WORKING ON THE NOLTISALIS DATABASE: MEASUREMENT OF NONLINEAR PROPERTIES IN HEART RATE VARIABILITY SIGNALS

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Abstract- **We present results obtained from the analysis of 50 heart rate variability series (HRV) which have been extracted from Holter recordings in the 24-hours in normal subjects and pathological patients. Data have been collected inside a multicentric research program, which aimed at the nonlinear analysis of HRV series. Multifractal approaches such as generalized structure functions have been used to characterize the HRV signal. Moreover, classical parameters for the analysis of the HRV signal over long time scales have been considered to perform a proper comparison. We considered classical time-domain indexes, "monofractal" characteristics ($1/f^{\alpha}$ spectrum; detrended fluctuation analysis) and a regularity statistic (approximate entropy).**

The hypothesis of nonlinearity for the HRV signal has been verified by computing the generalized structure function on a set of surrogate data (amplitude adjusted surrogate data). In most cases, the multifractal spectrum of the original HRV series significantly differs (t-test), from those obtained from surrogate signals. This result can be associated with the presence of nonlinear correlations in the HRV signal. Moreover, results show that nonlinear parameters can be used to separate normal subjects from patients suffering from cardiovascular diseases.

Keywords **- Heart rate variability, nonlinear dynamics, multifractal analysis.**

I. INTRODUCTION

The control mechanisms of cardiovascular system can be studied by analyzing one of the system observed variables, mainly the electrocardiographic signal (ECG) and in particular the series of R-R intervals, called heart rate variability (HRV) signal, which is directly derived from it [1]

Heart rate variability signal analysis has become a widely employed tool in the diagnosis of cardiovascular diseases. Recent studies [2] attempted a standardization of the methods generally employed, both in time and frequency domain. The proposed approaches suppose the HRV signal as produced by linear mechanisms with some superimposed noise. More recently, a strong investigation effort has been dedicated to analysis in the field of nonlinear parameters [3][4]. Certainly, several nonlinear mechanisms play a role in the control of cardiovascular system, but the question about their important (and detectable) action in the modulation of the HRV series remain open.

For this reason we organized a study group having the goal to assess nonlinear properties in experimental time series from biologic origin. We concentrated on the analysis of HRV time series as they contain information about neural mechanisms controlling the heart and, in the same time, can assure good performances in terms of quality and length of the data.

The work on the Noltisalis database has two main objectives: (i) to gain additional information on the long period behavior of the cardiovascular system and (ii) to test statistical indexes, able to significantly discriminate pathological subjects, with a possible diagnostic application [5]. The new information obtained within objective (i) could be used, in the future, to construct a new model of the mechanisms generating and controlling the heart rate or to refine an existing one. The measurement of nonlinear properties of HRV signal considered several parameters. Among them, classical time-domain statistics or spectral analysis approaches are commonly used even in the diagnostic process.[2] Other methods are still research matter, as the multifractal analysis approach or other parameters from nonlinear analysis field [6].

II. THE NOLTISALIS DATABASE

The Noltisalis database was collected by the cooperation of several university departments and rehabilitation clinics in Italy. The acronym Noltisalis stands for "Nonlinear time series analysis" and highlights the objectives of the multicentric project: to study the nonlinear nature of the heart rate variability signal from a time series perspective [5] [7].

The database is composed by 50 RR series extracted from 24-hours Holter recordings and by other signals coming both from physiologic measurements and models [8] and from simulations of classic nonlinear models (Henon, Lorenz and Rossler; 5 series each). ECG data were recorded using different Holter devices. Through proper analysis software, HRV series were calculated. The five subsets, which compose data set of the 24-hours Holter series, correspond to different physiopathological conditions. Table 1 summarizes the structure of the database concerning the HRV series.

III. METHODOLOGY

A Classical Parameters for Statistical Characterization

Classical statistics, which have been considered in the paper, include time-domain measures of HRV [2]. Among possible time-domain indexes, a set of four measures has been considered. The suffix NN means that only normal-to-normal RR intervals in the ECG signal generate the measure. SDNN is the standard deviation of the RR series. RMSSD is the square root of the mean squared differences of successive RR intervals and it provides a common estimate of short-term components of HRV. SDANN is the standard deviation of the reduced series obtained by averaging the whole sequence over 5-minutes windows.

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Abstract

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TABLE I
STRUCTURE OF THE NOLTISALIS DATABASE

Population	Code	N of Series	Device
Normal	NR	10	custom
Hypertension	IP	10	Del Mar Avionics
myocardial infarction (after)	MI	10	custom
Heart failure (A)	SC	5	custom
Heart failure (B)	SC	5	Oxford Medilog Excel
heart transplanted	TR	10	Oxford Medilog Excel

Table1 The 50 RR 24-hours series in the Noltisalis database are classified into five populations. For each of them the number of subjects is indicated. Some recordings were obtained with custom Holter recorders.

HTI is the "Heart Triangular Index". It is inversely proportional to the peak of the probability density of the RR intervals, which can be estimated by means of normalized histograms. The mean RR interval μNN was computed as a reference only.

B Monofractal Approach

As has been observed in many physical, biological and physiological systems, experimental time series can exhibit a power law PSD form that is called 1/f noise.

This behavior has been observed even in RR series in 24 hours [9]. The model

$$\log PSD(f) = C - \alpha \log f \qquad (2)$$

has been fitted on the power spectrum $PSD(f)$ obtained via FFT technique. The α slope is usually computed by regressing power values in the frequency range (0.02-0.04] Hz in log-log scale. It was found that $\alpha \approx 1$ identified the HRV of normal subjects. Fig. 1 displays an example of periodogram in log-log scale.

Stationary stochastic processes displaying power law PSD of the form $PSD(f) = Cf^{\alpha}$ are also called scaling or self-affine [10] Techniques presented in this section aimed at quantify the degree of self-affinity in a time series, by providing the estimation of the scaling exponent $H \in [0,1]$, through different approaches. Self-affinity means that if the time scale is rescaled by a factor Δ and the signal itself is rescaled by a factor Δ^{-H}, then the transformed time series has the same statistical properties as the original one. H can be computed directly on the RR series:

$$\langle |RR_{n+\Delta} - RR_n| \rangle = \Delta^H \langle |RR_{n+1} - RR_n| \rangle. \qquad (1)$$

By plotting $\langle |RR_{n+\Delta} - RR_n| \rangle$ versus Δ on a log-log scale, we obtain a graph which is a straight line whose slope is the value of H. A self-affine signal is, by definition, fractal.

Detrended Fluctuation Analysis (DFA) is a fractal-related method estimating the scaling exponents α (the slope of the power spectrum) [11]. DFA provides a couple of scaling exponent n_1 and n_2, which should be robust against the non-stationarity of time series. The exponent n_1 is called "short-term fractal exponent" and it is computed on short scales ($\Delta <$ 16) as the n_2, which is identified as "long-term fractal exponent", expresses the scaling on longer scales ($100 \leq \Delta \leq 4000$). n_2 is related to the slope of the power spectrum by the relation $\alpha = 2n_2 - 1$. We computed both exponents on the entire database.

C. Multifractal Approach: Generalized Structure Functions

The more general class of fractals are multi-scale fractals, or *multifractals*, which are characterized by multiple subdivisions of the original into N objects, each one magnified by a different factor r_i, with i=1,2,...,N.

The method computes a multifractal spectrum, h_q. When the h_q values decrease as a function of the order q, the process is multifractal; For q=1 exponent $h_1 \equiv H$ scaling monofractal exponent. The computation of the multifractal spectrum on the Noltisalis series followed the generalized structure function approach [12]. Generalized structure functions,

$$GSF(\Delta, q) \equiv \langle |X_{n+\Delta} - X_n|^q \rangle \qquad (3)$$

were computed for each RR series in the database. The index q varies from q = 1, · , 10 and $\Delta < N/2$. GSF for a NR healthy subject are displayed in figure 2 panel (a). As expected, the plot shows three different regions: (i) a steep growth for the smallest time lags ($\approx\leq$ 16); (ii) a good linear scaling region at inter-mediate scales ($\Delta \in [100; 5000]$) and (iii) a third region at large scales where the hypothesis of signal stationarity breaks down and the behavior gets unpredictable ($\Delta > 5000$).

The linear scaling region is the more important one. We expect a fractal process to present GSF linearly scaling. In this region, for Δ in the interval [100, 5000], the model $GSF(\Delta, q) = AD^{jhq}$ was fitted onto each structure function. Moreover a true multifractal process is characterized by decreasing scaling exponents for increasing q ($h_q < h_p$ for $q > p$). Panel (b) of figure 2 reports the h_q exponents, computed on the GSF of panel (a). The construction of 10 surrogate data series for each original HRV signal, through the Amplitude-Adjusted Fourier Transform technique allowed excluding

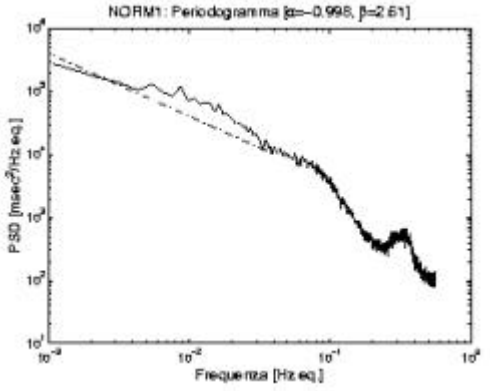

Fig. 1 Log-log plot obtained from a 24 hour RR signal in a Normal subject of the Noltisalis database; α=-0.998.

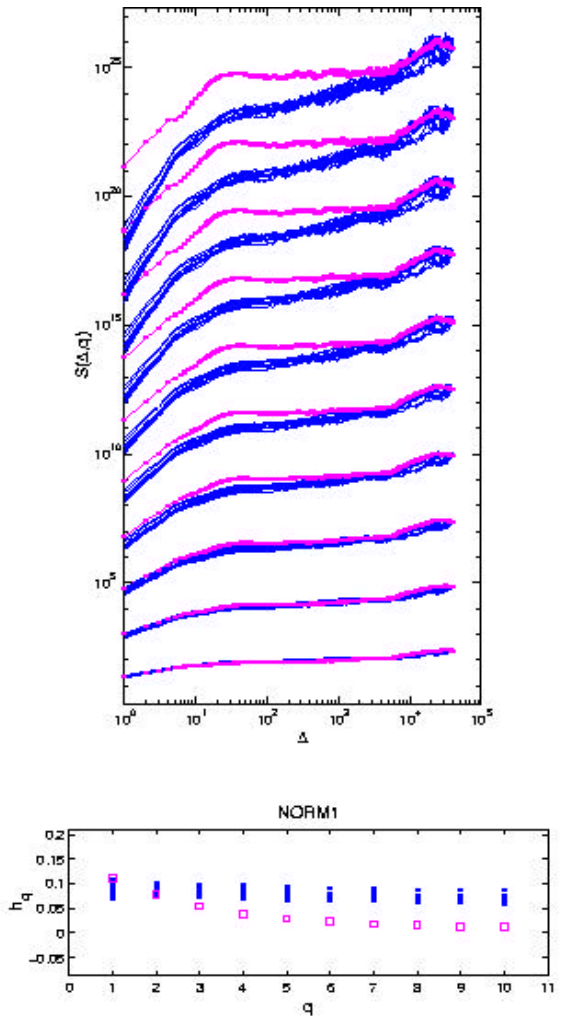

Fig. 2: Upper panel shows structure functions S(Δ,q) for the HRV series of a Noltisalis database subject (NR1), for q=1..10 (bottom to top), in the range Δ∈ [100,5000]. Structure functions for surrogate data are displayed as well. Lower panel reports the values of h_q: squares are values from RR series as dots come from surrogate data

spurious multifractality in the data [13]. In fact, GSF of surrogate data, as shown in Fig.2, confirm h_q values (blue lines and dots) are constant as expected for a colored noise..

IV. RESULTS

The multifractal spectrum of the exponents h_q which has been computed through the structure functions method in HRV series, shows a decreasing course, for increasing q. This behavior is often the marker of multifractal processes and may be associated with the presence of nonlinear correlations in the signal. Moreover this behavior can be associated to the nonlinear nature of the HRV signal. In fact, 32 over 50 h_q spectra were statistically different ($p<0.01$) from their surrogate series. This finding would realistically support the hypothesis of a multifractal structure in RR series even if the values we obtained for the h_q exponents were small (approximately <0.12 for normal subjects). Moreover, results from the different techniques we employed, seem to confirm the presence of dynamic nonlinearities in the RR series, thus providing a contribution in the investigation of the nonlinear nature of the beat-to-beat series.

The second objective of the work was that of testing calculated parameters in order to find statistical indexes that were able to significantly discriminate pathological patients from healthy subjects.

Table 2 compares the performance of each parameter considered in the study, in term of its ability to discriminate a pathological population from the healthy one, by means of a t-test. Parameters are grouped (from the top):in (i) statistical & geometrical, (ii) fractal, (iii) multifractal and (iv) from various origin. The significance levels are: ✓✓✓ ($p < 0.001$), ✓✓ ($p < 0.01$) and ✓ ($p < 0.05$).

The multifractal exponents h_q performed the best classification.

$h_1 \equiv H$ was the only index, among those considered, which was able to distinguish all the four pathologic populations from the normal one confirming its clinical importance and its diagnostic ability [15].

Inside monofractal parameters, the slope α of the power spectrum is also a marker of self-affinity. α slope confirms its clinical relevance. In fact α demonstrated an excellent ability in the prediction of patient mortality, higher than other traditional power spectral parameters that quantify the RR variability [4]. We found that the RR series in the database display a very good scaling in the frequency range (0-0.04] Hz_{eq} . Values are summarized in Fig. 3. For each subject belonging to the Noltisalis database, the value of α slope is displayed. Columns 1 to 5 in the x axis correspond to Normal, Hypertensive, Myocardial Infarction, Heart Failure and Transplanted subjects respectively. This result implies that the current value of the heart rate varies not only as a function of its most recent values but also as a function of its long-term history in a scale-invariant manner.

Values of each multifractal exponent have been compared along the whole database. h_q proved to be very effective in this discrimination between normal and pathological patients, in particular with $q = 1, 2$ and 3.

A multivariate approach putting together multifractal indexes and classical time and frequency domain parameters could be a possible diagnostic application of the described approach to the analysis of HRV time series.

In summary, the various methods employed did not contradict the statement that a nonlinear process generates the RR series. Some results presented in the paper are remarkable and significant from a methodological point of view. In particular, results with multifractal exponents suggested that they can be used simply as statistical indexes as they performed better than any other considered methods in the discrimination between healthy subjects and patients with cardiac diseases. In our opinion this observed improvement indicates that new properties of the HRV signal are taken into account and exploited by the approach described in the paper.

TABLE II
EVALUATION OF PARAMETERS

NORM vs/	IP	MI	SC	TR
μNN	✓	-	-	✓
SDNN	-	✓✓	✓✓✓	✓✓✓
RMSSD	-	-	✓✓	✓✓✓
SDANN	-	✓✓	✓✓✓	✓✓✓
HTI	-	✓✓	✓✓	✓✓✓
a spectrum	✓	-	-	✓✓✓
n_1 DFA	-	-	-	✓✓✓
n_2 DFA	✓✓✓	-	-	✓✓✓
h_1 @ H	✓✓	✓	✓✓✓	✓✓✓
h_2	✓✓	-	✓✓✓	✓✓✓
h_3	✓	-	✓✓✓	✓✓✓
h_R	-	-	-	✓✓
ApEn night	-	-	-	✓
ApEn day	-	-	-	-

Table 2: Parameters are grouped (from the top):in (i) statistical & geometrical, (ii) fractal, (iii) multifractal and (iv) from various origin. The significance levels are: ✓✓✓ ($p < 0.001$), ✓✓ ($p < 0.01$) and ✓ ($p < 0.05$). "μNN" is the mean RR interval; "SDNN", "RMSSD", "SDANN" and "HTI" are classical time-domain measures (see text); "α" is the power spectrum slope (log-log graph) in the lower frequencies; "n_1" & "n_2" are the DFA fractal exponents; "h_q" are the q^{th} scaling exponents obtained through Generalized Structure Function approach; "ApEn night" and " ApEn day" are the approximate entropies ($m = 2$, $r = 0.2 \cdot$ SDNN) computed in six night hours (from 24.00 to 6.00) and six day hours (from 12.00 to 18.00) of RR series, respectively [14].

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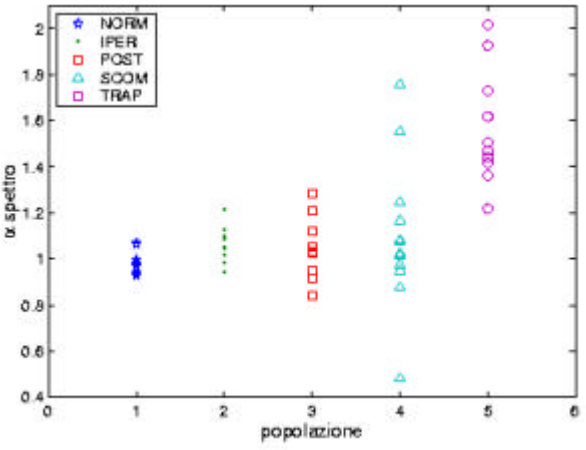

Fig. 3: α slope values of the spectrum, calculated in the 24 hours RR series in the Noltisalis database. Values of all 50 subjects are shown. Column 1 corresponds to Normal, Col 2 to Hypertensive, Col 3 to Myocardial Infarction, Col 4 to Heart Failure and Col 5 to Transplanted patients.