $Y = \{Y_i,\ i = 1, \ldots, N\}$. The time series is transformed into symbol sequence $y^{\xi} = \{y_i^{\xi},\ i = 1, \ldots, N\}$ having fixed number of $\xi$ values labeled from zero to $\xi - 1$. The heartbeat time series was transformed into symbol sequences by using quantization level 2 (symbols '0' and '1') and following criterion:

$$y^{\xi} = \begin{cases} 1 & \left|Y_i - \bar{Y}\right| \geq \tau \\ 0 & \left|Y_i - \bar{Y}\right| < \tau \end{cases} \tag{1}$$

Where $\tau$ is the threshold and Y is the mean value of the time series. The symbol sequence is then divided to make word sequence of length L of three or more symbols.

$$\psi_{L,i}^{\xi} = y_i^{\xi},\ y_{i+1}^{\xi}, y_{i+2}^{\xi}, ..., y_{i+L-1}^{\xi} \tag{2}$$

Finally the code series is generated as

$$\omega_{L,i} = y_i^{\xi}\xi^{L-1} + y_{i-1}^{\xi}\xi^{L-2} + y_{i-2}^{\xi}\xi^{L-3} + ... + y_{i-L+1}^{\xi}\xi^{0} \tag{3}$$

For a symbol sequence of length L, number of all possible words is $\xi^L$, where $\xi$ is the quantization level. Shannon entropy of order L is defined as

$$SE(L,\xi) = -\sum p(y_L^{\xi}) \log_2 (p(y_L^{\xi})) \tag{4}$$

The estimate is affected by random error in numbers and also by a systematic error or bias. Eguia et al. (2000) report the leading correction for the entropy [8]. The Corrected Shannon Entropy (CSE) can be obtained as

$$CSE(L,\xi) = SE(L,\xi) + \frac{\omega_R - 1}{2M \ln 2} \tag{5}$$

Where $M$ is the total number of words and is the number of occurring words among the possible words. The value of CSE will be maximum for a certain word length L and quantization level ξ, when all M words occur with uniform distribution in a data series.

$$CSE^{\max}(L,\xi) = -\log_2\left(\frac{1}{M}\right) + \left(\frac{M-1}{2M \ln 2}\right) \tag{6}$$

NCSE is defined as

$$NCSE(L,\xi) = \frac{CSE(L,\xi)}{CSE^{\max}(L,\xi)} \tag{7}$$

We have used the quantization level $\xi = 2$ for data symbolization and word length $L = 3$ for the formation of word code series. All possible word are $2^3 = 8$ (0–7).

The data was not normally distributed and Kruskal–Wallis test, the non-parametric analogue of ANOVA was used for comparing three groups. The significant results of Kruskal–Wallis test reveal that at least one of the samples is different from other samples and does not identify which sample pairs actually differ. For paired comparison, after Kruskal–Wallis test we conducted a series of Wilcoxon Mann–Whitney tests to investigate which groups significantly differ. Bonferroni correction was used to control for inflation of type I error and significance level was adjusted to ($p < 0.05/3 = 0.016$) for interpreting results. In order to elaborate the robustness of the NCSE for classification of different groups, paired comparison using Wilcoxon Mann–Whitney test was reported in the table. The area under receiver operator curve was derived to quantify the classification accuracy between different groups at various threshold values [13].

## *Data sets*

The RR interval time series data sets for analysis were taken from the physionet databases [9]. The fluctuations in the cardiac inter beat interval (RR interval) time series data of normal sinus rhythm (NSR) subject, congestive heart failure (CHF) subjects and Atrial Fibrillation (AF) subjects were studied [9]. The data of NSR subjects was taken from 24-hour holter monitor recordings of 72 subjects consisting of 35 men and 37 female (54 from RR-interval normal sinus rhythm database and 18 from MIT BIH normal sinus rhythm database). The age of the measured group was $54.6 \pm 16.2$ (mean ± SD) range 20–78 years. ECG data was sampled at 128 Hz. Atrial Fibrillation (AF) data was taken from "MIT-BIH Atrial Fibrillation database (afdb)" [9]. The

*Table 1*

Paired sample comparison of 72 NSR, 15 CHF_C and 24 AF subjects using Wilcoxon Mann–Whitney test with Bonferroni correction (0.05/3 = 0.016) for interpreting results

| T (ms) | NCSE percentile | | | Mean ranks of paired groups and level of significance | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25th | 50th | 75th | NSR vs CHF_C | | | NSR vs AF | | | CHF_C vs AF | | |
| | median | | | NSR | CHF_C | Sig. | NSR | AF | Sig. | CHF_C | AF | Sig. |
| 2 | 0.592 | 0.692 | 0.777 | 45.60 | 36.33 | n.s. | 59.43 | 15.71 | *** | 29.53 | 14.04 | *** |
| 4 | 0.594 | 0.694 | 0.778 | 45.31 | 37.70 | n.s. | 59.19 | 16.42 | *** | 29.67 | 13.96 | *** |
| 6 | 0.663 | 0.770 | 0.848 | 37.31 | 76.13 | *** | 48.09 | 49.73 | n.s. | 30.20 | 13.63 | *** |
| 8 | 0.764 | 0.845 | 0.919 | 38.43 | 7073 | *** | 52.76 | 35.71 | ** | 30.00 | 13.75 | *** |
| 10 | 0.883 | 0.945 | 0.979 | 47.59 | 26.77 | ** | 56.13 | 25.63 | *** | 22.40 | 18.50 | n.s. |
| 12 | 0.881 | 0.945 | 0.980 | 47.74 | 26.07 | ** | 55.97 | 26.08 | *** | 21.93 | 18.79 | n.s. |
| 14 | 0.847 | 0.933 | 0.976 | 50.56 | 12.53 | *** | 56.97 | 23.15 | *** | 16.07 | 22.46 | n.s. |
| 16 | 0.810 | 0.908 | 0.969 | 49.79 | 16.20 | *** | 55.08 | 28.75 | *** | 15.53 | 22.89 | ** |
| 18 | 0.710 | 0.812 | 0.929 | 49.03 | 19.83 | *** | 50.49 | 42.52 | n.s | 12.00 | 24.50 | ** |
| 20 | 0.697 | 0.812 | 0.929 | 49.17 | 19.20 | *** | 50.43 | 42.13 | n.s | 12.60 | 24.63 | *** |
| 25 | 0.490 | 0.650 | 0.852 | 48.19 | 23.90 | *** | 45.54 | 57.38 | n.s. | 11.00 | 25.63 | *** |
| 30 | 0.469 | 0.549 | 0.849 | 49.07 | 19.67 | *** | 45.92 | 56.25 | n.s. | 10.60 | 25.88 | *** |
| 35 | 0.386 | 0.429 | 0.777 | 47.53 | 28.53 | * | 42.40 | 66.81 | *** | 10.67 | 25.83 | *** |
| 40 | 0.310 | 0.379 | 0.684 | 46.36 | 32.67 | n.s. | 40.21 | 73.38 | *** | 10.67 | 25.83 | *** |

n.s. = non-significant, *sig. < 0.016, **sig. < 0.003, ***sig. < 0.0003.

individual recordings were of 10 hours duration. The CHF group comprised of 44 subjects, 29 men and 15 women aged 55.5 ± 11.4, range 22–78 years. The data of 29 CHF subjects was obtained from RR interval congestive heart failure data and 15 from MIT_BIH Bidmic congestive heart failure database [9]. CHF subjects can be classified into four groups according to New York Heart Association (NYHA) functional classification system. This system classifies the patients according to the symptoms to everyday activity and quality of life of patient. Based on NYHA functional classification system, CHF subject were divided into three classes. Class CHF_A comprises of 12 CHF subjects belonging to NYHA classes I and II. Class CHF_B includes those 17 subjects which are classified as NYHA class III in congestive heart failure RR interval database. CHF_C includes 15 subjects from MIT_BIH Bidmic congestive heart failure database who are suffering from severe heart failure and classified as NYHA Class III_IV by the authors of the database.

## RESULTS

The normalized corrected Shannon entropy (NCSE) of symbol sequences derived from interbeat interval time series of NSR, CHF_A, CHF_B, CHF_C and AF subjects was computed. The time series data was converted into symbol sequences by using

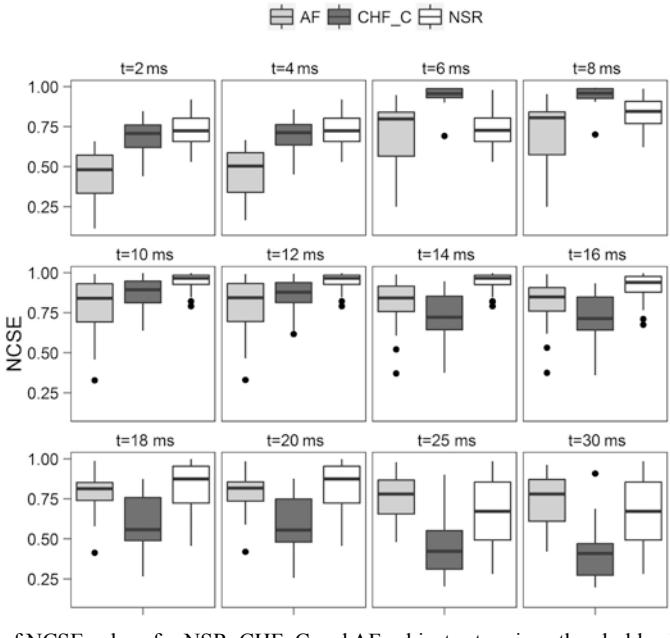


*Fig. 1.* Boxplot of NCSE values for NSR, CHF_C and AF subjects at various threshold values. The single black line inside each box is the median NCSE value at a specified threshold. The edges of the box represent 25th and 75th percentile. The 50% of subjects in a group lie within the box and remaining 50% of subjects lie between the box and whiskers with some exceptions called outliers. The outliers are the NCSE values represented by (•) that lie outside the boundaries of whiskers

word length 3 and quantization level 2. The procedure for word length and quantization level selection is detailed in the reference [2].

In Figure 1, the shape and spread of NCSE values for NSR, CHF_C and AF subjects is presented using boxplot at various thresholds. The boxplot is a useful way to visualize the range, medians value, normality and skewness of distribution. The median values of NCSE derived from the time series of all three groups increased at smaller thresholds and then after reaching a maximum value gradually decreased with the increase in threshold value. The NCSE value of NSR subjects reached a maximum value at threshold value of 10 ms, CHF_C subjects at 8 ms and AF subjects at 12 ms. The maximal NCSE value for NSR subjects (0.9729) was higher than the maximal NCSE value of both CHF_C group (0.9589) and AF subjects (0.8492). In Table 1, the paired comparison of NSR vs CHF_C, NSR vs AF and CHF_C vs AF subjects at various thresholds using Wilcoxon Mann–Whitney test is presented. The table includes NCSE percentiles, mean ranks and significance level of paired groups at various threshold values. Higher mean rank shows higher NCSE value that indicates which groups can be considered as having higher complexity. The mean ranks of NSR subjects were significantly higher in the threshold range 10–35 ms for CHF_C subjects. The mean ranks of NSR subjects were significantly higher than AF for threshold values less than 16 ms except 6 ms. The findings indicate that the healthy subjects are more complex than both pathological groups at various threshold ranges.

*Table 2*

Area under receiver operator curve at different threshold values. Area under ROC depicts degree of separation between the groups (AUC = 0.5 is equivalent to simple guessing and AUC = 1 is equivalent to perfect separation between the classes)

| τ (ms) | NSR vs CHF_C | NSR vs AF | CHF_C vs AF |
|---|---|---|---|
| 2 | 0.61 | 0.96 | 0.90 |
| 4 | 0.59 | 0.95 | 0.90 |
| 6 | 0.95 | 0.52 | 0.93 |
| 8 | 0.87 | 0.68 | 0.92 |
| 10 | 0.74 | 0.82 | 0.60 |
| 12 | 0.75 | 0.81 | 0.58 |
| 14 | 0.94 | 0.85 | 0.66 |
| 16 | 0.89 | 0.77 | 0.69 |
| 18 | 0.84 | 0.58 | 0.80 |
| 20 | 0.84 | 0.59 | 0.81 |
| 25 | 0.78 | 0.62 | 0.88 |
| 30 | 0.84 | 0.61 | 0.89 |
| 35 | 0.71 | 0.75 | 0.89 |
| 40 | 0.66 | 0.85 | 0.89 |

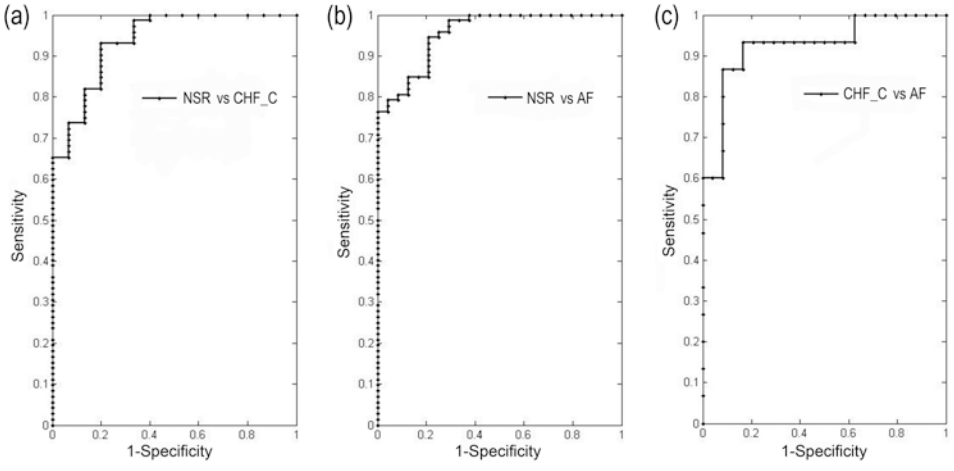


*Fig. 2.* Receiver operator curve for optimal separation between (a) NSR vs CHF_C (b) NSR vs AF (c) CHF_C vs AF subjects. Area under ROC depicts degree of separation between the groups (AUC = 0.5 is equivalent to simple guessing and AUC = 1 is equivalent to perfect separation between the classes)

In Table 2, area under receiver operator curve at different thresholds for separating various groups is given. The area under receiver operator (AUC) is well-recognized index for quantifying the degree of separation between the groups. The maximum value of AUC is 1, showing perfect separation of two groups and a value of 0.5 correspond to group separation by pure chance. The optimal separation between NSR vs AF subjects is obtained at threshold of 2 ms (AUC = 0.96, p-value = $2.84 \times 10^{-11}$), the optimal separation between NSR vs CHF_C (AUC = 0.94, p-value = $7.17 \times 10^{-08}$) and CHF_C and AF (AUC = 0.93, p-value = $1.07 \times 10^{-05}$) groups was obtained at threshold of 6 ms. The receiver operator curve for optimal separation various groups is shown in the Fig. 2.

As observed in Table 2, maximum separation between NSR and CHF_C can be achieved at the threshold of 6 ms and maximum separation between NSR and AF can be achieved at the threshold of 2 ms. Therefore, NCSE values of NSR, CHF_C and AF are plotted in Figure 3 for thresholds of 6 ms and 2 ms. It can be observed from the figure that all three classes are separable with good accuracy. Moreover, NSR class has similar values for threshold of 2 ms and 6 ms where change in the threshold value from 2 ms to 6 ms has caused lot of change in the NCSE values of AF and CHF_C.

Hence, a simple rule based classifier is implemented which is described as below,

$$\text{Rule 1: } If\ NCSE(6ms) \le NCSE(2ms) + 0.04,\ Class = NSR$$

$$\text{Rule 2: } If\ NCSE(6ms) > NCSE(2ms) + 0.04\ AND$$
$$NCSE(6ms) \ge -2.05 NCSE(2ms) + 2.1905,\ Class = \text{CHF}$$

$$\text{Rule 3: } If\ NCSE(6ms) > NCSE(2ms) + 0.04\ AND$$
$$NCSE(6ms) < -2.05 NCSE(2ms) + 2.1905,\ Class = \text{AF}$$

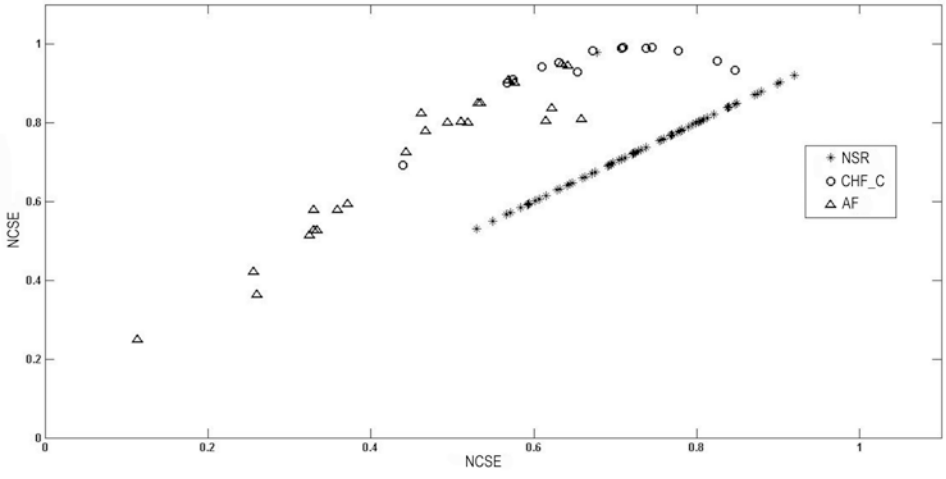


*Fig. 3.* NCSE values of NSR, CHF_C and AF at $\tau = 2$ ms and $\tau = 6$ ms

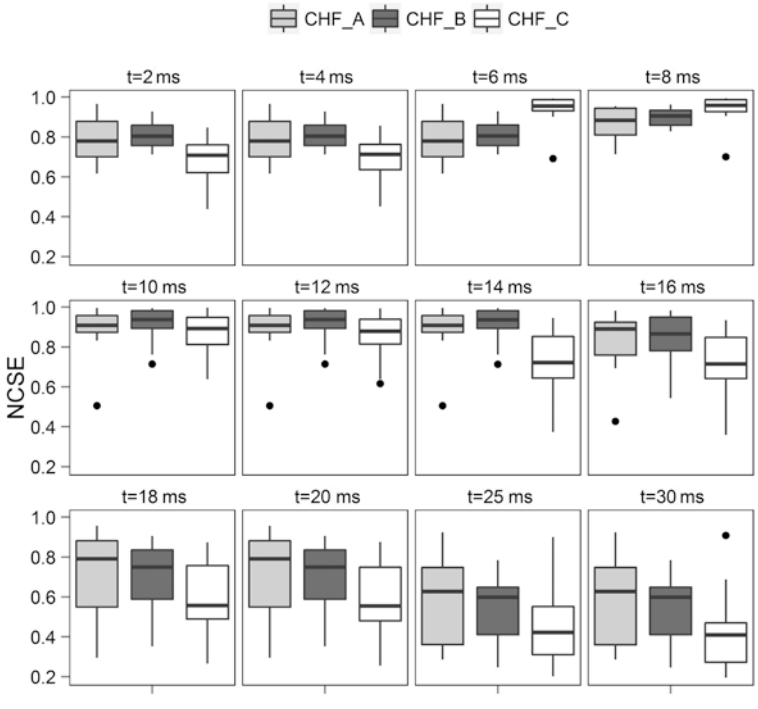


*Fig. 4.* Boxplot of NCSE values for CHF_A, CHF_B and CHF_C subjects at various threshold values. The single black line inside each box is the median NCSE value at a specified threshold. The edges of the box represent 25th and 75th percentile. The 50% of subjects in a group lie within the box and remaining 50% of subjects lie between the box and whiskers with some exceptions called outliers. The outliers are the NCSE values represented by (●) that lie outside the boundaries of whiskers

Applying these rules, confusion matrix for classes of NSR, CHF_C and AF is given in Table 3. An overall accuracy of 95% is achieved and sensitivities of NSR, CHF_C and AF are found to be 99%, 80% and 92% respectively. Specificities of NSR, CHF_C and AF are found to be 100%, 80% and 88%, respectively.

Physicians often assess the heart failure stages according to the NYHA functional classification system. In present study, CHF subjects were divided into three classes based on the NYHA functional classification system. In Fig. 4, median and interquartile ranges of NCSE values for CHF_A, CHF_B subjects and CHF_C at various thresholds are represented using boxplot. The NCSE values for all groups initially

*Table 3*
Confusion matrix of NSR, CHF_C and AF.
The rows represent the actual classes and columns represent predicted classes

| | NSR | CHF_C | AF |
|---|---|---|---|
| NSR | 71 | 0 | 0 |
| CHF | 1 | 12 | 2 |
| AF | 0 | 3 | 22 |

*Table 4*
Paired sample comparison of 12 CHF_A, 17 CHF_B and 15 CHF_C with NSR subjects at threshold of 6 ms using Wilcoxon Mann–Whitney test with Bonferroni correction (0.05/3 = 0.016) for interpreting results

| | CHF_A | | |
|---|---|---|---|
| NCSE percentile (6 ms threshold) | 25th | 50th | 75th |
| | 0.6633 | 0.7801 | 0.8832 |
| P value with NSR | n.s. | | |
| AUC with NSR | 0.63 | | |
| | CHF_B | | |
| NCSE percentile (6 ms threshold) | 25th | 50th | 75th |
| | 0.9294 | 0.9558 | 0.9891 |
| P value with NSR | * | | |
| AUC with NSR | 0.75 | | |
| | CHF_C | | |
| NCSE percentile (6 ms threshold) | 25th | 50th | 75th |
| | 0.7482 | 0.8049 | 0.8721 |
| P value with NSR | ** | | |
| AUC with NSR | 0.95 | | |

n.s. = non-significant, *sig. < 0.016, **sig. < 0.0003. Area under ROC depicts degree of separation between the groups (AUC = 0.5 is equivalent to simple guessing and AUC = 1 is equivalent to perfect separation between the classes).

increased with the increase in the threshold value and then after reaching maximum value started to decrease. The NCSE values of CHF_A subjects were initially smaller than that of CHF_B subjects at threshold values less than 18 ms and then progressively increased with the increase in the threshold value. However, no statistically significant difference is found between CHF_A and CHF_B. On comparing mild class subjects (CHF_A) and severe disease class subjects (CHF_C), NCSE of CHF_C subjects was initially smaller than CHF_A subjects, then increased rapidly at threshold of 6 ms and decreased progressively for threshold values greater than 10 ms. At threshold values of 14 and 16 ms, the NCSE of CHF_A subjects is significantly higher than CHF_C subjects. The results showed that the complexity of CHF_C group is smaller than CHF_A at thresholds range of 10 ms to 40 ms.

Table 4 shows values of NCSE at 6 ms for CHF_A, CHF_B and CHF_C cases. The value of NCSE is increased with the severity of the disease at the threshold value of 6 ms. The values of AUC and p-value show that as severity of the disease gets milder, the NCSE values approach to the NCSE values of NSR at threshold value of 6 ms. NCSE values of CHF_B at 6 ms are significantly different from NCSE (p-value = 0.009) and AUC is 0.75. As the severity of disease is increased from CHF_A to CHF_C, AUC also increased from 0.63 to 0.95.

## DISCUSSION

HRV is a reliable and reproducible technique used to assess autonomic function that serves as marker of cardiovascular disease. Human heart is not a periodic oscillator and a large range of complex rhythms are displayed by it in both health and disease states. Linear time and frequency domain measures are often mot sufficient to quantify these complex dynamics. Various efforts have been made to apply nonlinear techniques to analyze HRV [6, 7, 11, 14, 18, 20].

Symbolic dynamics is a promising tool in several fields of complexity analysis. The application of Symbolic analysis to analyze the behavior of physiological system requires a partition of the signal in order to convert it into symbol sequences. A well-chosen partition is vitally important for reflecting whole internal complex of dynamical systems. In our previous study [2], the complexity of stride interval time series of control and neurodegenerative disease subjects was assessed using threshold dependent symbolic entropy. Normalized corrected Shannon entropy (NCSE) was used for quantifying the dynamics of healthy and pathological signals by varying threshold value. The value of NCSE depends on the distribution of patterns generated on the basis of partitions at different threshold values. The uniform distribution of patterns manifests equal pattern probability. The NCSE will reach to a maximum value showing that time series is more complex. If the distribution of patterns is non-uniform or dominated by a specific pattern, the NCSE will decrease and time series will be less complex. The distribution of patterns is affected by the value of threshold chosen.

The rule based classifier implemented by extracting the information in the heart rate signals separated the healthy and pathological groups (CHF and AF) with good accuracy. An optimal amount of variability in the rhythms of biological system such as heart rate signals is directly related to the health and is characterized by higher complexity. Under pathological conditions, variations in the heart rate signals are either periodic (CHF) indicating decrease in the optimal amount of variability or random (AF) manifesting increase beyond the optimal variability [6]. The alternations in the optimal variability (either increase or decrease) are associated with disease resulting in the loss of complexity. NCSE yielded significantly higher complexity for healthy subjects than the both pathological subjects and decreased with disease severity. The results support the hypothesis that loss of complexity is a defining feature of pathological dynamics. The findings reveal that NCSE within wide range of threshold values is a resilient candidate for measuring inherent complexity of biological signals in a good agreement with recent affirmations of multiscale entropy [6, 7].

## CONCLUSIONS

In the present study, threshold based symbolic entropy was applied to cardiac interbeat interval signals of healthy and pathological subjects. The symbolic sequences were quantified using normalized corrected Shannon entropy (NCSE). On the basis of the information extracted from these signals a rule based classifier was implemented for classification of healthy, low variability disease (CHF) subjects and high variability disease (AF) subjects. This classifier separated the different with good accuracy at various threshold values. The results demonstrated that NCSE was found to be significantly higher in the optimal variability group (NSR subjects) than both high and low variability pathological groups. The higher NCSE value shows that dynamics of healthy subjects are more complex that represents the underlying physiological system is capable of making flexible adaptations in an ever changing environment. The findings reveal that NCSE within wide range of threshold values is a resilient candidate for measuring inherent complexity of biological signals in a good agreement with recent affirmations of multiscale entropy.

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