Rank-based Multi-Scale Entropy Analysis of Heart Rate Variability

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Abstract

The method of MultiScale Entropy (MSE) is an invaluable tool to quantify and compare the complexity of physiological time series at different time scales. Although MSE traditionally employs sample entropy to measure the unpredictability of each coarse-grained series, the same framework can be applied to other metrics.

Here we investigate the use of a rank-based entropy measure within the MSE framework. Like in the traditional method, the series are studied in an embedding space of dimension m. The novel entropy assesses the unpredictability of the series quantifying the "amount of shuffling" that the ranks of the mutual distances between pairs of m-long vectors undergo when considering the next observation.

The algorithm was tested on recordings from the Fantasia database in a time-varying fashion using non-overlapping 300-samples windows. The method was able to find statistically significant differences between young and healthy elderly subjects at 7 scales/time-windows after accounting for multiple comparisons using the Holm-Bonferroni correction.

These promising results suggest the possibility of using this measure to perform a time-varying assessment of complexity with increased accuracy and temporal resolution.

1. Introduction

Entropy is a measure of a system's uncertainty and can differentiate deterministic and stochastic systems. It is a widely used method to assess the complexity of physiological time-series with important applications in many fields like cardiology, neurophysiology and human postural sway. The sample entropy (S_{E}) — an important tool to quantify the level of disorder of a time series [1] — has achieved significant results detecting sepsis from neonatal HR data [2] and diagnosing atrial fibrillation [3]. It can be estimated from a finite-length time series $\{x_i\}_{i=1}^{N}$ as:

$$S_{\mathrm{E}} = -\ln\left(\frac{A}{B}\right) \tag{1}$$

where B is the total number of vectors $v_i^m = [x_i, x_{i+1}, ..., x_{i+m-1}]$ of m consecutive points that lie within a distance ρ, while A is the total number of segments of $m+1$ points that are still within distance ρ. In this context, the distance between two vectors is the maximum absolute difference between their corresponding components, i.e. the distance defined by the infinity norm. The fraction $\frac{A}{B}$ in (1) is an unbiased estimator of the conditional probability:

$$\begin{aligned} &P\left(\left\|v_i^{m+1} - v_j^{m+1}\right\|_\infty < \rho \;\middle|\; \left\|v_i^m - v_j^m\right\|_\infty < \rho\right) \\ &\equiv P\left(\left|x_{i+m} - x_{j+m}\right| < \rho \;\middle|\; \left\|v_i^m - v_j^m\right\|_\infty < \rho\right) \end{aligned} \tag{2}$$

where $\rho = r\sigma$ and σ is the standard deviation of the series. The normalized tolerance r is usually chosen in an interval $r_{\min} < r < r_{\max}$. Most authors recommend $r_{\min} = 0.1$ and $r_{\max} = 0.25$ for the entropy analysis of heart-rate variability [4].

The multi-scale entropy (MSE) is a more recent method proposed in [5][6]. It is based on sample entropy and compares the complexity of physiological time series at different time scales. The MSE method constructs a coarse-grained variant y_j^τ of the original time series and computes its entropy measure. The coarse-grained series is obtained dividing the one-dimensional discrete time series into non-overlapping windows of length equal to a scale factor τ, and averaging the data points within each window:

$$y_j^\tau = \frac{1}{\tau}\sum_{i=1}^{\tau} x_{(j-1)\tau+i}, \quad 1 \le j \le N/\tau. \tag{3}$$

The entropy measure is finally calculated for each coarse-grained time series, obtaining the function $S_{\mathrm{E}}(\tau)$.

In this paper, we introduce a novel entropy metric based on the ranking of mutual distances between pairs of m-long vectors.

2. Methods

2.1. Rank-based entropy

A family of alternative entropy metrics can be defined based on the "amount of shuffling" that the ranks of the mutual distances between pairs of m-long vectors undergo when considering the next observation.

In this paper, we describe one of these metrics which can be operationally defined in terms of the following steps. We start by computing, for $1 \leq i < j \leq N-m$, the vectors of mutual distances:

$$d_{k(i,j)} = \left\| v_i^m - v_j^m \right\|_\infty \tag{4}$$

$$d'_{k(i,j)} = |x_{i+m} - x_{j+m}| \tag{5}$$

where $k = k(i,j)$ is the index assigned to each (i,j) pair, with $1 \leq k \leq K = (N-m-1)(N-m)/2$. We then consider the vector d_k and find the permutation $\pi(k)$ such that the vector $s_k = d_{\pi(k)}$ is sorted in ascending order. Intuitively, if x_{i+m} represents the next observation and v_i^m the recent "history" (or state) of a deterministic system[1], pairs (v_i^m, v_j^m) of close vectors should project into pairs of close observations (x_{i+m}, x_{j+m}). As a consequence, the vector $s'_k = d'_{\pi(k)}$ should be almost sorted too. Conversely, if the system is completely random, the distance between pairs of state vectors should bear no information about the closeness of the following observations, and the vector s'_k should be, in general, unsorted.

We quantify this idea into a concrete measure using the notion of inversion count. Given a vector w, its inversion count is the number of pairs of indices i and j such that $i < j$ and $w_i > w_j$. It represents a measure of the vector's disorder and it coincides with the number of actions (swaps) that a bubble sort algorithm needs to take to sort the vector. In assessing the degree of disorder of s'_k, we are specifically interested in observation points that result from pairs of close state vectors. Therefore, we determine the largest index k_ρ satisfying $s_{k_\rho} < \rho$ and then compute the number I of inversions pairs (k_1, k_2) such that $k_1 < k_\rho$, $k_1 < k_2$, and $s'_{k_1} > s'_{k_2}$. Finally, we define the new entropy as

$$R_\mathrm{E} = -\ln\left(1 - \frac{I}{(2K - k_\rho - 1)\, k_\rho/2}\right). \tag{6}$$

The role of the parameter r used to determine $\rho = r\sigma$ is different in R_E than in S_E. In a sense, rather than defining a hard threshold for the distance between state vectors, r determines the maximum rank of the set of distances that will contribute to the final entropy measure. For this reason, its choice is less critical than in the case of S_E and we simply set $r = r_{\max} = 0.25$.

The new entropy can also be used within a multi-scale framework simply by constructing coarse-grained versions of the original time series as in (3) and computing the entropy measure corresponding to each scale factor. In the following we will show the application of this rank-based MSE to short and noisy artificial data sets as well as to real-world heart beat series.

[1] Assuming m is sufficiently long to capture the system's dynamics.

2.2. Simulated signals

An effective entropy metric should be able to measure the degree of predictability of a time series, and in particular to determine whether it was generated by a deterministic or a stochastic system. Ideally, it should be able to perform this assessment without resorting to the use of other properties of the signal such as the probability distribution of its values or the frequency spectrum. Secondly, a robust metric should yield useful results even when the system's observations are corrupted by a small amount of additive noise.

To test our algorithm we compared the entropy of a given time series x_i, generated from a deterministic system in chaotic regime, with that of its surrogate generated using the iAAFT algorithm [7], which has approximately the same histogram and the same frequency spectrum amplitude but new uniformly random phases. Clearly, we expect the surrogate signal — which is stochastic — to have a higher entropy than the original deterministic signal.

Because the entropy of a system is estimated from finite-length time series, the resulting measure is affected by statistical fluctuations. We generated $M = 200$ time series x_i^m of length $N = 400$ with different initial conditions, and we computed the corresponding entropies R_E^m. For each series, we also computed the surrogate series $\{\tilde{x}_i^m\} = \mathrm{iAAFT}(\{x_i^m\})$ and its entropy $\tilde{R}_\mathrm{E}^m$. Ideally, our metric should report a difference between the entropy of the surrogates and that of the original data which is significantly larger than the intrinsic fluctuations due to the finite-length estimation process. To quantify this desirable property, we assessed the discrimination accuracy of our entropy metric as:

$$a = \frac{C\left[\tilde{R}_\mathrm{E}^m\right] - C\left[R_\mathrm{E}^m\right]}{D\left[\tilde{R}_\mathrm{E}^m\right] + D\left[R_\mathrm{E}^m\right]} \tag{7}$$

where $C[\cdot]$ is a measure of central tendency while $D[\cdot]$ is a measure of dispersion. If $C[\cdot]$ and $D[\cdot]$ are, respectively, estimators of mean and standard deviation, the accuracy a is the reciprocal of the Davies-Bouldin index, a widely used metric for evaluating clustering algorithms. In our case, we used the median as measure of central tendency and $1.4826\,\mathrm{MAD}[\cdot]$ (median absolute deviation) as measure of dispersion.

To further validate the metric, we tested its robustness to additive observation noise. Each series, x_i^m, was corrupted with white Gaussian noise, n_i^m, and finally the entropy of $\{x_i^m + n_i^m\}$ and that of $\mathrm{iAAFT}(\{x_i^m + n_i^m\})$ were measured. We repeated the procedure for different values of the signal-to-noise ratio (SNR).

The first type of signals that we used to test the novel procedure was generated using the logistic map:

$$x_{n+1} = \mu x_n(1 - x_n) \quad (8)$$

where x_0 is a real number in the interval $[0, 1]$ and the parameter μ is the rate of growth. We adopted the value $\mu = 3.9$ for which the map exhibits chaotic behaviour.

The second test was conducted on signals generated using the Lorenz flow:

$$\frac{dx}{dt} = \sigma(y-x);\ \frac{dy}{dt} = x(\rho-z)-y;\ \frac{dz}{dt} = xy-\beta z \quad (9)$$

with values $\sigma = 10$, $\beta = \frac{8}{3}$ and $\rho = 28$ for which the dynamics evolve around a chaotic attractor. The time series was obtained as $x_i = x(i\delta)$ where the time lag $\delta = 0.6$ was chosen using the autocorrelation function.

2.3. Real signals

We also tested our algorithm on real data from the "Fantasia" database [8] which is publicly available from Physionet [9]. The series of NN intervals were further preprocessed using an artifact removal filter based on the "filt" function of the "hrv-toolkit" available on Physionet. To break the artificial ties created by the 250 Hz sampling of the ECG, a random noise uniformly distributed in $[-2\text{ms}, 2\text{ms}]$ was added to the time series. Then, each subject's NN series was divided in 15 non-overlapping time windows of 300 samples each and the rank-based MSE was independently computed for each time window.

3. Results

3.1. Simulation results

For the logistic map, the rank-based entropy gives a value 0.130 ± 0.004 ($C[\cdot] \pm D[\cdot]$) while for the surrogate data it goes up to 0.546 ± 0.014. This corresponds to a discrimination accuracy $a \simeq 23$, which is approximately twice that obtained with the sample entropy $a \simeq 12$. This improvement stands even in the presence of noise, as reported in Fig. 1-left. Remarkably, the entropies computed from the different realizations of the logistic map are well separated from those of their surrogates even with a SNR as low as 4.4 dB (i.e. when the standard deviation of the noise is 60% that of the signal).

For the series generated from the Lorenz flow, the rank-based entropy is 0.430 ± 0.026 while for the surrogate data it increases to 0.687 ± 0.022. This leads to a discrimination accuracy $a \simeq 5.5$ which is slightly lower than that of the sample entropy $a \simeq 6.5$. When the series are contaminated with noise, R_E seems to perform slightly better than S_E as reported in Fig. 1-right.

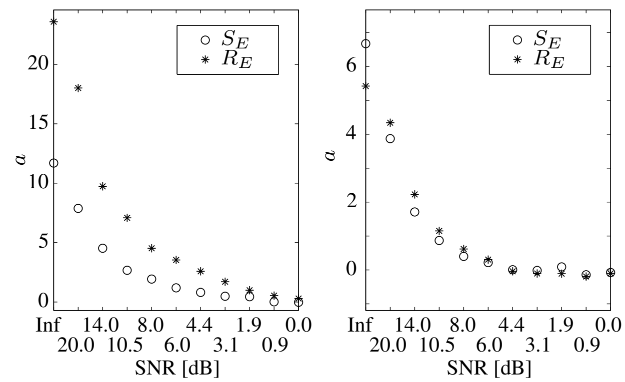

Figure 1: Discrimination accuracy index (see (7)) assessing the ability of the two metrics (S_E and R_E) to detect the increased entropy of the surrogate data compared to the original series (logistic map on the left, Lorenz flow on the right), as a function of the SNR.

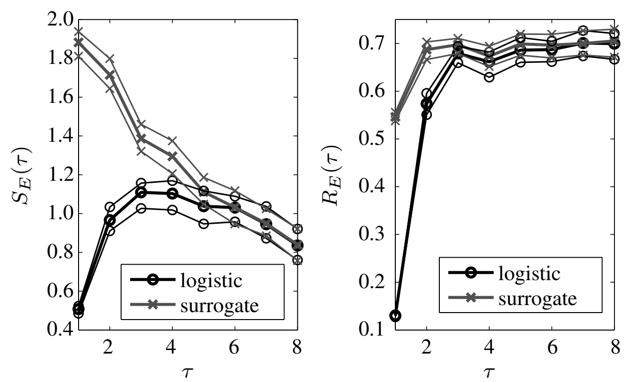

Figure 2: MSE computed using the conventional S_E (left) and using R_E (right) for the logistic map and for the surrogate data. The central thick line represents the median while the thin lines report the first and third quartile of the values obtained from the 200 realizations.

Finally, the full MSE plots computed using R_E and using S_E are reported in Fig. 2 and Fig. 3 for the logistic map and for the Lorenz flow, respectively.

3.2. Real data results

The entropy values obtained with R_E at scales 1 to 4 for young and elderly subjects are reported in Fig. 4. We observe that the entropy of the elderly is generally lower than that of young subjects, especially for scales 2 and higher, as previously observed in [6]. At the single scale/time level, the difference is statistically significant ($p < 0.05$, using a Mann-Whitney U test) for 2 time windows at scale

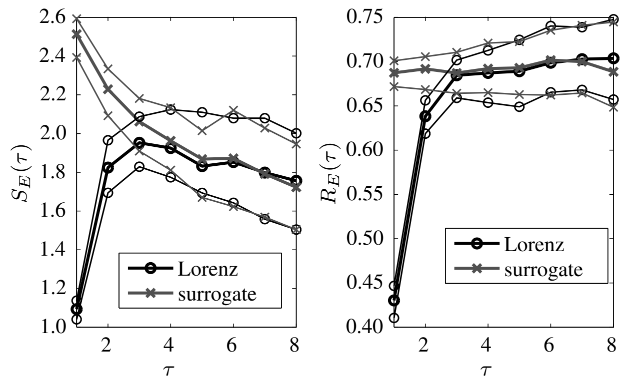

Figure 3: Same as Fig. 2, for the Lorenz flow.

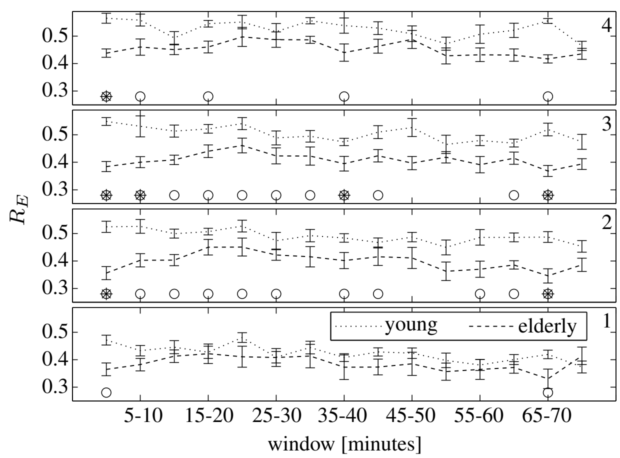

Figure 4: Entropy R_{E} computed at scales 1 (bottom) to 4 (top) on fifteen 300-samples windows. Each plot shows the $\mathrm{Median} \pm 1.4826\,\mathrm{MAD}\,/\sqrt{n}$ for young (dotted line) and elderly subjects (dashed line). The circles denote scales/times for which the difference between young and elderly subjects is statistically significant ($p < 0.05$). The stars mark those that remain statistically significant after accounting for multiple comparisons.

1, for 11 at scales 2 and 3, and for 5 at scale 4. If one is interested in assessing a statistical difference between the two age populations at all scales/times, it is worth noting that a total of 7 differences remain statistically significant even after accounting for multiple comparisons using the Holm-Bonferroni correction.

Using the conventional MSE, instead, only for 14 time/scales out of 60 the differences between the two populations are statistically significant. None of them remains significant after accounting for multiple comparisons.

4. Conclusions

We presented a novel rank-based entropy measure which can be used within a multi-scale framework. Tested on simulated time series with known properties, the novel metric showed a higher robustness to noise when distinguishing the output of a logistic map from its surrogate. On real data, the rank-based MSE outperformed the conventional one in finding statistically significant differences between young and healthy elderly subjects using 300-samples-long RR series. These encouraging results suggest the possibility of using this measure to perform a time-varying assessment of complexity with increased accuracy and temporal resolution.

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