Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Nonlinear analysis of Heart Rate Variability signal for the characterization of Cardiac Heart Failure patients

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Abstract— **The purpose of this work is to characterize the heart rate variability (HRV) of patients affected by Congestive Heart Failure (CHF) and to find out the main difference between this pathological condition and the physiological state. Parameters adopted in this work are: the Detrended Fluctuation Analysis (DFA) and the Higuchi Exponent to assess long correlations and self-similarity; the regularity estimators, Approximate Entropy (ApEn) and Sample Entropy (SampEn) and the Multiscale Entropy (MSE). Furthermore we proposed a new regularity index, the Gaussian Entropy (GaussEn) which is a modification of the previous ApEn and SampEn. The results show the proposed parameters do an effective separation of physiological and pathological subject conditions. These results are part of a study evaluating the nonlinear index prognostic value toward cardiac death.**

Keywords—**Nonlinear analysis, CHF, Self-similarity, HRV, Entropy**

I. Introduction

Heart Rate Variability (HRV) is a widely investigated signal and it is an important marker of autonomic nervous system dysfunction [1]. Much attention was dedicated in last decades to linear methods, but the complex origin of the signal makes the traditional linear approach often inadequate and limited. This is the reason why non linear methods developed with the chaos theory became even more widespread and common [2].

The purpose of this work is to characterize the HRV of patients affected by Congestive Heart Failure (CHF) and to find out the main difference between this pathological condition and the physiological state.

In order to identify the more significant indexes we compared parameters from different methods. In particular, we adopted the Detrended Fluctuation Analysis (DFA) [3] and the Higuchi Exponent [4] to asses long correlations and self-similarity of HRV signal. We computed also regularity estimators, Approximate Entropy (ApEn) [5], Sample Entropy (SampEn) [6] and the Multiscale Entropy (MSE) [7]. Furthermore we proposed a new regularity index, the Gaussian Entropy (GaussEn) which is a modification of the previous ApEn and SampEn.

II. Methodology

A. Detrended Fluctuation Analysis (DFA)

The Detrended Fluctuation analysis technique was used to quantify the fractal correlation properties of R-R interval data. This method is a modified root mean square analysis of a random walk. In the present study, we used the scaling exponent α_1, which measures the strength of the short term (< 9 beats) correlation properties of R-R interval data, and α_2 (>10 beats), which measures long term correlation. The details of this method have been described previously [3].

B. Higuchi Exponent

Higuchi exponent is an index assessing the self-similarity in signals. The slope values obtained by this method are in agreement with the power spectral density slopes. Usually the function shows more than a slope and so it is convenient to use more than a single interval of interpolation [4].

In the present study we used the scaling exponent β_1 which measure the strength of the short term (<10 beats) correlation properties and β_2 the strength of the long term (>20 beats) correlation properties.

C Approximate and Sample Entropy

The Approximate Entropy measure, with a tolerance *r*, the regularity of patterns comparing them to a given pattern of length *m* (*m* and *r* are fixed values: *m* is the detail level at which the signal is analyzed and *r* is the threshold, which filters out irregularities) [5]. The Sample Entropy is a modification of ApEn. The differences with respect to ApEn are: (i) self-matches are not counted, (ii) only the first N-*m* vectors of length *m* are considered and (iii) the conditional probabilities are not estimated in a template manner: they do not adopt as probability measure the ratio of the logaritmic sums, but they compute directly the logarithm of conditional probability [6].

The parameters adopted for this work are *m*=2 and *r*=0.15 of the time series std.

D. Gaussian Entropy

In the present study we proposed a new algorithm to estimate the signal regularity, the Gaussian Entropy (GaussEn). It is a modification of the Approximate Entropy. The procedure to compute the GaussEn is the following: given N data points $\{u(i)\}$, the algorithm constructs the sequences $x_m(i)=[u(i),...,u(i+m-1)]$ and it computes, for each i≤N-*m*+1, the quantity:

$$n_{im}(r) = \sum_{j=1, j\neq i}^{N-m+1} \exp\left(-\frac{d[x_m(i) - x_m(j)]^2}{10 \times r^2} \right) \qquad (1)$$

where $d[x_m(i), x_m(j)] = \max_{k=0\div m-1} \{|u(i+k) - u(j+k)|\}$ and *r* is a fixed parameter to weigh the distance between two vectors, like for the ApEn *r* is a percentage of signal

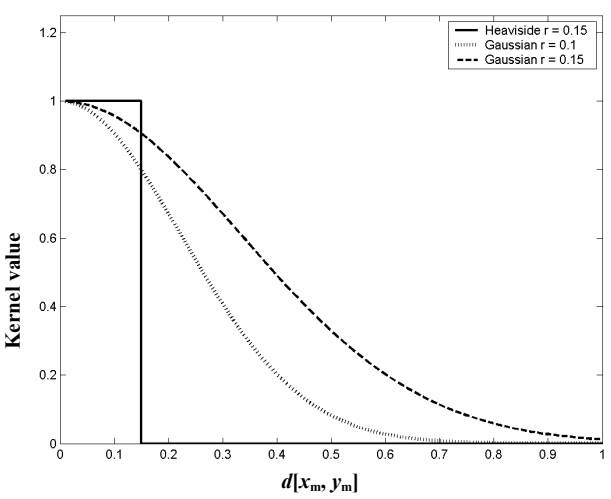

Figure 1: Difference between Heaviside function and Gaussian kernels.

standard deviation. The procedure computes then the quantity:

$$\Phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1}\ln\left(\frac{n_{im}(r)}{N-m}\right) \quad (2)$$

Finally the Gaussian Entropy is defined as:

$$\mathrm{GausEn}(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (3).$$

This algorithm differs from ApEn and SampEn because estimates the distance between two vectors not by an Heaviside threshold but by a gaussian kernel as shown in Figure 1.

The Gaussian Entropy has an important property: it monotonically decreases for increasing r values without discontinuities. This feature allows the GaussEn to be in any case consistent. The consistency is the general property for which if $\mathrm{GaussEn}(m_1,r_1)(S) \le \mathrm{GaussEn}(m_1,r_1,)(T)$ then it must be $\mathrm{GaussEn}(m_2,r_2)(S) \le \mathrm{GaussEn}(m_2,r_2,)(T)$. The choice of r and m values is thus less critical. The parameters adopted for this work are m=2 and r=0.1.

E. Multiscale Entropy

The entropy estimators previously outlined provides an indication about the complexity only of the entire time series. As proposed in [7], the analysis of signal regularity at different time scales can supply further information about the dynamical system which generated the time series. For this purpose, the so-called multiscale entropy (MSE) was developed. The procedure, given a time series of N points $\{x_i\}$, constructs consecutive coarse-grained time series $\{y^{(\tau)}\}$, determined by the factor τ, as fallows:

$$y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i \ , \ 1 \le j \le \mathrm{N}/\tau, \quad (1)$$

$\{y^{(1)}\}$ is the original time series, whereas the length of each coarse-grained time series is equal to N/ τ.

For each sequences $\{y^{(\tau)}\}$ an entropy measure is then calculated and it is plotted as a function of the scale factor τ.

If we consider a gaussian noise, the entropy values decrease when the scale factor τ increases, on the contrary a 1/f noise preserves quite constant entropy values for all scale factors [9]. Therefore we can suppose that not only the entropy values computed for different τ can characterize the signal, but also the entropy values trend can be a significant marker of the system generating the signals.

For this reasons, we proposed as new index, the slope of MSE values interpolating line, in particular we have considered the slopes of the intercept on short term scales ($\tau \le 5$) for the multiscale ApEn and on higher scale ($6 < \tau < 15$) for both the multiscale SampEn and GaussEn.

III. DATA ACQUISITION

A. Subjects

We studied 200 stable mild-to-moderate CHF patients in sinus rhythm admitted to the Heart Failure Unit of the Scientific Institute of Montescano (Italy). The patients belong to the 2nd and 3rd NYHA class, the average age of the patients is 54 years (min 47, max 58 yrs). Inclusion criteria were stable clinical condition during the last two weeks, 24 hour Holter recording (sampling frequency 128 Hz). The local ethic committee approved the study and all patients gave their informed consent[8].

The control group was selected from Normal Sinus Rhythm RR Interval Database by Physionet [10]. It includes RR intervals time series of 24 hours Holter recordings belonging to 54 healthy subjects (30 men, 24 women) aged 61±11. Sampling frequency is 128 Hz.

B. Signal Pre-Processing

Holter recordings of CHF patients were processed using an Elatec system (ElaMedical, software release 3.0). Each beat was first automatically labeled by the Holter analysis software and then edited by an expert technician. Annotated RR time series were processed to correct for ectopic beats (linear interpolation).

Pathological and physiological time series were corrected to minimize errors: whenever an RR-interval differs by more than 30% from the mean of the 6 previous values it was considered as an artifact and so it was substituted with the mean of the previous 6 samples.

In the first part of our work we analyze the entire time series. Successively, we selected 5 one-hour sequences and 10 sequences of 15 min for each subject. All the sub-sequences refer to daytime.

IV. RESULTS

A. DFA

By applying DFA method to the whole 24 hour series we have found results consistent with other studies: α_1 and α_2 values are significantly different between physiological

and pathological subjects and α_1/α_2 ratio is >1 for normal group and <1 in CHF group (control group: α_1=1.24±0.19 and α_2=1.10±0.11; CHF: α_1=1.13±0.24 and α_2=1.22±0.14; *p*-value α_1 <0.01, *p*-value α_2 <10^{-7}). As outlined, the long term exponent performed better and therefore it can be considered a good indicator of CHF condition.

From the analysis on 15 and 60 min long series, we have obtained similar results. Short term and long term exponent in 15-minutes series were: Control group: α_1=1.20±0.28, α_2=1.06±0.15; CHF: α_1=1.09±0.27 α_2=1.18±0.18; p-value<0.0001 for α_1 and α_2.In the 60-minutes series: Control group: α_1=1.20±0.25, α_2=1.07±0.12; CHF: α_1=1.08±0.26, α_2=1.19±0.16; p-value α_1, α_2<10^{-9}. Figure 2 illustrates an example.

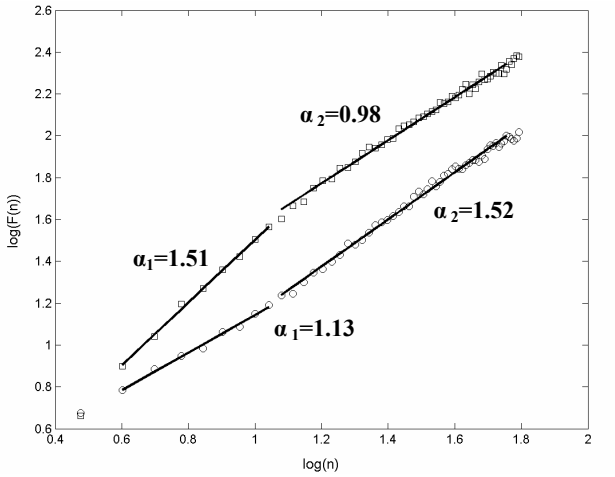

Figure 2: Example of a pathological and an healthy subject DFA analysis from 60 min traces. The upper curves refer to the healthy subjects, whereas the lower ones to the CHF patient.

B. Higuchi

We have obtained important results but not so significant as the previous ones, obtained by DFA method. The analysis on 24 hour time series has not given statistically significant results (control group: β_1=1.66±0.09; β_2=1.84±0.07; CHF: β_1=1.69±0.11; β_2=1.85±0.05; p-value β_1 >0.05 and p-value β_2 <0.05).

The analysis on 15 and 60 minute time series has performed better: the 15 minute time series show the first slope more significant than the second one (control group: β_1=1.67±0.13, β_2=1.06±0.15; CHF: β_1=1.71±0.13, β_2=1.18±0.18; p-value β_1<10^{-8} and p-value β_2<10^{-7}), whereas the 60 minute sequences show the second slope more discriminating than the first one (control group: β_1=1.67±0.11, β_2=1.81±0.13; CHF: β_1=1.71 ±0.12, β_2=1.84±0.08; p-value β_1<10^{-5} and p-value β_2<10^{-8}).

C. Approximate and Sample Entropy

Approximate and Sample Entropy have shown good results both for 24 hour and 60 minutes time series. Furthermore we obtained higher entropy values in pathological subjects than in physiological (control group: ApEn(2,0.15)= 0.77±0.28, SampEn(2,0.15)= 0.58±0.24; CHF: ApEn(2,0.15)= 0.93±0.30; SampEn(2,0.15)= 0.73±0.27; p-value ApEn <0.001, p-value SampEn <0.001).

The higher values in pathological patients can be related to an increase of unpredictability of their signals. In the same time, the incidence of ectopic beats in CHF is a factor requiring a deeper investigation as it is normally higher in CHF than in healthy subjects.

Nevertheless, ApEn and SampEn have produced significant results also in 15 minutes sequences (control group: ApEn=1.19±0.30, SampEn=1.34±0.52 and CHF: ApEn=1.25±0.21, SampEn=1.44±0.46; p-value ApEn<10^{-7} and p-value SampEn<10^{-4}).

D. Gaussian Entropy

By applying GaussEn to 60 and 15 minute long time series we obtained values which are consistent with the results obtained from the other entropy estimators: pathological subjects have higher entropy values than physiological ones.

The analysis on 60 minute time series produced significant results (control group: GaussEn=0.53±0.20, CHF: GaussEn=0.59±0.20; p-value GaussEn<10^{-5}).

Furthermore, the GaussEn high rate of convergence produced good performance also for the 15 minute time series (control group: GaussEn=0.70±0.27; CHF: GaussEn=0.77±0.27; p-value GaussEn<10^{-8}).

We excluded from this analysis the computation on 24 hour time series because GaussEn algorithm is very time expensive.

E. Multiscale Entropy

The results have shown that pathological and physiological subjects have different values and slopes. The MSE values of healthy group has a trend monotonically increasing whereas CHF patients have a negative slope β_1 for the first two scales and a positive slope β_2 for the successive scales. This negative trend had been already found in a previous work by Goldberger [7]. Our analyses confirm this feature: all entropy estimators adopted for the MSE analysis provide a negative slope β_1.

Figure 3 shows that physiological subjects have a constant trend for the middle scale factor, while pathological ones show higher Multiscale Entropy values and an increasing trend.

The results are significantly discriminating for both slopes, in particular β_1 is significant for the multiscale ApEn (control group: β_1=-0.02±0.08; CHF: β_1=-0.007±0.09 and p-value β_1<10^{-7}). β2 is significant both for the multiscale SampEn (control group: β_2=0.0043±0.015; CHF:

β_2=0.023±0.015; p-value β_2=0) and for the multiscale GaussEn (control group: β_2=0.0043±0.011; CHF: β_2=0.017±0.014; p-value β_2=0). This difference is probably due to the slower convergence of the ApEn algorithm in respect to the other entropy estimators.

The application of Multiscale Entropy to 15 minutes time series has not been possible because the samples are not enough for this analysis.

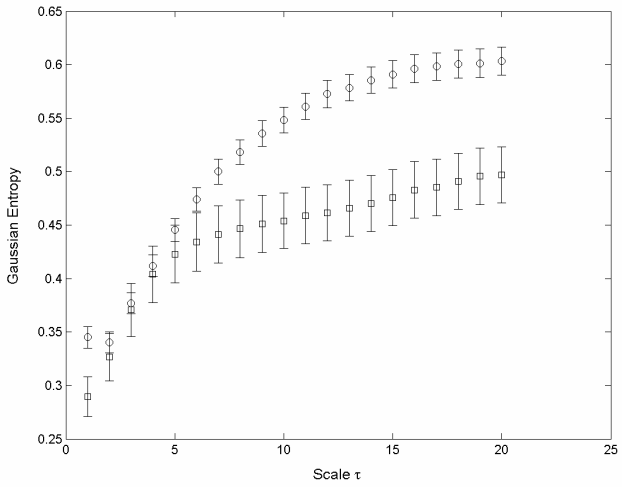

Figure 3: Plot of the Gaussian Entropy calculated in a pathological CHF patient (lower values in the plot) and in a healthy subject (higher values). 60 min HRV were considered for the analysis

V. Discussion

Our results show that many non-linear indexes are good indicators of CHF condition. For example, the different slopes and the different type of crossover in DFA function confirmed to be skilled marker of CHF condition. In addition, these results are consistent with previous works. This demonstrates how self-similarity and long term correlations features are significantly different in HRV time series of pathological subjects from physiological ones [2].

In contrast with the work of Costa et al.[7] where CHF patients had shown lower values of entropy than physiological patients, our results presented higher entropy values for pathological subjects and lower entropy values for physiological ones.

This difference is probably due to the different CHF population, the subjects described in [7] were more compromised, whereas our subjects belonged only to the 2nd and 3rd NYHA class. It is possible that our pathological subjects have a behavior more similar to physiological ones but with the typical ectopic beats. These beats do not have a predictable frequency leading to an entropy increase.

Notice that the MSE trends obtained in the present study are however coherent with those illustrated in [7]. In particular, the similarities to that study are: negative slopes at first scale factors and a minimum of MSE function at scale 2 for the CHF patients, finally the increasing trend in pathological subjects for τ>6 in contrast to the quite stable MSE trend in normal subjects.

VI. Conclusion

The results of our study have confirmed how nonlinear methods are useful to classify CHF patients and healthy subjects. Many of these methods have been able to produce reliable results not only in 24 hour sequences analysis but also in 60 minute time series. Moreover some of this methods have produced significant results even in 15 min time series.

The reduction of time series length leads in a save of computing time needed to estimate these indexes and thus in a major suitability in clinical practice.

As a further development we are going to build up an automatic classifier based on a supervised neural network architecture having an input of 10 parameters obtained by our analysis selected upon their statistical significance.

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