Multiscale Entropy and Multiscale Time Irreversibility for Atrial Fibrillation and Heart Failure from 7-Day Holter

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Abstract

To prevent the sudden death risk, several methods have been proposed in the literature based on Heart Rate Variability (HRV), which is related with the state of the autonomic nervous system. To quantify the HRV, the measurement of the irregularity based on Entropy methods, Multiscale Entropy (MSE), and Multiscale Time Irreversibility (MTI) have been proposed. In contrast to traditional irregularity measures, these methods take into account the multiple time scales inherent in healthy physiologic dynamics. Higher entropy values generally account for healthier states than for some pathologies, with the hypothesis that decreasing entropy points to perturbations of the complex physiological mechanisms. To date, the MSE and MTI have been analyzed for monitoring of a maximum of 24 hours, and a limit of 20 scales. In this work, MSE and MTI are applied to 7-days monitoring analysis of two data sets, namely, 3 patients with Atrial Fibrillation and 3 patients with Heart Failure, by increasing the number of scales up to 100, thanks to the long-term duration of the holter recordings. Our results show that the larger scales available in long-term monitoring contain relevant information about the patient's condition, which changes according to the pathology and the patient. These results paves the way to scrutinize these techniques in more detail for their use in long-term cardiac monitoring scenarios.

1. Introduction

Sudden cardiac death is one of the leading causes of mortality in the world, as confirmed by World Health Organization (WHO), due to unrecognized congenital cardiovascular disease. In this context, an anticipated diagnosis may help to reduce the cardiac mortality rate. The rhythm of the heart depends on both the sympathetic and the parasympathetic branches of the Autonomic Nervous System (ANS). Heart Rate Variability (HRV) is one of the main markers to study the relationship between the ANS and cardiovascular diseases, and it is defined as the variation in the time intervals between consecutive heart beats that occurs in the heart as a consequence of a complex internal dynamic balance.

HRV has aroused increasing interests as a non-invasive diagnostic method for different cardiovascular pathologies. Part of its interests lies in its non-invasive nature and in the study of HRV only needing to know the time instants of occurrence of the beats. The heart does not behave like a periodic oscillator, instead, its rhythm is modulated by the ANS. The simultaneous actuation of the two ANS branches causes oscillations of the cardiac frequency, giving rise to the presence of HRV. The main reasons for the use of HRV as maker of cardiac risk are its description capacity as irregularity measurement, and its potential value for prognosis and diagnosis of several cardiovascular diseases [1].

There are several procedures which can provide us with HRV indices in the literature, and among them, nonlinear methods extract relevant information from HRV signals in terms of their complexity. Nonlinear indices are based on the fact that fluctuations in the RR intervals can exhibit characteristics from complex dynamic systems. With this hypothesis, and roughly speaking, healthy states will correspond to more complex patterns than pathological states. However, some pathologies, are associated with highly erratic fluctuations with statistical properties resembling uncorrelated noise. Traditional algorithms could yield higher irregularity indices for such pathological signals when compared to healthy dynamics, even though the latter represent more physiologically complex states. This possible inconsistency may be due to the fact that traditional algorithms are based on single scale analysis, and they could not take into account the complex temporal fluctuations inherent to healthy physiologic control systems. It is usual that studies based on 1-day Holter (1-DH) monitoring conclude that relevant information could be obtained from longer duration recordings, however, few studies have scrutinized nonlinear indices in long-term holter monitoring, despite its current and increasing availability in the clinical practice.

In this paper, Multiscale Entropy (MSE) and Multiscale Time Irreversibility (MTI) methods have been used to study

and analyse the nature of the HRV signal, by using 7-day Holter (7-DH) recordings, hence scrutinizing the possibilities of these relevant nonlinear measurements when using larger scales than the usual ones until now.

The structure of the paper is as follows. First, the 7-DH recordings in Heart Failure (HF) and Atrial Fibrillation (AF) patients and the HRV nonlinear methods are presented. Next, the data analysis is described, and following, the results are presented. Finally, conclusions are summarized.

2. ECG data base

In our study, we used 7-DH measured on patients having stable HF (3 and 3 patients with diagnostics HF and AF respectively). Those patients had left ventricular ejection fraction $\leq 50\,\%$ and were clinically stable. The device (Lifecard CFTM, Del Mar Reynolds, Issaquah, Washington) was exploited to extract the 3-channel Electrocardiographic recordings with x-y-z orthogonal leads. Then, the raw electrocardiographic data were stored respecting proprietary format, and exported to the International Society for Holter and Noninvasive Electrocardiology Standard (ISHNE) by using custom-made software, accordly to the standard specifications. The standard Holter analysis software (ELA Medical^{TM}, Sorin Group, Paris, France) was used to process the data. It is worth noting that when needed, a trained cardiologist performed a visual check of the QRS complex classification and every arrhythmic event, Therefore, manual corrections were made. Recordings were preprocessed to exclude artifacts and ectopic beats. Moreover, RR intervals lower than 200 ms and greater than 2000 ms were eliminated, as well as those which differed more than $20\,\%$ from the previous and the subsequent RR intervals. All the recordings had at least $85\,\%$ of sinus beats. The nonlinear indices were computed on the RR interval series.

3. MSE and MTI Algorithms for HRV

There are different techniques for HRV analysis, which are often structured in families (such as temporal, spectral, geometrical or nonlinear methods), giving rise to a large number of proposed algorithms. As we mentioned, we focused on the nonlinear MSE and MTI algorithms for HRV analysis, because they have shown interesting descriptive properties on 1-DH recordings on several pathologies.

3.1. MSE Analysis

The Sample Entropy ($SampEn$) was introduced by J.S Richmann and J.R Moorman [6] to solve the limitations of the Approximate Entropy ($ApEn$) [5], since the $ApEn$ compares each series pattern with itself, which leads to the error that is the existence of similarity in series, therefore the results are not very consistent. $SampEn$ is the negative of the natural logarithm of the conditional probability that two similar patterns of m points remain similar if we increase the number of points to $m+1$.

The MSE was introduced by Madalena Costa [2, 3] to solve the problems that ApEn and SampEn could not solve, using a new concept which is the multiscale analysis. For a discrete time series, a new series is constructed, whose terms are the average of the consecutive elements of the original series without overlapping. In this way, for a time series with 1 scale corresponds to the original series, for 2 scales, the series will be formed by the average of the elements taken from two by two, and so on. Finally we calculate the SampEn for each one of the new generated series. We represent the values obtained versus the scale factor, we can note the dependence of the entropy with the time scale. The maximum value of the scale depends on the number of samples in the time series. According to previous studies [3], this maximum was 20 when working with 24-hour Holter, which involves series with length greater than 20.000 signal samples. The MSE requires four input parameters: rr (signal from which the MSE is to be estimated), τ (number of scales for the analysis), r (noise filter) and m (length of the vectors to be compared). Consequently, MSE is denoted here as $MSE(rr, \tau, r, m)$. Given the discrete time series $x_1, ..., x_i, ..., x_N$, we obtain the consecutive time series y^τ, determined by the scaling factor τ as follows:

- First, the original time series is divided into non-overlapping intervals with window size of the same length as τ. Then the mean is obtained for each of the sample windows.
- Each element of the series y^τ is calculated according to the equation:

$$y^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \quad 1 \leq j \leq \frac{N}{\tau} \qquad (1)$$

  For the first scale, the time series y^1 is the original time series. The length of each time series obtained is equal to the length of the original series divided by the scale factor τ.
- To normalize, the entropy index is calculated for each time series, representing it as a scale factor τ function.

3.2. MTI Analysis

The consistency loss of the statistical properties of a signal is measured by MTI when the signal reading undergoes a change through time inversion, which allows us to obtain and quantify an asymmetry index [3]. This asymmetry index is higher in healthy systems (with more complex dynamics) and it decreases in syndromic systems with pathologies and with aging. On the other hand, physiological time series generate complex fluctuations in multiple depending time scales, just as the existence of different hierarchical and interrelated regulatory systems. Therefore, it is important that the measure of irreversibility respects this multiple scale inherent in the body systems, which gives rise to the so-called MTI. Recent studies attempted to demonstrate that the loss of self-organization of a living organism is clearly related to a pathology or aging, and hence, to the loss of temporal irreversibility [4].

Considering the time series $X = x_i$, for $1 \leq i \leq N$:

- For the first scale, the time series are:

$$Y = y_1, \quad y_i = x_{i+1} - x_i, \quad 1 \leq i \leq N-1 \tag{2}$$

- Then we calculate the difference A_1 as follows:

$$A_1 = \frac{\sum_{i=1}^{N-j} H[-yi] - \sum_{i=1}^{N-j} H[yi]}{N-1} \tag{3}$$

where H is the Heaviside function that can be expressed as:

$$H(a) = \begin{cases} 0 \;\; if \; a \prec 0 \\ \\ 1 \;\; if \; a \succeq 0 \end{cases} \quad 1 \leq i \leq N-1 \tag{4}$$

- For the j^{th} scale, the time series are:

$$Y = y_j, \quad y_i = x_{i+j} - x_i, \quad 1 \leq i \leq N-j \tag{5}$$

- Then, the difference A_j is calculated by:

$$A_j = \frac{\sum_{i=1}^{N-j} H[-yi] - \sum_{i=1}^{N-j} H[yi]}{N-j}, \quad 1 \leq i \leq N-j \tag{6}$$

- The asymmetry index (irreversibility) is obtained as:

$$\sum_{j=1}^{J} A_j \tag{7}$$

for a pre-determined range of scales.

4. Experiments and Results

4.1. MSE Results

In this subsection, we analyze the MSE results of 7 days registers of AF and HF patients. We also analyse how, the results can vary from a patient to another when increasing the scaling factor, although they have the same type of pathology.

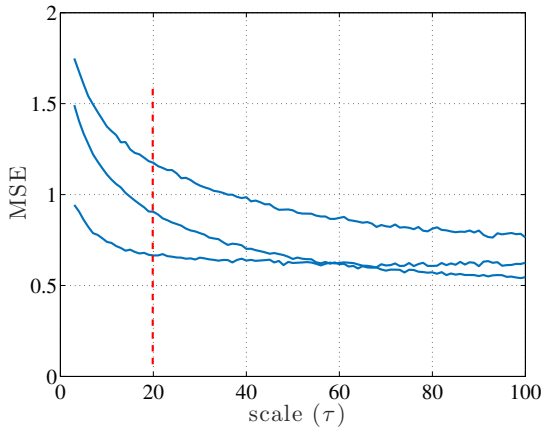

Figure 1. *Obtained MSE up to 100 scales in 3 patients with AF.Vertical line denotes the scale for which MSE is obtained with 1-DH recordings in precedent studies.*

Figure 1 shows decreasing values of MSE for 3 patients with AF up to a maximum of 100 scales. We can note that

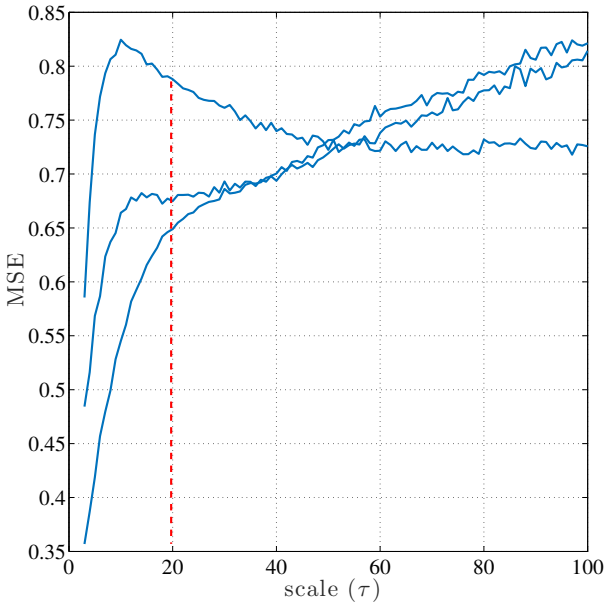

Figure 2. *Obtained MSE up to 100 scales in 3 patients with HF. Vertical line denotes the scale for which MSE is obtained with 1-DH recordings in precedent studies.*

the trend of the curve change for increasing scales. Previous studies based on 1-DH recordings have analyzed up to scale 20 (red dashed line) [2, 3], however, changes in the dynamics of some patients can be observed in larger scales. Also the relative entropy values between patients change with the scale, for example, Fig. 1 shows that from scale 60 approximately the relation between the entropy values of two AF patients is reverted. We can also see that the exponential-like decrease seems to be present in the three patients, however, in two of them there is a trend to continue decreasing even after the 100 scales, whereas one of them reaches a practically constant entropy over 40 scales.

Figure 2 shows the MSE estimated up to 100 scales in 3 patients with HF. It can be seen that the complexity is different in both patients for lower scales, and if we only observed them, even it could seem that they reach a continuous high level. However, the analysis on larger scales shows that the complexity continues to grow almost linearly, and that all the patients exhibit a very similar behavior on that range of large scales.

4.2. MTI Results

In this subsection, we analyze the MTI results on the same patients with AF and HF. From Figure 3, where the MTI is represented for 3 patients with AF, a decreasing trend is clearly seen with increasing scales in two patients, whereas a positive drift is seen in one patient. In general, the trend can be clearly established when looking at the larger scales, whereas the observation from a single day Holter would have been less well-defined in terms of its exponential-like shape. A similar kind of trend can be seen in patients with HF in Figure 4, however, the MTI curves for these patients with HF exhibit a larger magnitude compared with the MTI curves for patients with AF, except in one patient, where

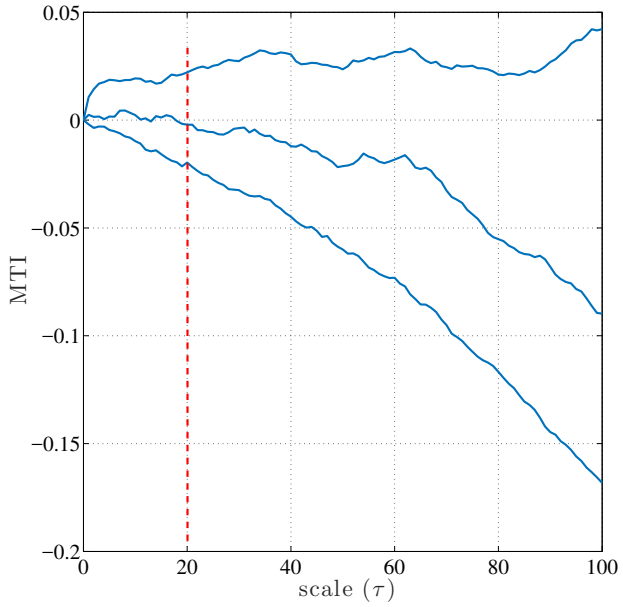

Figure 3. *Obtained MTI up to 100 scales in 3 patients with AF. Vertical line denotes the scale for which MSE is obtained with 1-DH recordings in precedent studies.*

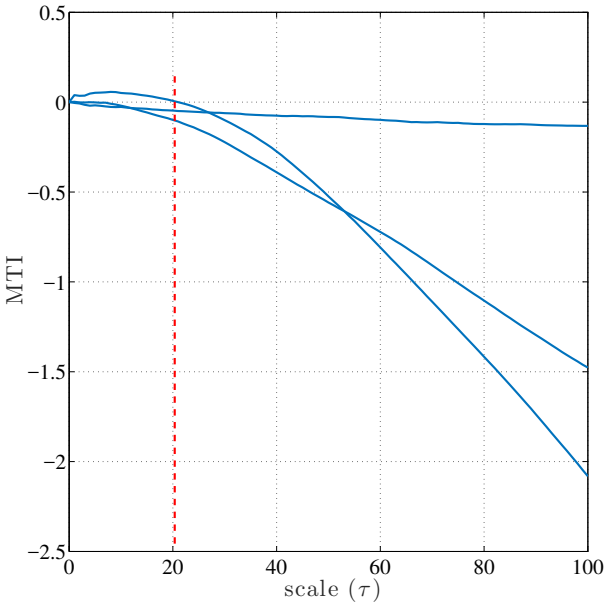

Figure 4. *Obtained MTI up to 100 scales in 3 patients with HF. Vertical line denotes the scale for which MSE is obtained with 1-DH recordings in precedent studies.*

again a near constant trend is obtained throughout scales.

5. Conclusion

In this work, we have addressed the calculation of two representative multiscale indices, namely, MSE and MTI, on 7-DH recordings. We have worked on 3 examples of AF patients and on 3 examples of HF patients. From these results, it turns evident that, when present, the trends are consistent between the scales provided with 1-DH and the additional scales provided with the 7-DH, but the second ones give a deeper view of this kind of representations. Changes in the dynamics of some patients can be observed in large scales. Also the relative entropy values between patients change with the scale. Note that these results are consistent with the MSE in terms of HF showing larger complexity in general for large scales than AF.

Our future research will consider first to perform the same multiscale analysis (MSE and MTI) in healthy subjects, in order to study the dynamic behavior in normal conditions when increasing the scales number. Then, an individual study of each patient will be made, to determine if there are correlations between the MSE and MTI values obtained. Certainly a larger database for AF and for HF will be informative, and finally, the clinical variables provided by the health recording for each patient will surely be informative when understanding the different behavior observed in this work for some patients.

Acknowledgments

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