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Entropy Measures of Irregularity and Complexity for Surface Electrocardiogram Time Series in Patients with Congestive Heart Failure

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Abstract

Congestive heart failure (CHF) remains to be one of the major cardiovascular disorders in the world. Due to the prevalence of CHF related issues, it is prudent to seek out new prognostic predictors that would facilitate the prevention, monitoring, and treatment of the disease on a daily basis. A detection approach using entropy measures extracted from surface electrocardiograms (ECGs) and classification for congestive heart failure (CHF) is presented in this paper. Four different entropies are used: approximate entropy (ApEn), sample entropy (SampEn), permutation entropy (PE), and energy entropy (EE). These entropies are employed to evaluate the irregularity and complexity of ECG time series and discuss the viability of recognizing CHF patients from normal subjects. Student's t-tests and receiver operating characteristic (ROC) plots show that among the four entropies, EE outperforms other three entropies. These tests also indicate the feasibility of using surface ECGs to effectively discriminate CHF patients from normal subjects.

Keywords: *Complexity, Congestive heart failure, Energy Entropy, Irregularity, Surface Electrocardiogram*

1. Introduction

Congestive heart failure (CHF) occurs when heart cannot effectively supply blood for a healthy physiological state. CHF usually occurs when the cardiac tissue becomes ischemic due to coronary vessel blockage or cardiac diseases, like cardiomyopathy, weaken the heart muscles. This in turn decreases the cardiac mechanical functionality and disrupts the normal electrophysiological processes. Despite numerous recent advances in the field of medicine, CHF has been difficult to manage with in clinical practice and mortality rate has remained high [1]. Due to the prevalence of CHF related issues, it is prudent to seek out methodologies that would facilitate the prevention, monitoring, and treatment of heart disease on a daily basis. The majority of the studies in the literature used HRV measures for the detection and prognosis of the disease [1]-[12]. A small number of studies used surface ECG characteristic and/or morphology for CHF detection [13]-[18]. In a recent publication we showed that symbolic dynamics analysis applied to surface ECG signals could effectively discriminate CHF patients from healthy subjects [19]. In this work we adopt the latter approach. Cardiovascular

regulation involves a complex system of different interacting control mechanisms. Clinical studies have shown that cardiovascular dysfunctions reduce the complexity in HR dynamics. Therefore it seems reasonable to hypothesize that the cardiovascular dysfunctions must also alter the regularity and complexity of the ECG rhythmic variations. Measures from nonlinear dynamics must, in principle, allow insight into the evolution of complexity of underlying cardiac activity. Entropy-based measures are powerful methods that can be used to analyze the degree of irregularity and complexity of short time series. Also entropy measures have been shown to characterize chaotic behavior in time series data [20]. Further, these measures have properties that make them suitable for physiological data analysis. In this study, we compare the discrimination power of modified energy entropy (an entropy related feature) with those of three entropy measures (approximate entropy, sample entropy and permutation entropy) in separating normal subjects from patients with CHF. The prime advantage of using these measures lies in the possibility of applying them to both deterministic and stochastic systems. This study represents the first step in demonstrating the feasibility of using entropy measures for recognition of raw ECG signal changes in CHF subjects.

2. Methods and materials

The following subsection 2.1 discusses the surface ECG records used for analysis. The next five subsections 2.2, 2.3, 2.4, 2.5, and 2.6 discuss in depth the measures of complexity and irregularity used in this study. Subsection 2.7 describes the statistical tests and receiver operating characteristic (ROC) plots to evaluate the performance parameters.

2.1 Clinical data

The surface ECG records used are from the benchmark PhysioNet databases [21]. The work involved 18 ECG records from MIT-BIH normal sinus rhythm (NSR) database and ECG records of 15 subjects with severe CHF (NYHA class 3-4) from BIDMC CHF database. The NSR database includes 5 men, aged 26 to 45 years, and 13 women, aged 20 to 50 years. The CHF database includes 11 men, aged 22 to 71 years, and 4 women, aged 54 to 63 years. From each record the modified limb lead II was only considered for analysis. The resolution is 200 samples per mV. The sampling frequency of normal sinus rhythm signal is 128 Hz and that of CHF signal is 250 Hz. Since the sampling frequency does influence upon the calculated parameters it is necessary to have the same sampling frequency for all the records. For this reason ECG signals from normal database are first re-sampled at 250 Hz. Then each record, in normal sinus rhythm and CHF databases, is divided into segments of equal time duration (18 sec), with 4500 samples/segment. A total of 3510 segments from normal sinus rhythm and a total of 2925 segments from CHF data base are analyzed.

2.2 Measures of irregularity and complexity

Entropy is a concept which addresses randomness and predictability, with smaller entropy associated with higher predictability and larger values associated with randomness [22]. In the framework of time series analysis, entropy is defined as a measure of rate of generation of information [23]. Mainly there are two families of entropy estimators: spectral entropies and embedding entropies [24]. Spectral entropies

are evaluated from frequency spectra, while embedding entropies, usually are computed directly from time series. In this study three embedding entropies (approximate entropy, sample entropy, and permutation entropy) and a measure related to spectral entropy (modified energy entropy) are used. These nonlinear measures are tested, each computed for different lengths of ECG time series to investigate irregularity and complexity.

2.3 Approximate entropy (ApEn)

Approximate entropy (ApEn) is a nonlinear measure of irregularity and complexity in the data without any *a priori* knowledge of the system generating them [25]-[29]. The presence of repetitive patterns of fluctuation in the time series renders it more predictable than a time series in which such patterns are absent. The approximate entropy measures the logarithmic probability that a series of data points a certain distance apart will exhibit similar relative characteristics on the next incremental comparison with the state space. Time series with a greater likelihood of remaining the same distance apart upon comparison will result in lower approximate entropy values, while data points that exhibit large differences in distances between data points will result in higher values. ApEn is scale invariant and model independent, evaluates both dominant and subordinant patterns in the data, and discriminates series for which clear feature recognition is difficult. It is immune to low level noise and robust to meaningful information with a reasonable number of data points. Large values of ApEn indicate more irregularity in the data and vice versa. In the following a short description of the formal implementation of the ApEn is given, for further details see [26]. Given a time series with M data points, x(1), x(2),…, x(M). To compute ApEn m-dimensional vector sequences, $p_m(i)$, are constructed from data series like $[p_m(1), p_m(2), \ldots, p_m(M-m+1)]$, where $1 \leq i \leq M-m+1$. If the distance between two vectors $p_m(i)$ and $p_m(j)$ is defined as $|p_m(i) - p_m(j)|$, then

$C_i^m(d)$ = [Number of vectors such that $| p_m(i) - p_m(j)| < d$] / (M-m+1), where m specifies the pattern length and d defines the criterion of similarity. $C_i^m(d)$ is considered as the mean of the fraction of patterns of length m that resemble the pattern of the same length that begins at index i. ApEn is computed using the eqn. (5) below.

Let $\Phi^m(d) = \sum_i ln(C_i^m(d)) / (M-m+1)$ *for* $1 \leq i \leq M-m+1$

and $\Phi^{m+1}(d) = \sum_i ln(C_i^{m+1}(d) / (M-m)$ *for* $1 \leq i \leq M-m$

then $ApEn(m, d, M) = \Phi^m(d) - \Phi^{m+1}(d)$ (1)

Pincus and Goldberger [27] have shown that with $m = 2$, $d = 10-25\%$ of the standard deviation of the M data points/ samples ($M \geq 100$ data points) will lead to statistically reliable and reproducible results. Comparisons between sequences must be made with the same values of m, d, and M. In this study, $m = 2$, $d = 0.2$ and $M = 4500$ are used. Smaller values of ApEn imply a greater likelihood that similar patterns of measurements will be followed by additional similar measurements. If the time series is highly irregular, the occurrence of similar patterns will not be predictive for the following measurements, and ApEn will be relatively large. This is the key to a measure of irregularity: small values of ApEn indicate regularity and large values imply substantial fluctuations or irregularity in the time series. The values typically vary in the range 0 to 2 [28]. Values near zero are consistent with greater periodicity or regularity. Conversely, values closer to two represent greater irregularity. ApEn for a periodic

signal such as sine wave will be close to zero, while for a random signal such as white noise will be near two. Deterministic signals will have ApEn values in between depending on the order of regularity.

2.4 Sample entropy (SampEn)

Approximate entropy algorithm counts each sequence as matching itself to avoid the occurrence of ln(0) in the calculations. This leads to bias of approximate entropy and as an implication approximate entropy lacks two important properties. First, approximate entropy depends more on record length and will lead to lower values for short records. Second, it lacks relative consistency. This means, if approximate entropy for one data set is higher than the other, it should, but does not remain higher for all conditions tested. This drawback is important and it is to be noted that approximate entropy is a relative measure for comparing data sets [27]. These problems associated with approximate entropy are resolved by using sample entropy which reduces the above mentioned bias. The sample entropy, on the other hand, "is largely independent of record length and shows relative consistency where approximate entropy does not" [25]. The sample entropy represents the negative natural logarithm of the conditional probability that two sequences similar for *m* points remain similar at the next point [30]. Given a time series with N data points, $x_1, x_2, \ldots, x_N$. To compute SampEn m-dimensional vector sequences, $y_i(m) = \{x_i, x_{i+1}, \ldots, x_{i+m-1}\}$, where $1 \leq i \leq N-m+1$. Then

$$B_i^m(r) = \left(\sum_j \theta(r - ||y_j(m) - y_i(m)||_\infty) \right) / (N-m-1) \quad \text{for } j \neq i,\ 1 \leq j \leq N-m \tag{2}$$

where θ is the Heaviside function, $||.||_\infty$ is the maximum norm defined by $||y_j(m) - y_i(m)||_\infty = \max_{0 \leq k \leq m-1} |x_{j+k} - x_{i+k}|$. The sum in the above equation represents the number of vectors $y_j(m)$ that are within a circular distance r from $y_i(m)$ in the reconstructed phase space. However, the cases of self matches indicated by $j = i$ are avoided from the count. This brings down the bias in the estimation of SampEn [25]. In the next step the density is computed as

$$B^m(r) = \left(\sum_i B_i^m(r) \right) / (N-m) \quad \text{for } 1 \leq i \leq N-m \tag{3}$$

Computations similar to above are then performed on a $(m+1)$-dimensional reconstructed space to arrive at the equations below.

$$A_i^m(r) = \left(\sum_j \theta(r - ||y_j(m+1) - y_i(m+1)||_\infty) \right) / (N-m-1) \quad \text{for } j \neq i,\ 1 \leq j \leq N-m \tag{4}$$

$$A^m(r) = \left(\sum_i A_i^m(r) \right) / (N-m) \quad \text{for } 1 \leq i \leq N-m \tag{5}$$

This leads to,

$$B(r) = (N-m-1)(N-m)B^m(r) / 2 \tag{6}$$

$$A(r) = (N-m-1)(N-m)A^m(r) / 2 \tag{7}$$

$B(r)$ and $A(r)$ respectively represent the total number of template matches in an m-dimensional and $(m+1)$-dimensional phase space within a tolerance r. The sample entropy is defined as the negative of natural logarithm of the conditional probability that a dataset of length N, having repeated itself for m samples within a specified tolerance r, will also repeat itself for $m+1$ samples without allowing self matches and is computed as

$$\text{SampEn}(m, r, N) = -\log(A(r) / B(r)) \tag{8}$$

In this work, $m = 2$, $d = 0.2$ and $M = 4500$ are chosen.

2.5 Permutation entropy (PE)

Permutation entropy (PE) was first introduced by Bandt and Pompe [31] as a convenient means of evaluating complexity features for time series based on order relation between the values of time series instead of values themselves. PE refers to the local order structure of the time series which corresponds to a quantitative complexity measure of a dynamical time series. PE approach is a simple, fast, robust and invariant method with respect to monotonous nonlinear transformations. Basically PE is a new method for ordinal time series analysis. It transforms a given time series into a series of ordinal patterns, each describing the order relations between the present and a fixed number of equidistant past values at a given time [32]. Let x_t (t = 1, 2, ...) represent a scalar time series. The embedding procedure produces vectors X_t [x_t, $x_{t+\tau}$, ..., $x_{t+m\tau}$] where m is the embedding dimension and τ is the time lag. Then, X_t can be arranged in an ascending order and for m different numbers, there will be $m!$ possible order patterns, usually called permutations. Bandt and Pompe have proposed a Shannon entropy based feature, PE, to quantify and visualize the changes in the time series. If each permutation is treated as a symbol, the vectors X_t can be treated as a symbol sequence and the distinct number of symbols, J, would be either less than or equal to $m!$. For the given time series x_t, the probability distributions of these distinct symbols are designated as p_1, p_2, ..., p_J. The PE for the time series is defined as

$$H_p(m) = - \sum_j p_j \ln(p_j) \qquad \text{for } 1 \leq j \leq J \tag{9}$$

The corresponding normalized PE is defined as

$$H_p = H_p(m) / \ln(m!) \tag{10}$$

The smallest value of H_p is zero and this corresponds to a regular, deterministic time series. This will be attained for a monotonously increasing or decreasing time series which can be readily predicted. The largest value of H_p is one and this corresponds to a random time series with all permutations having equal probability. That is, $0 \leq H_p \leq 1$ and H_p gives a measure of the departure of the time series under study from a complete random one. In general, larger the value of H_p, the more irregular the time series is. In this study, m = 4 and N = 4500 are selected.

2.6 Modified energy-entropy feature

Modified energy-entropy (EE) feature has been used in speech processing and has been found to be effective even in high noise environment [34]. This feature is a combination of the energy and the spectral entropy [35]-[36]. While energy and entropy are commonly used in bio-signal processing, they both have limitations in noisy environment. Spectral entropy though is useful in differentiating normal and pathological states; it fails in the presence of noise. Energy, on the other hand, performs well in noisy environment because of its additive property; energy of the sum of the signal and noise is always greater than the energy of noise alone. EE combines the advantages of these two features. EE is effective even in high noise environment [34]. The EE feature is computed for every segment of the time series as follows.

First estimate the energy E_i of the segment i as

$$E_i = \sum_k (S_k)^2 \qquad 1 \leq k \leq K \tag{11}$$

K is the number of samples in the i^{th} segment.

Next compute N-point DFT of the i^{th} segment of the time series and estimate the probability density function for the frequency component k as

$$p_i(k) = (|X(k)|) / (\sum_k |X(k)|) \quad (12)$$

The denominator summation is carried out over the range $1 \leq k \leq N$. $X(k)$ is the magnitude of the k^{th} frequency component, p_i is the corresponding probability density function and N is the length of DFT.

Then compute the entropy for the i^{th} segment as

$$H_i = \sum_k p_i(k) \log (p_i(k)) \quad 1 \leq k \leq N \quad (13)$$

Finally evaluate the modified energy-entropy feature for the i^{th} segment as

$$EEF_i = (1 + |E_i \,.\, H_i|)^{0.5} \quad (14)$$

Entropy is a measure of disorder or randomness. The more the randomness is, the higher the entropy will be. Larger value of this entropy implies higher complexity and a smaller value implies a lower complexity. In this study, K = 4500 and N = 8192 are chosen.

2.7 Statistical analysis and Receiver Operating Characteristic (ROC) plots

Unpaired significance tests (Student's *t*-tests) are used to evaluate the statistical differences between the different entropy values of normal and CHF groups. If significant differences between the two groups are found, then the potential of the nonlinear analysis method to discriminate between ECG series in healthy subjects or/and CHF patients is evaluated using receiver operating characteristic (ROC) plots in terms of area under ROC (AROC) and the following performance parameters: sensitivity, specificity, precision, and accuracy. ROC plots are used to gauge the predictive ability of a classifier over a wide range of values [37]. 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 cutoff 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). AROC is a single number summary of performance, the larger the value, the better is the diagnostic test. 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

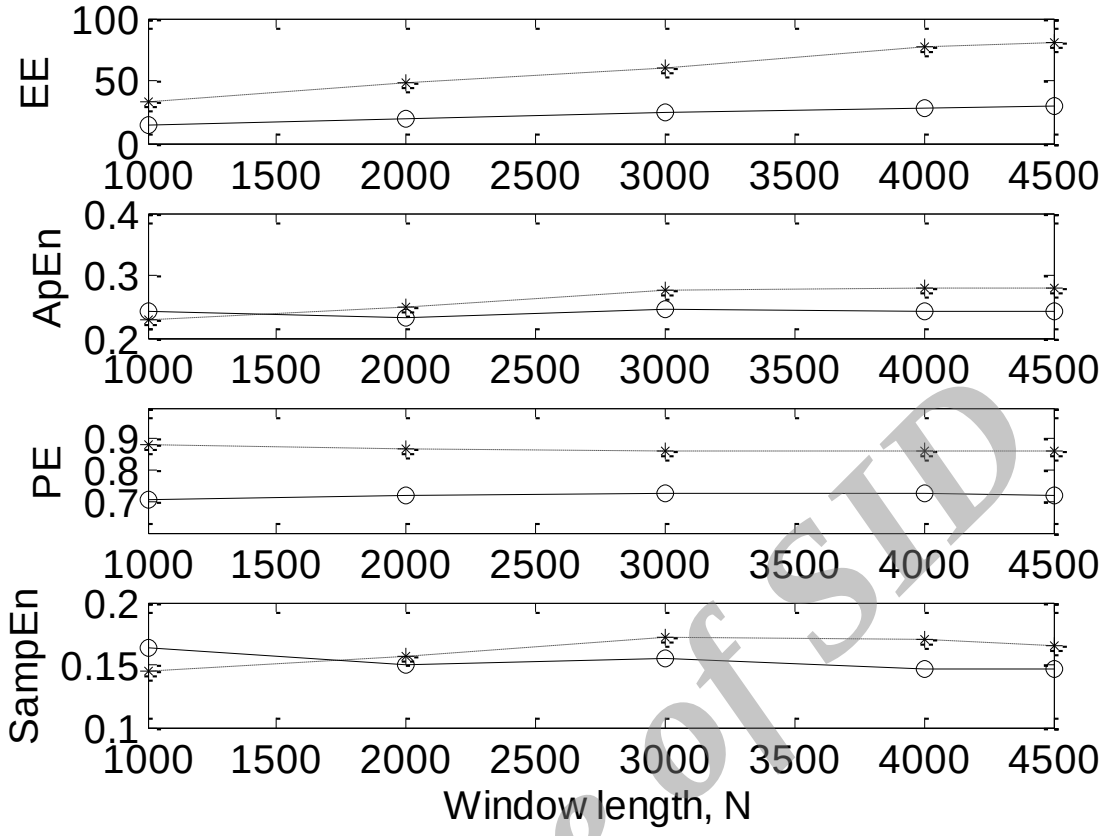

Figure 1. Values of EE, ApEn, PE, and SampEn for increasing window length, N.

The effect of data length, *N*, on the different entropies is first examined by varying *N* from 1000 to 4500 samples. All the four complexity and irregularity measures were estimated for normal and CHF subjects. The results were averaged based on *N* sample-epochs within each ECG recording of normal and CHF groups. A comparison of the results of entropies in normal and CHF groups for different data lengths is depicted in Figure 1. It is found that ApEn and SampEn can separate well the groups only for $N >$ 3000 samples. However, EE and PE are able to separate normal and CHF groups even for shorter data lengths. In this study it is found that $N = 4500$ samples leads to a reasonably good discrimination in all the cases. The ApEn, Sampn, PE, and EE values (mean ± SD) for the normal subjects and CHF patients and the corresponding *p* values of the unpaired Student's *t*-tests performed to examine the difference between the two groups are summarized in Table 1. As can be seen, corresponding to ApEn values not much significant differences are found between the two groups ($0.01 < p < 0.05$). It is found that, however, corresponding to SampEn, PE, and EE, significant differences between the two groups are in ascending order (all $p < 0.01$).

Table 1. Descriptive results of entropy analysis of raw ECG time series for Normal and CHF groups for N=4500. All values are expressed as mean ± SD. (non-paired Student's t-test; p < 0.01)

Entropy measure	**Normal**	**CHF**	***p*-value; tstat**
ApEn	0.2004±0.035	0.256±0.0382	p = 0.0267; tstat= 2.22
SampEn	0.1125±0.028	0.159±0.0280	p = 0.0058; tstat= 2.77
PE	0.7654±0.009	0.8847±0.0172	p = 0; tstat = 25.68
EE	22.59±3.3770	81.08±7.366	p = 0; tstat = 49.47

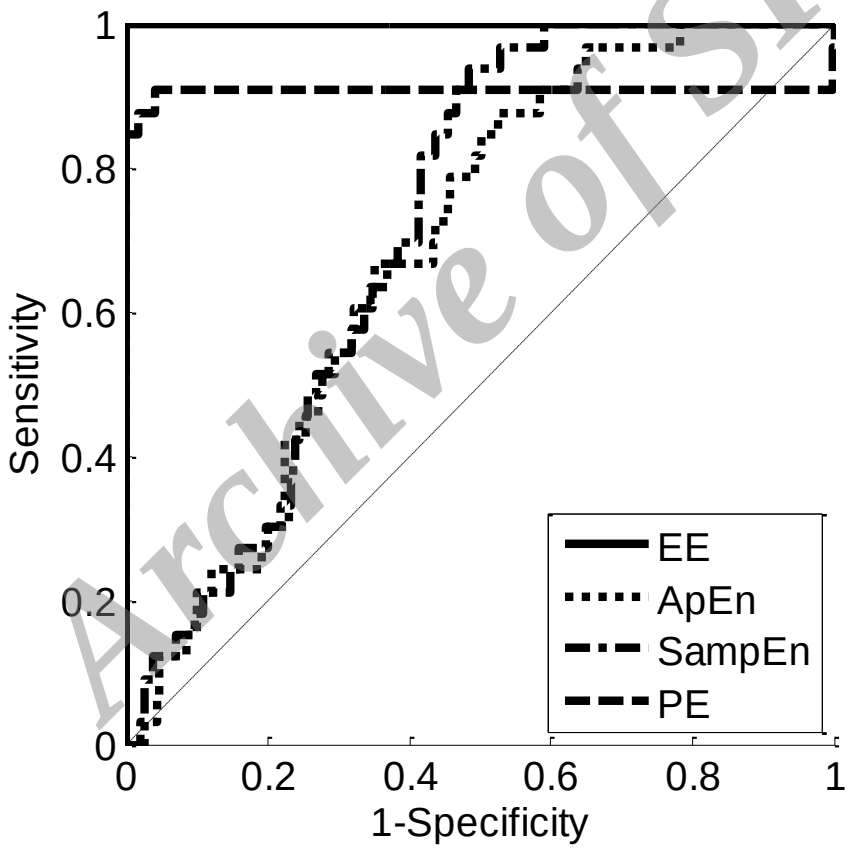

Figure 2. ROC plots to discriminate normal and CHF subjects using EE, ApEn, SampEn, and PE measures.

The new entropy method, EE, allows us to evaluate the information richness in the surface ECG time series as a combination of energy and spectral entropy. It is found that EE can effectively discriminate patients with CHF from normal subjects.

Table 2. Descriptive results of ROC analysis using ApEn, SampEn, PE, and EE for discriminating Normal and CHF groups for N=4500.

Complexity measure	AUC	Average sensitivity%	Average specificity%	Average precision%	Average accuracy%
ApEn	0.6900	66.7	64.9	6.7	65.0
SampEn	0.7189	81.8	58.3	7.0	59.2
PE	0.9075	90.9	96.0	46.2	95.8
EE	0.9999	100.0	99.0	97.1	99.9

4. Conclusion

The chief findings of this study are: (1) all the entropy measures of the surface ECG time series are increased in CHF subjects compared to normal subjects. This implies normal subjects show a large amount of similar epochs in addition to a considerable amount of non-similar epochs in their ECG time series. CHF patients lack similar epochs observed in normal subjects. (2) Among the four entropy measures EE demonstrated the best discrimination between normal and CHF subjects. (3) The study indicates the feasibility of using surface ECGs, instead of beat-to-beat intervals, to effectively separate pathological condition of CHF patients from normal subjects.

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