Multiscale entropy profiling to estimate complexity of heart rate dynamics

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In the analysis of signal regularity from a physiological system such as the human heart, Approximate entropy (H_A) and Sample entropy (H_S) have been the most popular statistical tools used so far. While studying heart rate dynamics, it nevertheless becomes more important to extract information about complexities associated with the heart, rather than the regularity of signal patterns produced by it. A complex physiological system does not necessarily produce irregular signals and vice versa. In order to equip a regularity statistic to see through the respective system's level of complexity, the idea of multiscaling was introduced in H_S estimation. Multiscaling ideally requires an input signal to be (a) long and (b) stationary. However, the longer the data is the less stationary it is. The requirement multiscaling places on its data length largely limits its accuracy. We propose a novel method of entropy profiling that makes multiscaling require very short signal segments, granting better prospects of signal stationarity and estimation accuracy. With entropy profiling, an efficient multiscale H_S based analysis requires only 500-beat signals of atrial fibrillated data, as opposed to the earlier case that required at least 20 000 beats.

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I. INTRODUCTION

Complexity of a physiological system cannot always be attributed to the presence of chaos or order in it [1–3]. Although statistical measures such as Approximate Entropy (H_A) and Sample Entropy (H_S) are designed to retrieve information about system complexity, in reality they only provide information about regularity [2,4,5]. In 2002, Costa *et al.* [1] introduced the concept of multiscale entropy (MSE) to measure system complexity, where a scale dependent entropy is obtained by considering coarse grained variables of an original time series. In this approach, regularity estimated at the higher scales eventually reveals the system's complexity. The method was devised in order to address the issue of abnormal physiologic signals (less complex) having higher entropy values (H_A or H_S) than their healthy counterparts (more complex), in some cardiac pathologies like atrial fibrillation [1,3,6–9]. In their work, Costa *et al.* have shown how a multiscaled H_S estimation can accurately estimate 'complexity' based information from heart rate time series signals of patients with Atrial Fibrillation (AF) and Congestive Heart Failure (CHF) [1,3].

One big limitation of MSE is the dependency on longer data length N [2,3], since coarse graining in MSE analysis reduces the data length with increasing scale factor. In addition, longer data length reduces the accuracy of MSE analysis, since such a signal is more prone to be non-stationary [2,3]. Enabling MSE to analyze short-term signals can overcome these limitations. A few improvements and generalizations to MSE analysis such as modified MSE (MMSE), short time MSE (sMSE), and refined generalized MSE (RMSE_{σ^2}) showed application of MSE analysis on short-term synthetic data [10–12], however their applicability on physiologic signals are unknown.

Dependency of MSE on long-term signal is inherited from the embedded irregularity estimation technique (H_S). At an embedding dimension m, the H_S algorithm needs a minimum data length of $\simeq 30^m$ to ensure a meaningful estimation [5,13]. In MSE analysis, coarse graining process reduces the data length by the factor of scale. Therefore, Costa *et al.* have demonstrated multiscaling results on AF and CHF data using 20 000 points with a maximum scale factor of 20 (at $m = 2$) [1]. When only 1000 points of the same AF data are used, multiscaling fails to capture complexity information at the given m. [evident from Fig. 1(a)]. In 2011, Lake *et al.* [14] proposed a new regularity statistic CosEn (Coefficient of H_S), where the concept of a 'minimum numerator count' is used to select the optimal value of threshold r. This regularity statistic removes the data length limitation seen in H_S estimation. Another study [15] has used the 'minimum numerator count' idea on FuzzyMEn (Fuzzy Measure Entropy) and further improved the efficiency (with respect to CosEn) of AF detection on 12-beat data. However, the 'minimum numerator count' method requires the user to keep varying r and repeat estimation steps till the optimal point is reached. A recent study published by our group [16,17] introduces the novel concept of 'entropy profiling' to estimate regularity, where the r selection is completely data driven [16,17]. This 'entropy profiling' method was found suitable for analyzing short-length heart rate time series signal in different physiological conditions [16,17].

In this study, we hypothesize that integrating entropy profiling with multiscaling approach will make MSE independent of data length. We believe the proposed MSE analysis technique will advance the field of measuring system complexity using short-term signal.

II. DATA AND METHODS

RR (distance between two consecutive R peaks in an electrocardiogram) interval data corresponding to the ECG

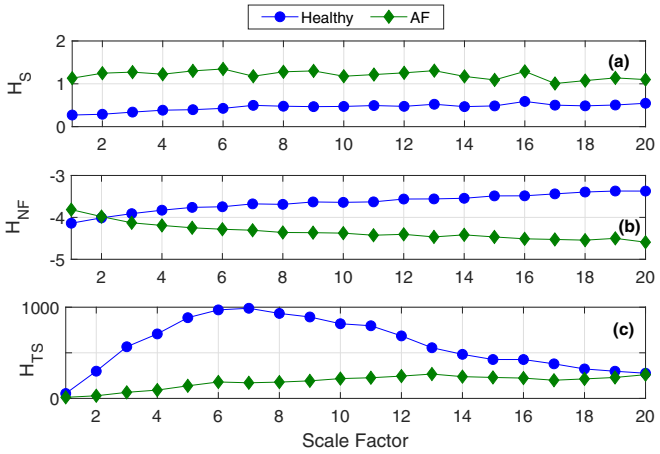

FIG. 1. MSE analysis of RR-interval time series derived from healthy subjects and atrial fibrillation subjects using (a) H_S, (b) $H_{\rm NF}$, and (c) $H_{\rm TS}$ at $N = 1000$.

recordings of 18 'healthy' and 25 'atrial fibrillated (AF)' subjects have been used here. The data were obtained from the MIT-BIH module of the PhysioNet database [18]. The MIT-BIH database contains long-term ECG recordings of subjects referred to the Arrhythmia Laboratory at Boston's Beth Israel Hospital. The normal sinus rhythm database contains 18 long-term ECG recordings (24 h duration each, sampled at 128 Hz) of subjects who were found to have no significant arrhythmia; they include five men, aged 26 to 45, and 13 women, aged 20 to 50. The AF database contains 25 long-term ECG recordings (10 h duration each, sampled at 250 Hz) of human subjects with atrial fibrillation (mostly paroxysmal) [19]. After extraction of all RR interval data from the the PhysioNet database [18], each signal segment is selected from the beginning to $N = 20, 30, 50, 100, 500$, and 1000.

A. Sample entropy

H_S is an approximation of the conditional probability [13] of two segments matching at a length of $m+1$ if they match at m, where the match is decided by the tolerance parameter r. A time series $\{x(n) : 1 \leqslant n \leqslant N\}$ is divided into $(N-m)$ overlapping vectors, each of length m, given by $\{X_i^m : 1 \leqslant i \leqslant (N-m)\}$, where $X_i^m = \{x(i+k) : 0 \leqslant k \leqslant m-1\}$. $C_i^m(r)$ is then the probability of a vector X_j^m to lie within a distance r of the vector X_i^m, $1 \leqslant j \leqslant (N-m)$, $j \neq i$, distance given by $d_{ij}^m = \{\max|X_i^m - X_j^m| : 1 \leqslant j \leqslant (N-m), j \neq i\}$. So, for an ith template vector, the distance vector for an embedding dimension m will be of the following form: $d_i^m = d_{ij}^m : 1 \leqslant j \leqslant (N-m),\ j \neq i$. Similarly, we obtain $d_i^{m+1} = d_{ij}^{m+1} : 1 \leqslant j \leqslant (N-m),\ j \neq i$ at an embedding dimension $m+1$ and compute $C_i^{m+1}(r)$.

1. H_S estimate

$$H_S(N, m, r) = \ln \frac{\Phi^m(r)}{\Phi^{m+1}(r)}, \tag{1}$$

where

$$\Phi^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} C_i^m(r). \tag{2}$$

For all experiments conducted in this study, H_S is evaluated at an r value of $0.15 * SD$ of signal and an m value of 2.

2. H_S profile

Instead of choosing a single value of tolerance r to estimate H_S, we compute a complete set of data driven r values and generate a profile of H_S values [17]. Let D be the matrix containing all elements of d^m and d^{m+1}. Then, we define U as the set of all unique elements of D, sorted in ascending order. Also, let $n_{\rm bin}$ be the number of elements in U. The cumulative distribution function f_i^m is then calculated as

$$f_{iq}^m = p\big(d_i^m \leqslant U_q\big); \text{for } 1 \leqslant q \leqslant n_{\rm bin}, \tag{3}$$

where p is the probability. Here, each value of q represents an r value in the profile. Thus,

$$H_S(q) = \ln \frac{\Phi^m(q)}{\Phi^{m+1}(q)} \tag{4}$$

for $1 \leqslant q \leqslant n_{\rm bin}$ to get the complete profile of H_S values, where

$$\Phi^m(q) = \frac{1}{N-m} \sum_{i=1}^{N-m} \big(f_{iq}^m\big). \tag{5}$$

3. Total sample entropy ($H_{\rm TS}$)

$H_{\rm TS}$ is calculated by adding up all the individual values of H_S along the H_S profile of a signal

$$H_{\rm TS} = \sum_{q=1}^{n_{\rm bin}} H_S(q). \tag{6}$$

B. Normalized fuzzy measure entropy

From the given time series, a set each of local and global vector sequences are formed (as elaborated in [15]); L_i^m and G_i^m, respectively, at an embedding dimension m. Then, the local and global similarity degrees or fuzzy functions are computed as

$$D_{L_{ij}^m}(n_L, r_L) = \exp\left(-\left(\frac{d_{L_{ij}^m}}{r_L}\right)^{n_L}\right) \tag{7}$$

and

$$D_{G_{ij}^m}(n_G, r_G) = \exp\left(-\left(\frac{d_{G_{ij}^m}}{r_G}\right)^{n_G}\right), \tag{8}$$

where $d_{L_{ij}^m}$ and $d_{G_{ij}^m}$ are the distances between the local and global vector sequences respectively, computed as per [15]. The mean values of these fuzzy functions are computed as $B_{L^m}(n_L, r_L)$ and $B_{G^m}(n_G, r_G)$, respectively. The same steps when repeated with an embedding dimension $m+1$, produce mean fuzzy functions $A_{L^{m+1}}(n_L, r_L)$ and $A_{G^{m+1}}(n_G, r_G)$. The fuzzy local and global measure entropies are then estimated as

$$H_{\rm LF} = \ln\left(\frac{B_{L^m}(n_L, r_L)}{A_{L^{m+1}}(n_L, r_L)}\right) + \ln(2r_L) - \ln(RR_{\rm mean}) \tag{9}$$

and

$$H_{\rm GF} = \ln\left(\frac{B_{G^m}(n_G, r_G)}{A_{G^{m+1}}(n_G, r_G)}\right) + \ln(2r_G) - \ln(RR_{\rm mean}), \tag{10}$$

respectively. Finally, normalized fuzzy measure entropy is given by

$$H_{\mathrm{NF}} = H_{\mathrm{LF}} + H_{\mathrm{GF}}. \tag{11}$$

Here, r_L and r_G are the local and global thresholds of distance and are estimated using the minimum numerator count method [14,15]. Also, n_L and n_G are called the local and global similarity weights and both carry a value of 2 here.

C. Multiscale entropy (MSE)

The time series $\{x(n) : 1 \leqslant n \leqslant N\}$ is divided into $\frac{N}{\tau}$ non-overlapping segments, each of length τ, where τ is the scale factor. The mean of elements in each of the consecutive segments form the new coarse grained time series; $y^{\tau}(n) : 1 \leqslant n \leqslant \frac{N}{\tau}$, where

$$y^{\tau}(n) = \frac{1}{\tau} \sum_{i=(n-1)\tau+1}^{n\tau} x(i). \tag{12}$$

For every coarse grained time series, the entropy estimate (here, H_S, H_{NF}, or H_{TS}) is then obtained.

For all entropy estimations, we use an $m = 2$.

D. Statistical analysis

In our study, we have used area under the ROC (Receiver Operating Characteristic) curve in order to test the efficiency of our measures in signal classification. The area under the ROC curve (AUC) is the probability that a classifier ranks a randomly chosen instance X higher than a randomly chosen instance Y, X, and Y being samples taken from two independent populations. An AUC value of 0.5 indicates that the distributions of the features are similar in the two groups with no discriminatory power. Conversely, an ROC area value of 1.0 would mean that the distribution of the features of the two groups do not overlap at all. MATLAB R2014b Statistics toolbox was used to perform all statistical operations.

III. RESULTS AND DISCUSSION

A. Measure of regularity or complexity?

For the largest data length used in our study, i.e., $N = 1000$, we estimate the respective multiscaled versions of H_S, H_{NF}, and H_{TS} using scales 1 to 20. As can be seen from Fig. 1(a), multiscaling on H_S consistently places healthy signals' entropy below that of the diseased ones, indicating a misleading complexity judgement. Looking at Fig. 1(b) and (c), we understand how multiscaling on H_{NF} and H_{TS} changes the scenario in favor of an accurate complexity analysis, where the healthy signals have a much higher entropy compared to their diseased counterparts.

B. Data length requirement for multiscaling

To find the minimum length of original data that would show an impact when subjected to multiscaling, we estimated H_{NF} and H_{TS} at different scales for a decreasing order of data length $N = 1000, 500, 100, 50, 30, 20$. As can be seen from Figs. 2 and 3, the effect of multiscaling on both measures tends to decay, as data length decreases. In case of H_{NF}, at $N = 50$, 30, and 20 [panels (d)–(f) of Fig. 2], the measure no longer

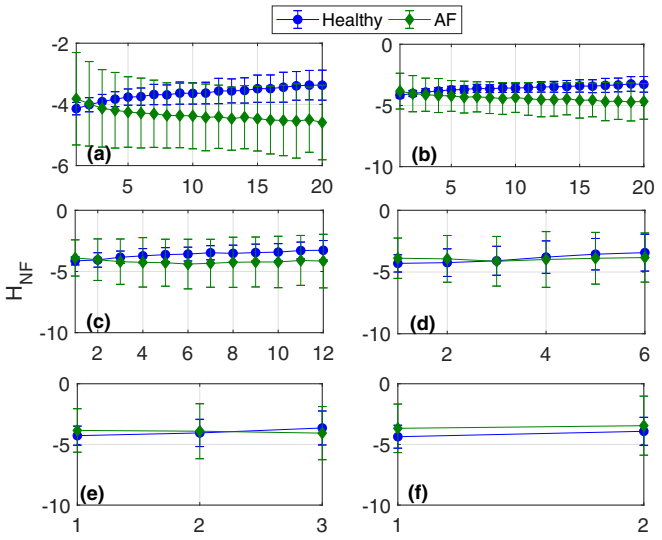

FIG. 2. The mean ± SD values of H_{NF} across a varying scale factor, in differentiating healthy from AF signals. Analysis presented at data lengths (a) 1000, (b) 500, (c) 100, (d) 50, (e) 30, and (f) 20.

reveals consistent or indisputable complexity information and in fact eventually falls back to being a 'regularity' statistic at $N = 20$. For H_{TS}, the same behavior can be seen from panels (d)–(f) of Fig. 3. Also, at $N = 100$ [panel (c) of Fig. 3], the demarcation between healthy and AF signals, thereby complexity information, remains insufficient at the higher scale factors. The maximum scale factor intended for use in our experiments was 20. But, for data lengths 100, 50, 30, and 20 of H_{NF} and 50, 30, and 20 of H_{TS}, multiscaling could not be done at all of these scales. The minimum length of coarse grained signal that could be handled by H_{NF} was 8, while for H_{TS}, it was 5. Hence, the choice of maximum scale factor, given a data length N will have to be $\frac{N}{8}$ for H_{NF} and $\frac{N}{5}$ for H_{TS}.

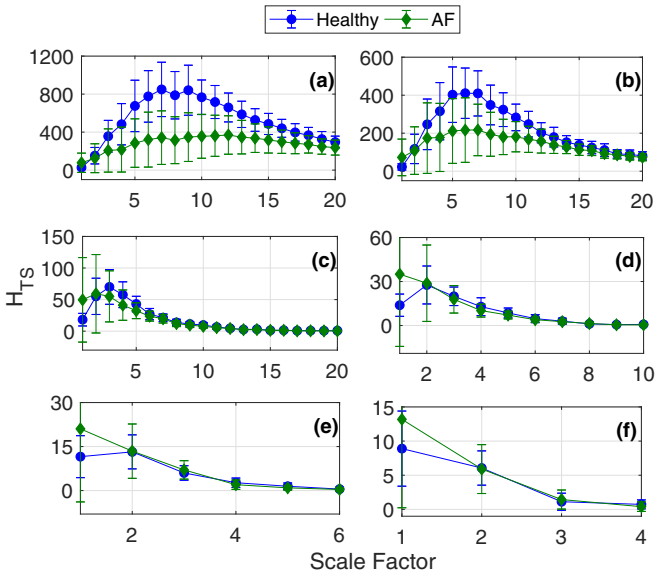

FIG. 3. The mean ± SD values of H_{TS} across a varying scale factor, in differentiating healthy from AF signals. Analysis presented at data lengths (a) 1000, (b) 500, (c) 100, (d) 50, (e) 30, and (f) 20.

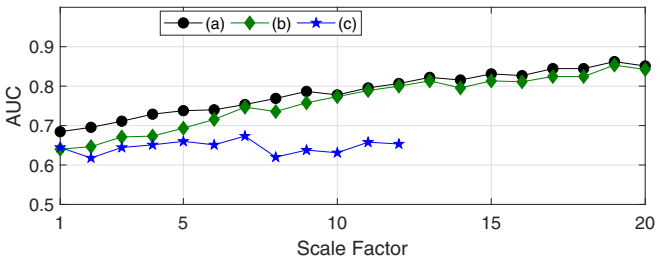

FIG. 4. AUC values of H_{NF} across a varying scale factor, in differentiating healthy from AF signals. Analysis presented at data lengths (a) 1000, (b) 500, (c) 100.

Costa *et al.*'s [1] MSE analysis required 20 000 data points for a maximum scale factor of 20 (at $m = 2$), in extraction of complexity information. Under the same conditions, to reach up to a maximum scale factor of 20, our method (H_{TS}) requires only 100 data points. This is because, while traditional H_S needs a minimum of $N \simeq 1000$ (at $m = 2$) for an accurate estimation, H_S profiling (and therefore H_{TS}) can do an accurate estimation even with an N as low as 5 (at $m = 2$).

C. Efficiency as a complexity measure

Taking the minimum data length requirement to be 100 for both H_{NF} and H_{TS}, we next try to find out the maximum scale factor necessary to give us the best classification performance for $N \geqslant 100$. Lesser the scale factor required, lesser is the computational cost. The AUC values of H_{NF} and H_{TS} in classifying healthy from AF signals are shown at multiple scale factors in Figs. 4 and 5. At $N = 1000$, 500, and 100, the respective AUC_{max} values and corresponding scale factors are shown in Table I. As can be seen, at each of the data lengths, classification performance of H_{TS} is significantly higher than that of H_{NF}. Also, at every data length, H_{TS} reaches the highest performance at a much lower scale factor than H_{NF}. For H_{TS}, at $N = 100$, though complexity behavior at the higher scale factors was insufficient [panel (c) of Fig. 3], highest classification performance is obtained before the issue sets in.

Though H_{TS} and H_{NF} seem to be capable of handling almost similar lengths of short-term data, as far as classification performance and computational efficiency is concerned, using multiscaled H_{TS} over multiscaled H_{NF} is undoubtedly beneficial in detecting complexity of short-term AF signals.

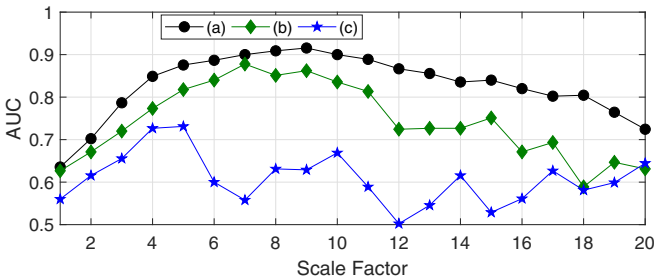

FIG. 5. AUC values of H_{TS} across a varying scale factor, in differentiating healthy from AF signals. Analysis presented at data lengths (a) 1000, (b) 500, (c) 100.

TABLE I. Highest classification performances of H_{NF} and H_{TS}.

Measure	Data length	AUC_{max}	Scale factor $_{AUC_{max}}$
H_{NF}	1000	0.8622	19
	500	0.8533	19
	100	0.6733	7
H_{TS}	1000	0.9156	9
	500	0.8778	7
	100	0.7311	5

D. CHM based multiscaling: Robustness in classification performance

Four random sets of healthy and AF signals, each of length 500 are generated for this section of analysis. We use $N = 500$ here (and not the minimum length requirement of 100) to see a 'consistent' behavior of H_{TS} as a complexity measure across all 20 scale factors used. The initial pool of data constitutes 18 healthy and 25 AF signals of varying data lengths (all above 20 000 beats). From each of these primary signals, we generate 40 non-overlapping secondary segments, each of length 500. To induce randomness, each 500-beat signal here will have a unique starting point (beat value) chosen from the original signal, followed by the next consecutive 499 points. Thus, each set will contain $(18X40) + (25X40) = 1720$ random 500-beat signals. (i) set 1: Uses $i = [1\ \{500(k) + 1; 1 \leqslant k \leqslant 39\}]$ as starting points for the 40 secondary segments. (ii) sets 2, 3, and 4 use 120 other unique starting points to generate their respective random 500-beat signals. At each scale factor, the mean $\pm$ SD of H_{TS} of the 18×40 healthy versus 25×40 AF signals is plot in Fig 6, for all four sets. Their respective performance analysis is shown in Fig. 7. As can be seen from the figures, the choice of signal segment can be random and this does not affect multiscale entropy

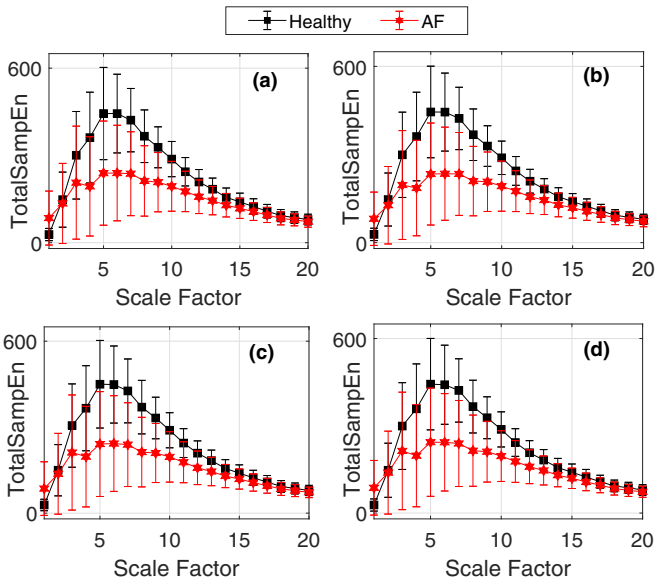

FIG. 6. H_S profiling based MSE analysis of four random sets of RR-interval time series derived from healthy subjects and atrial fibrillation subjects at data length $N = 500$. (a), (b), (c), and (d) correspond to random sets 1, 2, 3, and 4, respectively.

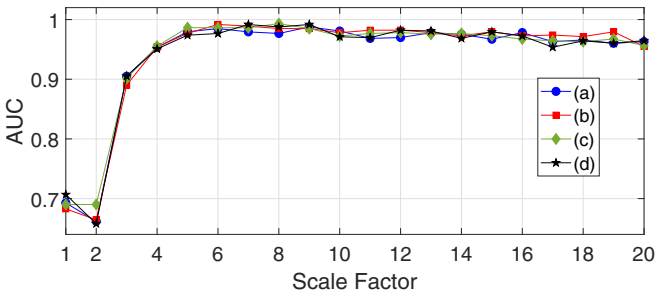

FIG. 7. AUC analysis of the classification using the four random sets; (a) set 1, (b) set 2, (c) set 3, and (d) set 4 of data.

profiling in any way. Thus, any random segment (from the original signal) of minimum length 500 is sufficient for an accurate classification of data based on complexity analysis. This proves the robustness of multiscale entropy profiling.

IV. CONCLUSION

Multiscale entropy analysis (MSE) has become an indispensable choice in order to examine complexity based information from physiologic data. Unfortunately, the method requires input data to be long-term as well as stationary, one contradicting the other. Owing to data length restrictions imposed by H_S estimation procedure, multiscale H_S analysis remains unsuitable for applications involving short-term physiologic data.

In this work, we have applied the recent concept of entropy 'profiling' instead of entropy 'estimation', so that multiscale H_S analysis can handle short-term physiologic data. For complexity based classification of AF signals from healthy cardiac signals, where MSE required a data length as high as 20 000, our method of entropy profiling requires only 500 data points; at an embedding dimension $m = 2$. Our study also shows that these 500 data points can be randomly picked from anywhere in the original data, thereby proving robustness of our approach. The practical implication of our method is not limited to detecting a clinical condition such as atrial fibrillation. While having the potential to be used on any pathological RR time-series signal, our method primarily focuses on identifying the actual physiological state of the underlying cardiac system, given very few samples of the respective RR time-series.

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