

Multiscale Entropy Analysis of Complex Heart Rate Dynamics: Discrimination of Age and Heart Failure Effects

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Abstract

Quantifying the complexity of physiologic time series has been of considerable interest. Several entropy-based measures have been proposed, although there is no straightforward correspondence between entropy and complexity. These traditional algorithms may generate misleading results because an increase in system entropy is not always associated with an increase in its complexity, and because the algorithms are based on single time scales.

Recently, we introduced a new method, multiscale entropy (MSE) analysis, to calculate entropy over a wide range of scales. In this study, we sought to determine whether loss of complexity due to aging could be distinguished from that due to major cardiac pathology. We analyzed RR time series from young subjects (n=26), elderly subjects (n=46) and subjects with congestive heart failure (n=43).

The mean MSE measures of each of the three groups revealed characteristic curves, suggesting that they capture fundamental changes in the heart rate dynamics due to age and disease. We used Fisher's linear discriminant to evaluate the use of MSE features for classification. In discriminant tests on the training data, we found that MSE features could separate elderly, young and heart failure subjects with 92% accuracy and that older healthy subjects (mean age=65.9) could be separated from subjects with heart failure (mean age=55.5) with 94% accuracy. Also, we discriminated data from heart failure subjects and elderly healthy subjects with a positive predictivity of 76% and a specificity of 83% using only the MSE features. Larger databases will be needed to confirm if automatic classification results can match separation results.

We conclude that MSE features capture differences in complexity due to aging and heart failure. These differences have implications for modeling neuroautonomic perturbations in health and disease.

1. Introduction

Heart rate variability is the output of multiple physiologic control mechanisms that operate over a wide range of time scales. As a result, cardiac interbeat interval (RR) time series under healthy conditions have a complex temporal structure with multiscale correlations [1, 2]. Our working hypothesis is that aging and disease result in a loss of complexity. The RR time series from elderly subjects and those with heart disease should represent the output of simpler dynamical systems, and therefore, will be anticipated to have less complex temporal structures than those of young healthy subjects.

Classical entropy and physiologic complexity concepts do not have a straightforward correspondence [3, 4]. Entropy is related to the degree of "randomness" of a time series and it is maximum for completely uncorrelated random signals. Complexity is related to the underlying structure of a time series and its information content. An increase of the entropy assigned to a time series usually, but not always, corresponds to an increase of underlying system complexity.

Entropy-based algorithms [5, 6] for measuring the complexity of physiologic time series have been widely used. They have proved to be useful in discriminating between healthy and disease states [7, 8], although some results may generate misleading conclusions. For example, the entropy that these algorithms assign to time series derived from the ventricular response in atrial fibrillation (AF) is higher than that assigned to sinus rhythm time series derived from healthy subjects. However, healthy systems generate much more complex outputs than diseased ones. Traditional algorithms are single-scale based and, therefore, fail to account for the multiple time scales inherent in physiologic systems. We have developed a novel method [9] to calculate multiscale entropy (MSE) from complex signals.

In 1991, Zhang [10, 11] proposed a new complexity measure that applies to physical systems. His measure,

defined as a weighted sum of scale-dependent entropies, has the advantage of yielding higher values for correlated noises than for uncorrelated ones. However, since it is based on Shannon’s definition of entropy, it requires a large number of almost noise-free data points [12]. Therefore, the possibility of applying Zhang’s measure to real world time series is very limited. In contrast, our method is based on the Approximate Entropy (ApEn) family of parameters, which have been widely applied to physiologic and medical time series analysis [5].

In previous work [9], the MSE method has been applied to heart rate time series from healthy subjects and subjects with AF and congestive heart failure (CHF). The resulting MSE curves for these groups have shown distinct patterns. This led us to question whether MSE could be used in an automatic algorithm to classify individual RR time series according to pathology. In previous work, we found that AF was easily distinguished. In this new work we address the greater challenge of distinguishing the effects of aging and CHF. We applied the MSE method to an expanded dataset of elderly and young healthy subjects and subjects with CHF. MSE profile curves were created for each subject (n=115). These profile curves were then used as features in Fisher’s linear discriminant and classified into three groups. Following the initial separation results, the “leave one out and test” method was used to simulate how the classifier would respond to non-training set data [13].

2. Multiscale entropy (MSE) method

The MSE method is described in [9]. Given a time series, $\{x_1, \dots, x_i, \dots, x_N\}$, we first construct consecutive coarse-grained time series by averaging a successively increasing number of data points in non-overlapping windows. Each element of the coarse-gained time series, $y_j^{(\tau)}$, is calculated accordingly to the equation:

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

where τ represents the scale factor and $1 \leq j \leq N/t$. For scale 1, the coarse-grained time series is simply the original time series.

Next, we calculated Sample entropy (SampEn) [6], a refinement of the original ApEn statistics [5], for each coarse-grained time series plotted as a function of the of scale factor τ .

3. Data

We applied the MSE method to the cardiac interbeat (RR) intervals time series derived from 24 hour ECG Holter recordings from healthy subjects and subjects with CHF.

All data analyzed here are available at <http://physionet.org> [14] and have been described in ref. [15].

The data for the normal control group were obtained from 24 hour Holter monitor recordings of 72 healthy subjects, 35 men and 37 women, aged 54.6 ± 16.2 years (mean \pm SD, range 20 – 78 years). ECG data were sampled at 128 Hz. The data for the CHF group were obtained from 24 hour Holter recordings of 43 subjects (28 men and 15 women) aged 55.5 ± 11.4 years (mean \pm SD, range 22 – 78 years). All datasets were filtered to exclude artifacts, missed detections and isolated ectopic beats. Furthermore NN intervals less than 2.0s and greater than 0.2s were excluded if the interval value differed by more than 20% from the mean of the forty surrounding interval values.

4. MSE analysis

We note that, for scale one, which is the only scale considered by traditional single-scale based methods, the entropy assigned to the time series of healthy young subjects and CHF subjects are not distinguishable, and time series of elderly healthy subjects are assigned the lowest entropy values. However, for all scales but the first one, healthy young subjects are assigned the highest entropy values, which shows that healthy dynamics are the most complex, contradicting the results obtained using the traditional SampEn or ApEn algorithms. The difference between SampEn values for healthy elderly and CHF subjects corresponding to scale 6 is statistically significant (≤ 0.05). However, for larger time scales, the SampEn values for these two groups considerable overlap. This indicates that MSE features other than absolute values of entropy may be necessary to discriminate between these groups.

The difference between the patterns of the MSE curves for healthy young, healthy elderly and CHF groups on small time scales may be due to the fact that the respiratory modulation of heart rate (respiratory sinus arrhythmia, RSA) is stronger in healthy subjects than in both elderly and CHF subjects. The RSA corresponds to a frequency peak centered close to 0.2 Hz over the RR interval power spectrum. Since entropy is a measure of regularity (orderliness), a higher amplitude of RSA is likely to result in a lower value of the entropy of the RR time series. The coarse-graining procedure filters out RSA oscillations from the RR time series, such that, for time scales larger than the average respiratory cycle length, the power spectrum of coarse-grained time series presents a $1/f$ decay over the entire frequency domain. Therefore, coarse-grained time series from healthy young subjects are likely more irregular (and are assigned higher entropy values) than the original time series.

For CHF patients, the entropy of coarse-grained time

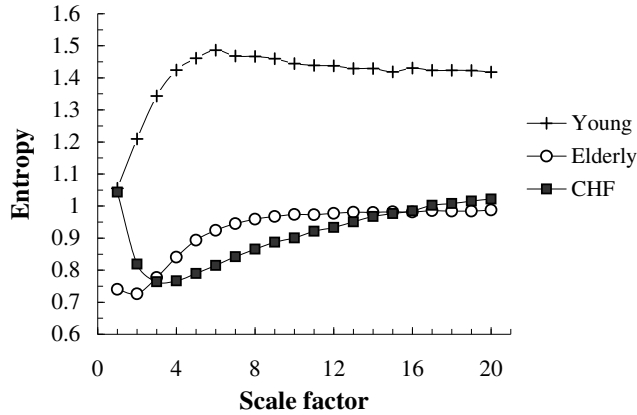


Figure 1. MSE analysis of interbeat interval time series derived from healthy young subjects, healthy elderly subjects and subjects with congestive heart failure (CHF). Symbols represent mean values for each class. The maximum standard error (SE) values are 0.059 for young, 0.043 for elderly, and 0.057 for CHF classes, respectively.

series decreases down to time scale 3 and then progressively increases. This result suggests that for CHF patients the control mechanisms regulating heart rate on relatively short time scales are the most affected.

5. Fisher discriminant analysis

We then used a Fisher's linear discriminant to determine if MSE profile curves could automatically classify individual subjects into the young healthy, elderly healthy and CHF groups. The Fisher discriminant is a technique used to reduce a high dimensional feature set, x , to a lower dimensional feature set y , such that the classes can be more easily separated in the lower dimensional space. The Fisher discriminant seeks to find the projection matrix \mathbf{w} such that when the original features are projected onto the new space according to

$$y = \mathbf{w}^t x, \quad (2)$$

the means of the projected classes are maximally separated and the scatter within each class is minimized. This matrix \mathbf{w} is the linear function for which the criterion function:

$$J(\mathbf{w}) = \frac{\mathbf{w}^t S_B \mathbf{w}}{\mathbf{w}^t S_W \mathbf{w}} \quad (3)$$

is maximized. In this equation, S_B and S_W represent the between class scatter and within class scatter, respectively. This expression is well known in mathematical physics as the generalized Rayleigh quotient. This equation can be most intuitively understood in the two class case where is

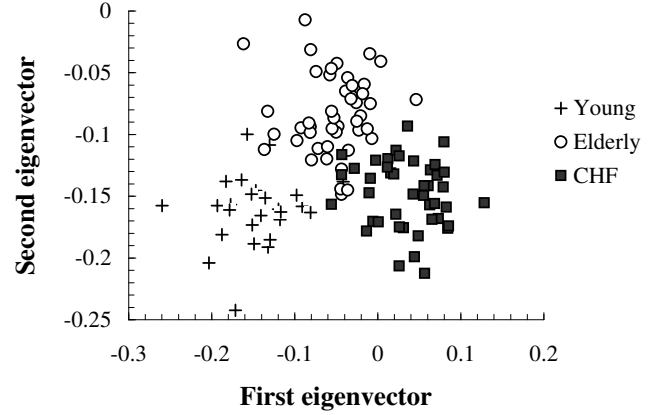


Figure 2. Projection of MSE features of the cardiac interbeat time series derived from healthy young subjects, healthy elderly and congestive heart failure (CHF) subjects. The forty dimensional feature vectors comprising the forty MSE values are projected down to two dimensions. A linear classifier was then used in this space to discriminate between the classes.

Linear Classifier Results

Recognized as:	Labeled As		
	Young	Elderly	CHF
Young	24	1	0
Elderly	2	42	3
CHF	0	3	40

Table 1. The application of the linear classifier in two dimensional space shows that young healthy subjects are entirely separated from CHF patients. There were three misclassifications between elderly and young and six misclassifications between elderly and CHF patients.

reduces to:

$$J(\mathbf{w}) = \frac{|\tilde{m}_1 - \tilde{m}_2|}{\tilde{s}_1^2 + \tilde{s}_2^2} \quad (4)$$

where \tilde{m}_1 and \tilde{m}_2 are the projected means of the two classes and \tilde{s}_1 and \tilde{s}_2 are the projected scatter of the two classes. This function is maximized when the distance between the means of the classes is maximized in the projected space and the scatter within each class is minimized. A full derivation of the solution of this problem can be found in the ref. [13].

In Figure 2 we present the results of the MSE method for the training set. For this analysis we generated MSE curves for two different values of the SampEn parameter r ($r=0.10$, $r=0.15$) [5] such that each dataset generated forty features (corresponding to time scales 1-20). These features were projected down to a two dimensional space as shown in Figure 2. From this figure it can be seen that the data separate into well-defined clusters. Using a

linear classifier in the two dimensional space we are able to correctly classify 106 out of 115 subjects, as illustrated in Table 1, giving approximately 92% separability in the training set.

To simulate how the classifier would respond to data outside the training set, we used the “leave one out and test” method where a classifier is trained on all except one subject, then the remaining “test” subject is classified. Using this method, we were able to discriminate data from the heart failure subjects from the older healthy subjects with a positive predictivity of 76% and a specificity of 83% using only the MSE features. Larger databases will be needed to confirm if automatic classification results can provide comparable results.

6. Discussion and conclusions

Previous findings using MSE show that complexity degrades with disease and aging [9]. However, using traditional single scale entropy-based measures, time series derived from healthy subjects and subjects with CHF may not be distinguishable. Furthermore, the poorest separation between young and elderly healthy subjects occurs for scale one. In contrast, the MSE method reveals that for larger time scales the highest entropy values are assigned to young healthy subjects. Therefore, MSE results are compatible with the concept that young healthy systems are the most complex and adaptive ones.

We have also shown that the characteristic MSE profile curves can be used in an automatic classification algorithm to separate young healthy, elderly healthy and CHF subjects. The accuracy of the results declined when the leave one out and test method was applied, suggesting that the classifier is overtrained to the test data. Nevertheless, high accuracies were still achieved in the two class case, supporting testing on expanded data sets to further assess clinical applicability.

The MSE method seems to have the capacity to distinguish between time series generated by different mechanisms. Furthermore, it may be applied to a wide variety of other physiologic and physical time series.

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