Multiscale analysis of heart rate, blood pressure and respiration time series

L. Angelini\textsuperscript{1,2,3}, R. Maestri\textsuperscript{4}, D. Marinazzo\textsuperscript{1,2,3}, L. Nitti\textsuperscript{1,3,5}, M. Pellicoro\textsuperscript{1,2,3}, G. D. Pinna\textsuperscript{4}, S. Stramaglia\textsuperscript{1,2,3}, S.A. Tupputi\textsuperscript{2}

\textsuperscript{1}TIRES-Center of Innovative Technologies for Signal Detection and Processing, Università di Bari, Italy
\textsuperscript{2}Dipartimento Interateneo di Fisica, Italy
\textsuperscript{3}Istituto Nazionale di Fisica Nucleare, Sezione di Bari, Italy
\textsuperscript{4}Dipartimento di Bioingegneria, Fondazione S. Maugeri, IRCCS, Istituto Scientifico di Montescano (PV), Italy
\textsuperscript{5}Dipartimento di Biochimica Medica, Biologia Medica e Fisica Medica, University of Bari, Italy

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We present the multiscale entropy analysis of short term physiological time series of simultaneously acquired samples of heart rate, blood pressure and lung volume, from healthy subjects and from subjects with Chronic Heart Failure. Evaluating the complexity of signals at the multiple time scales inherent in physiologic dynamics, we find that healthy subjects show more complex time series at large time scales; on the other hand, at fast time scales, which are more influenced by respiration, the pathologic dynamics of blood pressure is the most random. These results robustly separate healthy and pathologic groups. We also propose a multiscale approach to evaluate interactions between time series, by performing a multivariate autoregressive modelling of the coarse grained time series: this analysis provides several new quantitative indicators which are statistically correlated with the pathology.

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I. INTRODUCTION

Physiological systems are ruled by mechanisms operating across multiple temporal scales. Many approaches have been developed in the last years to analyze these complex signals, including, for example, studies of: Fourier spectra \textsuperscript{1}, chaotic dynamics \textsuperscript{2}, scaling properties \textsuperscript{3}, multifractal properties \textsuperscript{4}, correlation integrals \textsuperscript{5}, $1/f$ spectra \textsuperscript{6} and synchronization properties \textsuperscript{7}. A recently proposed approach, multiscale entropy analysis (MSE) \textsuperscript{8}, compares the degree of complexity of time series at varying temporal scale, and has been applied to 24 hours electrocardiographic recordings of healthy subjects, subjects with congestive heart failure, and subjects with atrial fibrillation. Results from this analysis support the general complexity − loss theory of aging and disease, since healthy and young dynamics are the most complex.

In this paper we apply the MSE analysis to short-term simultaneous recordings of electrocardiogram, respiration signal and arterial blood pressure, from healthy subjects and from subjects with Chronic Heart Failure (CHF), a disease associated with major abnormalities of autonomic cardiovascular control.

We also consider here a multiscale version of the classical multivariate autoregressive analysis of time series, to find scale-dependent patterns of interactions between the physiological time series here considered. The paper is organized as follows. In the next section we describe our data set, the methods and the results we obtain. Some conclusions are drawn in section III.

II. DATA, METHODS AND RESULTS

We briefly recall the MSE method \textsuperscript{8}. Given a one-dimensional discrete time series, consecutive coarse grained time series, corresponding to scale factor $\tau$, are constructed in the following way. First, the original time series is divided into nonoverlapping windows of length $\tau$; then, data points inside each window are averaged, so as to remove fluctuations with time scales smaller than $\tau$. For scale one, the coarse grained time series is simply the original time series; the length of each coarse grained time series is equal to the length of the original time series divided by the scale factor $\tau$. Finally an entropy measure $S_E$ is calculated for each coarse grained time series and plotted as function of the scale factor $\tau$. $S_E$ coincides with the parameter $S_E(m,r)$, introduced by Richman and Moorman \textsuperscript{9} and termed sample entropy, which is related to the probability that sequences from the time series, which are close (within $r$)
for \( m \) points, remain close at the subsequent data point. In the original proposal both the sequence length \( m \) and the tolerance parameter \( r \) were kept fixed as \( \tau \) was varied, so that changes in \( S_E \) on each scale were depending both on the regularity and the variability of the coarse grained sequences \( 10 \). In the present work we take \( r \), at each \( \tau \), inversely proportional to the standard deviation (SD) of the coarse grained time series, and consider separately how the SD of signals varies with the time scale.

Our data are from 47 healthy subjects and 275 stable mild to moderate CHF patients in sinus rhythm admitted to the Heart Failure Unit of the Scientific Institute of Montescano for evaluation and treatment of heart failure, usually in conjunction with evaluation for heart transplantation. Concerning the second group, cardiac death occurred in 54 patients during a 3-year-follow-up. In two different conditions of respiration, basal and paced breathing (at 0.25 Hz) \[11\], ten minutes long physiological recordings have been made on these subjects, leading to four time series. Firstly, the heart RR interval time series \( (rri) \); for each cardiac cycle, corresponding values of the systolic arterial pressure \( sap \), the diastolic arterial pressure \( dap \) and the instantaneous lung volume \( ilv \) were computed. The four time series have then been re-sampled at 2Hz using a cubic spline interpolation. Part of this data set (the \( sap \) time series) has been already analyzed in \[12\] using a different approach.

In figure 1 we depict the standard deviations of the coarse grained time series in basal condition. Due to the short length of the samples at our disposal, we consider \( \tau \leq 10 \) so as to have sufficient statistics at each scale; this implies that our analysis will be limited to part of the High Frequency (HF) band (0.15-0.45Hz), the band in which the respiratory rhythm of most people lies. In all cases, on average the standard deviation is a decreasing function of the scale; healthy subjects show greater variability than patients, except for \( ilv \) signals, where patients on average have the highest variability. Similar patterns of standard deviations are obtained in paced breathing conditions.

As already stated, to extract the sample entropy from these signals, we take \( r \) equal to a fixed percentage (15%) of the standard deviations of the coarse grained time series; we take \( m = 1 \). In figure 2 we depict the average \( S_E \) of \( rri \) time series of controls, patients and dead patients, in basal condition (high) and paced breathing (low). Concerning the basal case, we note that controls have always significantly higher entropy than CHF patients, at all scales, and that dead patients show slightly more regular \( rri \) time series than the average over all patients. The severity of the pathology seems to be correlated with the loss of entropy. On the right we depict, as a function of the scale factor \( \tau \), the probability that \( rri \) entropy values from controls and patients were drawn from the same distribution, evaluated by non parametric rank sum Wilcoxon test: the discrimination is excellent at intermediate \( \tau \)'s. This picture is in agreement with findings in \[3\], corresponding to controls and subjects with congestive heart failure in sinus rhythm, except for a different form of the entropy curve for patients, which indeed depends on the pathology. In the case of paced breathing the three curves get closer and the discrimination, between patients and controls, reduces: paced breathing seems, in the case of \( rri \) entropy, to reduce differences between patients and controls.

In figure 3 we depict \( S_E \) of \( sap \) time series. We find that at low \( \tau \) patients have higher entropy, whilst at large \( \tau \) they have lower entropy than controls. The crossover occurs at \( \tau = 3 \) in basal conditions, and \( \tau \sim 6 \) for paced breathing. The complexity – loss paradigm, hence, here holds only for large \( \tau \). This may be explained as an effect of respiration, whose influence seems to become weaker as \( \tau \) increases. This effect is more evident in conditions of paced breathing. Our results are consistent with those obtained in \[12\] using a different approach and with \( \tau = 1 \). It is interesting to observe that curves corresponding to dead patients are always farther, from the controls curve, than the average curve from all patients; departure from the controls curve seems to be connected with the severity of the disease.

In figure 4 we consider \( dap \) time series. We find a similar pattern to \( sap \): patients have higher entropy at low \( \tau \) and lower entropy than controls at large \( \tau \). Again the crossover occurs at \( \tau = 3 \) in basal conditions, and \( \tau = 6 \) for paced breathing.

Now we turn to consider \( ilv \) time series, as depicted in figure 5. In the basal case, controls have higher entropy at small scales. On the other hand controls show lower entropy than patients at \( \tau > 7 \): patients pathologically display fluctuations of \( ilv \) at larger scales than healthy subjects. Under paced breathing, controls are characterized by reduced fluctuations at high \( \tau \); at \( \tau = 4 \), when the window size is half of the respiration period, controls show a local minimum of the entropy. These phenomena are not observed for patients, where paced breathing is less effective in regularizing the \( ilv \) time series.

Next we implement a multiscale version of autoregressive modelling of time series (see, e.g., \[12\]). For each scale factor \( \tau \), we denote \( x = (rri, sap, dap, ilv) \) the four-dimensional vector of the coarse grained time series. At each scale, all coarse grained time series are normalized to have unit variance. A multivariate autoregressive model of unity order is then fitted (by standard least squares minimization) to data:

\[
x(t) = A x(t-1);
\]

A is a \( 4 \times 4 \) matrix, depending on \( \tau \), whose element \( A_{ij} \) measure the causal influence of \( j-th \) time series on the \( i-th \) one. Some of these matrix elements are found to be significantly different in patients and controls, as described in the following.
Firstly we consider the interactions between heart rate and blood pressure. In physiological conditions heart rate and arterial pressure are likely to affect each other as a consequence of the simultaneous feedback baroreflex regulation from sap-dap to rri and feedforward mechanical influence from rri to sap-dap [14].

In figure 6 the curves representing the causal relationship rri → sap are represented. Both in basal and paced breathing conditions, this coefficient is always negative and is stronger for controls. Two mechanisms determine the feedforward influence rri → sap. Firstly the Starling law, stating that when the diastolic filling of the heart is increased or decreased with a given volume, the volume of blood which is then ejected from the heart increases or decreases by the same amount. More blood in: more blood out. This mechanism favors an increase of sap-dap as the rri interval increases, i.e. a positive coefficient rri → sap. The second mechanism is diastolic decay, described by the Windkessel model of the capacitative property of arteries; as rri interval increases, this effect tends to lower sap-dap values and gives a negative contribution to the coefficient rri → sap. Our finding suggests that the second mechanism is dominant. The difference between patients and controls is significant at low and intermediate \( \tau \), and especially in basal conditions. The coefficient rri → dap shows a behavior very similar to those of rri → sap, i.e. it is always negative and is stronger for controls.

Evaluation of baroreflex regulation sap-dap → rri is an important clinical tool for diagnosis and prognosis in a variety of cardiac diseases [15]. Recent studies, see e.g. [16] and references therein, have suggested that spontaneous fluctuations of arterial pressure and rri offer a noninvasive method for assessing baroreflex sensitivity without use of provocative tests employing injection of a vasoconstrictive drug or manipulation of carotid baroreceptor. In fig. 7 we depict the interaction dap → rri as extracted by our approach, showing high discrimination between controls and patients. In basal conditions this coefficient is positive for controls and negative for patients. Moreover, this coefficient for patients is much influenced by respiration: in paced breathing conditions it is almost zero for patients, while being positive for controls. It is worth stressing that the interaction dap → rri, evaluated by the present approach, has only little relation with the baroreflex sensitivity index considered, e.g., in [16]; indeed the procedures for evaluating these quantities differ in several steps. For example in our approach all time series are centered and normalized, hence the interaction between arterial pressure and rri is described only qualitatively.

Human respiration interacts with heart rate, originating the well known phenomenon of respiratory sinus arrhythmia [17]. We find that the interaction rri → ilv is significantly \((p < 10^{-4})\) stronger in controls than patients, under paced breathing and using \( \tau = 4 \). We also find that the interaction ilv → rri is positive and significantly \((p < 10^{-5})\) stronger in controls, in basal conditions and at high frequencies \((\tau \leq 4)\).

Let us now turn to consider self interactions of time series. The matrix element \( A_{11} \) describes how much the rri signal depends on its value at the previous time. As it is shown in figure 8, in basal conditions \( A_{11} \) is significantly lower for controls. In paced breathing conditions significant difference is found at high \( \tau \). Also the self interaction of dap time series gives rise to an interesting pattern. It is stronger for controls, especially at low \( \tau \), leading to high discrimination between controls and patients at low \( \tau \) as figure 9 shows.

The interaction of systolic and diastolic arterial pressure in healthy subjects has been recently studied in [18]. In the present analysis we find significant differences between patients and controls when the interaction sap → dap is considered, see figure 10. For controls, this coefficient is always negative and its strength increases with \( \tau \).

It is known that respiration interacts in an open loop way with arterial pressure, mainly through a mechanical mechanism [14]. Our findings confirm it: indeed we find no significant sap → ilv interaction, but significant \((p < 10^{-3})\) differences between patients and controls are found when the interaction ilv → sap is considered: controls show reduced interaction w.r.t. patients.

III. CONCLUSIONS

In the present paper we have presented the multiscale entropy analysis of short term physiological time series. We have shown that the analysis of [9] can be successfully performed also on short rri recordings, still leading to separation between controls and patients. Moreover we extend the analysis by considering simultaneously acquired recordings of sap, dap and ilv. We have also proposed a multiscale approach to evaluate interactions between time series, by performing a multivariate autoregressive modelling of the coarse grained time series. This analysis has put in evidence interesting patterns of interactions between time series, while providing several new quantitative indicators which are statistically correlated with the CHF pathology, and which can be employed for diagnosis of CHF patients. Separating dead patients from alive patients is a very important task, since a good estimation of the probability of surviving of a given patient would be valuable when a decision has to be made with respect to the therapy to be undertaken. The separating performances provided by our indicators in this case are not good as those obtained separating patients and controls. Further work must be done to deal with the separation between dead patients and alive patients; in particular it will be interesting to repeat this analysis with longer recordings so as to take into account fluctuations.
in lower frequency bands.

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FIG. 1: Standard deviations are plotted versus $\tau$ for the coarse grained time series, in basal condition. Empty squares are the averages over the 47 healthy subjects, full circles are the averages over the 275 CHF patients, and empty circles are the averages over the 54 patients for whom cardiac death occurred. Top left: SD of rri time series. Top right: SD of dap time series. Bottom left: SD of sap time series. Bottom right: SD of ilv time series.

FIG. 2: Sample entropy of rri time series plotted versus $\tau$. Empty squares are the averages over the 47 healthy subjects, full circles are the averages over the 275 CHF patients, and empty circles are the averages over the 54 patients for whom cardiac death occurred. Top left: $S_E$ in basal condition. Top right: the probability that basal $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $S_E$ in paced breathing condition. Bottom right: the probability that paced breathing $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test.
FIG. 3: Sample entropy of sap time series plotted versus $\tau$. Empty squares are the averages over the 47 healthy subjects, full circles are the averages over the 275 CHF patients, and empty circles are the averages over the 54 patients for whom cardiac death occurred. Top left: $S_E$ in basal condition. Top right: the probability that basal $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $S_E$ in paced breathing condition. Bottom right: the probability that paced breathing $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test.

FIG. 4: Sample entropy of dap time series plotted versus $\tau$. Empty squares are the averages over the 47 healthy subjects, full circles are the averages over the 275 CHF patients, and empty circles are the averages over the 54 patients for whom cardiac death occurred. Top left: $S_E$ in basal condition. Top right: the probability that basal $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $S_E$ in paced breathing condition. Bottom right: the probability that paced breathing $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test.
FIG. 5: Sample entropy of ilv time series plotted versus $\tau$. Empty squares are the averages over the 47 healthy subjects, full circles are the averages over the 275 CHF patients, and empty circles are the averages over the 54 patients for whom cardiac death occurred. Top left: $S_E$ in basal condition. Top right: the probability that basal $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $S_E$ in paced breathing condition. Bottom right: the probability that paced breathing $S_E$ values from controls and patients were drawn from the same distribution, evaluated by non parametric test.

FIG. 6: The strength of the interaction $rri \rightarrow sap$, evaluated as described in the text, is plotted versus $\tau$. Empty squares are the averages over controls, full circles are the averages over patients, and empty circles are the averages over dead patients. Top left: $rri \rightarrow sap$ in basal condition. Top right: the probability that basal values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $rri \rightarrow sap$ in paced breathing condition. Bottom right: the probability that paced breathing values from controls and patients were drawn from the same distribution, evaluated by non parametric test.
FIG. 7: The strength of the interaction \( \text{dap} \rightarrow \text{rri} \), evaluated as described in the text, is plotted versus \( \tau \). Empty squares are the averages over controls, full circles are the averages over patients, and empty circles are the averages over dead patients. Top left: \( \text{dap} \rightarrow \text{rri} \) in basal condition. Top right: the probability that basal values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: \( \text{dap} \rightarrow \text{rri} \) in paced breathing condition. Bottom right: the probability that paced breathing values from controls and patients were drawn from the same distribution, evaluated by non parametric test.

FIG. 8: The strength of the interaction \( \text{rri} \rightarrow \text{rri} \), evaluated as described in the text, is plotted versus \( \tau \). Empty squares are the averages over controls, full circles are the averages over patients, and empty circles are the averages over dead patients. Top left: \( \text{rri} \rightarrow \text{rri} \) in basal condition. Top right: the probability that basal values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: \( \text{rri} \rightarrow \text{rri} \) in paced breathing condition. Bottom right: the probability that paced breathing values from controls and patients were drawn from the same distribution, evaluated by non parametric test.
FIG. 9: The strength of the interaction $\text{dap} \rightarrow \text{dap}$, evaluated as described in the text, is plotted versus $\tau$. Empty squares are the averages over controls, full circles are the averages over patients, and empty circles are the averages over dead patients. Top left: $\text{dap} \rightarrow \text{dap}$ in basal condition. Top right: the probability that basal values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $\text{dap} \rightarrow \text{dap}$ in paced breathing condition. Bottom right: the probability that paced breathing values from controls and patients were drawn from the same distribution, evaluated by non parametric test.

FIG. 10: The strength of the interaction $\text{sap} \rightarrow \text{dap}$, evaluated as described in the text, is plotted versus $\tau$. Empty squares are the averages over controls, full circles are the averages over patients, and empty circles are the averages over dead patients. Top left: $\text{sap} \rightarrow \text{dap}$ in basal condition. Top right: the probability that basal values from controls and patients were drawn from the same distribution, evaluated by non parametric test. Bottom left: $\text{sap} \rightarrow \text{dap}$ in paced breathing condition. Bottom right: the probability that paced breathing values from controls and patients were drawn from the same distribution, evaluated by non parametric test.