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Validation of the Area1 of Approximate Entropy (a1ApEn) in Empirical Data of Heart Rate

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Authors' contributions

All authors contributed equally in draft the manuscript, experimental protocols and analysis.

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ABSTRACT

Aims: To validate the use of the non-linear estimator a1ApEn in empirical data.
Study Design: Comparison of heart rate variability/complexity (HRV/C) between rest and low intensity exercise.
Methodology: R-R intervals were obtained from electrocardiogram recordings in 15 healthy volunteers during 30 minutes of rest followed by 30 minutes of treadmill walking (≅ 4 km/h). The R-R series were linearly detrended, checked for stationarity, and windows of 150 non-overlapping intervals were sequentially extracted. HRV/C estimators were obtained: standard deviation (SDNN), root mean square (RMSSD), power of frequency bands (LF, HF and VHF, i.e., above 0.40 Hz) by STFT, normalized power (nu), a1ApEn. Correlations were studied intra-individual between conditions and intra-population. Additionally, in the Fourier Transform data, phases were randomly shuffled, an inverse transform applied (reconstituted rR-R), and RMSSD and a1ApEn were computed. Finally, the scaling profile of a1ApEn between conditions was addressed.
Results: All the HRC/V estimators, except nuLF and nuVHF, showed a decrease in low intensity exercise. For intra-population, all the estimators, except VHF, demonstrated highly significant negative correlations with heart rate. In the reconstituted rR-R series, both RMSSD and a1ApEn

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increased due to the phase shuffling, while the effect being more intense in a1ApEn. The scaling profile of a1ApEn was compatible with normally distributed random noise in both rest and walk.
Conclusion: As is currently known, HRV/C estimators are intrinsically correlated to heart rate, and a1ApEn follows this rule. Differently from what is usually obtained for plain ApEn, here we show a decrease in complexity values with physical effort. Also, the rR-R analysis indicates that a1ApEn is more sensitive to temporal organization than RMSSD. At the same time, the scaling profile indicates that the complexity of heart rate control keeps the same features from rest to walk. Therefore, we show that a1ApEn is a valid tool in time-series analysis of empirical data.

Keywords: a1ApEn; time-series analysis; approximate entropy; heart rate; variability; complexity.

1. INTRODUCTION

Information entropy has, now, a long history, and it has become a very important general tool in the study of several data, particularly in the area of time-series analysis. A huge number of so-called "entropies" or, in general, entropy measures, were devised during the last decades and applied throughout many fields of research, in the context of "complexity analysis". Approximate Entropy (ApEn) is one of such tools [1,2], i.e. an information entropy measure widely employed, probably due to its very simple computation. However, as pointed out in some studies, ApEn has a main problem: it lacks an objective procedure in the choice of the parameters for the analysis [3,4].

In order to circumvent such a problem, some researchers developed entropy measures derived from ApEn [3,5,6]. We have recently developed an objective and adequate procedure to address the temporal organization of the series [7]. The procedure is to numerically compute the area under the curve of ApEn values obtained for window $m=1$ using all the range of tolerances r that covers the time-series. Moreover, the method possess benefits over the typically employed ApEn alternatives (conf. [7]). We named this estimator of complexity as a1ApEn (for "area under the curve of ApEn with window 1").

The preceding validation of a1ApEn was done in a number of simulated time-series coming from prototypical generating processes, as, for example, normally distributed random numbers or logistic map, as a secure way to validate the method. Now, we seek to complete the validation of the tool in data coming from real experiments.

Heart rate is a biological variable amply studied. It presents a degree of variation, known as heart rate variability (HRV), related to the control of arterial pressure, ventilatory coupling, thermoregulation, physical effort, etc (e.g., [8,9]). Heart rate variation is also studied in the sense of its complexity, i.e., in the sense of characterize the dimension or the dynamics of its control system [10–14]. Therefore, HRV/C becomes a very good candidate to be addressed by a1ApEn in order to validate the tool since we already know, at least in part, some expected results and also how to interpret its deviations.

The aim of the present study is to validate the estimator a1ApEn in an empirical setting using heart rate as the source of data.

2. METHODS

2.1 Subjects and Experimental Protocol

2.1.1 Subjects

25 healthy people volunteered to the study. All participants were instructed to be hydrated, to not drink coffee and alcohol in the day of the experiment and to avoid extreme physical activity in the previous days. From these initial 25 subjects, five had inadequate data collection during the exercise phase (see below) and other five had non-stationary data (see below). Therefore, this report is based on the remaining 15 subjects (nine males, mean age 26.6 ± 6.1, min = 20, max = 37; six females, mean age 24.3 ± 4.4, min = 19, max = 30; ages in years ± s.d.).

2.1.2 Experimental protocol

An initial 12-lead clinical electrocardiogram (ECG) was obtained from each volunteer to verify any disturbance in rhythm or in electrical conduction. After that, with the volunteer resting in supine position, a 3-lead CM5 (or Lewis) configuration ECG was recorded (sampling rate

of 1000 Hz - MP30 interface and the Biopac Student Lab Pro software - Biopac Systems Inc., Goleta, CA, USA), continuously, during 30 minutes. Then, the volunteer stood up and began to walk in a treadmill (speed ≅ 4 km/h) for another 30-minute period. All data were collected at room temperatures of 21-24℃.

2.2 R-R Time-Series

In each phase (rest and walk), the first and the last 5 minutes of the ECG recordings were discarded at once. This was done in order to avoid transients and anticipations that might interfere with cardiac variability. Therefore, each time-series to analysis comprises 20 minutes of data collection.

From the ECG raw data, R-R intervals were automatically obtained. After this, the R-R series were examined and eventual abnormal beats were excluded. These eventual abnormal beats comprised less than 1% of the R-R time-series. These procedures were performed through our own routine scripts in Matlab (Matlab R2013a, The MathWorks, Nantick).

The R-R series was, then, linearly detrended and checked for stationarity with built-in Matlab functions: **(a)** augmented Dickey-Fuller test for unit root using three models (autoregressive, autoregressive with drift and trend stationarity); and **(b)** variance ratio test for random walk. If non-stationarity was detected, we discarded an initial and/or a final portion of the series, maintaining at least 900 consecutive data points. If even after discarding these portions the remaining series was still non-stationary, the subject was rejected from any further analysis.

Non-overlapping vectors of 150 consecutive data points in the stationary R-R series were sequentially extracted. These vectors were the object of analysis, except for the scaling profile. The mean heart rate (f_c) of each vector was obtained from the corresponding section in the original (non-detrended) R-R series.

To obtain frequency bands (see below), Short-Term Fourier Transform (STFT) was applied on each vector. The f_c of each vector was employed to construct the corresponding frequency axis [15,16].

2.3 Heart Rate Variability Estimators

2.3.1 Standard deviation of normal-to-normal R-R intervals (SDNN)

This estimator is the usual standard deviation of the time-series. It gives an overall measure of variability.

2.3.2 Root mean square of the difference between adjacent R-R intervals (RMSSD)

This estimator accesses the degree of consecutive changes in the R-R intervals. It gives an overall measure of somehow rapid changes in heart rate.

2.3.3 Frequency bands

The usual partitioning of the frequency bands in HRV analysis is in Ultra Low Frequency (below 0.0033 Hz), Very Low Frequency (between 0.0033 and 0.040 Hz), Low Frequency (LF, between 0.040 and 0.150 Hz), High Frequency (HF, between 0.150 and 0.400 Hz, or above) (e.g., [9]). However, because 150 R-R intervals becomes a too short total period, we did not address both the Ultra and the Very Low bands (e.g. [8,17]). In addition, we fixed the HF band as the interval between 0.150 and 0.400 Hz, and separately examined what we named as the Very High Frequency band (VHF, above 0.400 Hz). The reason for this is presented in the Discussion section. The normalized powers (nu) were obtained dividing each partition by the total power of the spectrum.

2.4 Heart Rate Complexity Estimator

2.4.1 a1ApEn

A complete description of the a1ApEn estimator and its computation is given in [7]. Here we summarize it.

From a tolerance vector $\mathbf{r}$, obtained as a set that goes from the lowest value of distance that can be found among all the possible pairings in the time-series to the highest value of distance that can be formed among pairs, a normalized tolerance vector $\mathbf{r}^*$ is constructed as:

$$\mathbf{r}^* = \frac{1}{\max(\mathbf{r})} \cdot \mathbf{r} \quad (1)$$

The next step is to construct a curve of approximate entropy (ApEn) values using the original $\mathbf{r}$ vector for a window size $m=1$:

$$ApEn(1,\mathbf{r},N) = \phi^1(\mathbf{r}) - \phi^2(\mathbf{r}) \quad (2)$$

Where N is the size of the time-series (N = 150 for the analysis here, unless for the scaling profile, as described shortly), and ϕ^1 and ϕ^2 are countings for $m=1$ and 2, respectively, as defined in the ApEn procedure [18]. The last step is to compute the numeric integral of eqn. (2) in relation to the normalized tolerance vector $\mathbf{r}^*$:

$$a1ApEn(N) = \int_0^1 ApEn(1,\mathbf{r}^*,N)\cdot \mathrm{d}r^* \quad (3)$$

2.4.2 The scaling profile

As we show in another study ([19]), the correlation between a1ApEn values and the size N of vectors can indicate the underlying process that generates the time-series. Briefly, consider the sizes N_j where the subscript j indicates the length of a vector (e.g., j = 100, 200, 300, 400, 500). Then, a vector of size S is randomly sub-sampled in v vectors of size N_j ($S > N_j + 3\cdot v \ \forall\ j$), and v values of a1ApEn are thus computed. Let these v a1ApEn values be a set a_j. For each set a_j, the indicators minimum, mean and maximum a1ApEn values are selected and the correlation between each one of them and the logarithm of the sizes N_j is computed. Each correlation can be positive, negative or non-significant. The profile of the correlations of the indicators minimum (Min), Mean and maximum (Max) is associated to a certain type of process (the reader is advised to see [19] for detailed presentation).

The scaling profile is important in two settings. Firstly, to indicate the general underlying process behind the heart rate variations for the individuals as a population. Secondly, to verify whether individuals change their generating process when they go from rest to walk, i.e., whether the features that generate the cardiac control output change with the physical effort.

Because we fixed the time length of analysis (20 minutes, see above), the total length of a time-series of R-R intervals changed between subjects and conditions due to different heart rates. Short series had between 1100 and 1200 R-R intervals. Therefore, in order to guarantee a safe resampling procedure (see [19]), we employed j = 50, 150, 250, 350, 500, and v = 30.

A table of the scaling profile of prototypical series from different generating processes using the same *j* values and *v* as in the analysis of the empirical data was created for comparison (Table 1). The processes comprised NbRN: non-bounded random numbers (normally distributed random numbers and Lévy sets); BnRN: bounded random numbers (uniformly distributed random numbers $\in$ [0,1]), and deterministic maps (Hénon and logistic maps close to chaos).

Table 1. Correlation signals of the indicators for different generating processes

Process	Sub-type	Min	Mean	Max
NbRN	*ndrn*	**0**	**-**	**-**
		+	**0**	**-**
		+	**0**	**0**
	Lévy	**0**	**-**	**-**
BnRN	*udrn*	**+**	**+**	**+**
Deterministic maps	*Hénon*	**+**	**+**	**+**
		0	**+**	**+**
		+	**+**	**0**
	logistic	**+**	**+**	**0**

NbRN: non-bounded random numbers (ndrn: normally distributed random numbers); BbRN: non-bounded random numbers (udrn: uniformly distributed random numbers); (-) = negative significant correlation; (0) = non-significant correlation; (+) = positive significant correlation. The ndrn and Hénon processes comprises more than one line showing the variety of correlations obtained in the simulations

2.5 Inverse Fourier Transform with Phase Shuffling

In the STFT data from each 150 R-R intervals, the phases were randomly shuffled and an inverse FFT applied (built-in Matlab function). This results in a reconstructed time-series, rR-R, with the same mean, variance and frequency distribution from the original one. However, the temporal organization of the rR-R randomly differs from the temporal organization of the original data. SDNN, RMSSD and a1ApEn were computed in the rR-R series and compared to those from the original data.

2.6 Comparisons and Statistics

2.6.1 Comparison between rest and walk

For each volunteer, a mean value of the estimators was computed in each condition. These mean values entered, then, in paired comparisons (t-test).

2.6.2 Correlation of the estimators with heart rate and among each other

The Pearson correlation coefficients for the mean values of the estimators (see above) and their corresponding f_c were obtained, as well as the correlations among the estimators.

2.6.3 Comparison between original and phase-shuffled series

The mean values of SDNN, RMSSD and a1ApEn from the original R-R time-series and from the reconstructed ones were paired for comparison (t-test). Because RMSSD and a1ApEn values are of different magnitudes, each set of 60 values (30 from rest and 30 from walk) of these estimators was normalized (Euclidian norm) in order to address the impact of disrupting the original temporal organization of the data by the phase shuffling in each estimator.

3. RESULTS AND DISCUSSION

3.1 Comparison between Rest and Walk, and Correlations with Heart Rate

Table 2 presents mean values for the various estimators of HRV/C obtained in rest and during walking. Each line in REST and in WALK corresponds to the same volunteer. Table 3 presents the paired comparisons of the estimators between the two conditions. Notice that, except for the VHF case, all paired comparisons gave very significant results ($P < 0.05$).

As obviously expected, there is an increase in heart rate when the volunteers go from rest to walk. On the other hand, there is a decrease in SDNN and RMSSD, indicating an overall decrease in variability in the transition from rest to low intensity exercise. Indeed, most studies report a decrease in HRV estimators correlated to the level of physical effort (e.g., see review in [20]). Due to the overall decrease in variance (SDNN squared) the frequency bands show a decrease in their respective power. However, when we exam the normalized bands, we observe a very interesting pattern: there is a decrease in nuHF while nuLF and nuVHF increase. This is exactly what one would expect under the condition imposed by low intensity exercise. The standing position is accompanied by an increase in the baroreflex gain [21], which appears in the LF band. At the same time, there is an increase in the ventilatory rate and the cardiomotor coupling between leg muscles contractions and the heart [16,22]. These two effects give rise to frequency components above the usual HF band. Therefore, we can observe these phenomena in the normalized bands, as if the nuHF cedes power to nuLF and to nuVHF.

As presented above, it seems that, technically speaking, our data was adequately collected and processed. This is relevant to the debate in regards to whether there is a decrease or an increase in HRV estimators in low intensity exercise, and, more importantly for our present goals, it guarantees the analysis of complexity by the a1ApEn tool, to be presented in subsequent sections.

When we take the data set as a whole (i.e., data in Table 2 without discriminating subjects or conditions), we obtain an overall correlation of each estimator with heart rate. These results are shown in Table 4. As it can be seen, there is a strong correlation between heart rate and each HRV estimator (except plain VHF, in italics), as well as with a1ApEn.The correlation is negative, except for nuLF and nuVHF. This reassures the result presented above, i.e., that a transfer of power from the HF band to LF and VHF bands accompanies the increase in heat rate due to the low intensity physical effort and the standing position.

The topic of HRC behavior in exercise is still controversial. For instance, some authors report an increase in heart rate complexity, measured by Sample Approximate Entropy, at the onset of exercise and, then, a decrease as the activity continues [14]. Others report an initial decrease and a subsequent increase in HRC, measured via Poincaré plot, during physical effort [23]. Specifically for low intensity exercise, in a protocol extremely similar to the one of the present study, an increase in HRC, measured by fractal exponent and by ApEn, is reported [10].

Table 2. Mean values of HRV/C estimators during rest and walk

f_c (Hz)	SDNN (s)	RMSSD (s)	a1ApEn	LF (s^{-2})	HF (s^{-2})	VHF (s^{-2})	nuLF	nuHF	nuVHF
Rest									
1.422	0.044	0.028	0.236	4.38E-04	3.99E-04	4.26E-05	0.202	0.208	0.023
1.093	0.083	0.098	0.310	1.05E-03	2.09E-03	2.89E-04	0.149	0.298	0.042
0.946	0.161	0.196	0.339	3.92E-03	7.02E-03	5.57E-04	0.151	0.271	0.021
0.958	0.066	0.063	0.282	5.71E-04	6.70E-04	2.33E-05	0.134	0.165	0.005
1.054	0.132	0.155	0.368	1.90E-03	4.54E-03	1.05E-03	0.111	0.261	0.061
1.055	0.045	0.037	0.266	3.64E-04	2.82E-04	3.33E-05	0.181	0.143	0.015
0.917	0.067	0.062	0.238	8.18E-04	4.97E-04	7.83E-05	0.174	0.114	0.018
1.018	0.058	0.048	0.281	4.95E-04	4.12E-04	3.96E-05	0.156	0.129	0.012
1.186	0.078	0.042	0.189	1.86E-03	3.60E-04	5.75E-05	0.304	0.059	0.010
1.055	0.090	0.105	0.240	1.30E-03	1.88E-03	4.59E-04	0.156	0.229	0.056
1.261	0.068	0.071	0.313	5.03E-04	2.06E-03	1.59E-04	0.101	0.446	0.031
1.109	0.060	0.048	0.257	7.55E-04	5.24E-04	5.89E-05	0.203	0.148	0.019
1.302	0.042	0.039	0.268	4.84E-04	2.87E-04	1.36E-04	0.272	0.168	0.078
1.111	0.058	0.038	0.260	6.26E-04	4.66E-04	2.08E-05	0.208	0.157	0.007
0.999	0.031	0.019	0.199	1.70E-04	6.20E-05	6.70E-06	0.178	0.073	0.008
Walk									
1.857	0.015	0.008	0.193	1.05E-04	2.88E-05	8.63E-06	0.455	0.146	0.040
1.743	0.019	0.009	0.186	2.05E-04	1.59E-05	1.85E-05	0.557	0.042	0.057
1.560	0.037	0.036	0.272	3.95E-04	1.89E-04	2.68E-04	0.292	0.131	0.209
1.346	0.022	0.015	0.235	1.53E-04	3.46E-05	3.25E-05	0.289	0.069	0.067
1.921	0.012	0.007	0.254	3.32E-05	5.08E-06	1.50E-05	0.245	0.030	0.121
1.463	0.038	0.035	0.315	3.68E-04	2.43E-04	2.06E-04	0.256	0.166	0.154
1.550	0.030	0.017	0.215	3.08E-04	4.00E-05	5.12E-05	0.322	0.047	0.057
1.498	0.036	0.024	0.254	4.02E-04	8.58E-05	1.12E-04	0.314	0.070	0.100
1.651	0.031	0.015	0.180	4.99E-04	8.12E-05	2.44E-05	0.535	0.085	0.028
1.820	0.016	0.009	0.216	1.39E-04	2.17E-05	1.70E-05	0.509	0.084	0.066
2.012	0.009	0.004	0.212	4.21E-05	6.04E-06	5.15E-06	0.508	0.073	0.069
1.457	0.033	0.025	0.218	4.10E-04	8.95E-05	1.04E-04	0.367	0.085	0.093
1.806	0.019	0.009	0.201	2.18E-04	2.11E-05	1.35E-05	0.585	0.057	0.039
1.817	0.024	0.012	0.193	3.07E-04	9.11E-05	1.41E-05	0.446	0.161	0.029
1.446	0.038	0.031	0.269	4.53E-04	6.89E-05	1.96E-04	0.303	0.048	0.144

Table 3. Paired comparisons of the HRV/C estimators presented Table 2

	f_c	SDNN	RMSSD	a1ApEn	LF	HF	VHF	nuLF	nuHF	nuVHF
REST	1.099	0.072	0.070	0.270	0.001	0.001	0.000	0.179	0.191	0.027
WALK	1.663	0.025	0.017	0.228	0.000	0.000	0.000	0.399	0.086	0.085
Δ	0.564	-0.047	-0.053	-0.042	-0.001	-0.001	-0.000	0.220	-0.105	0.058
P-value	.000	.000	.000	.004	.004	.008	.06	.000	.001	.001
Trend	↑	↓	↓	↓	↓	↓	↓	↑	↓	↑

REST and WALK: grand mean of each condition. Δ: difference between grand mean of WALK and REST. P-value: value of the paired comparison (paired t-test). Up-pointing arrows: increasing trend. Down-pointing arrows: decreasing trend

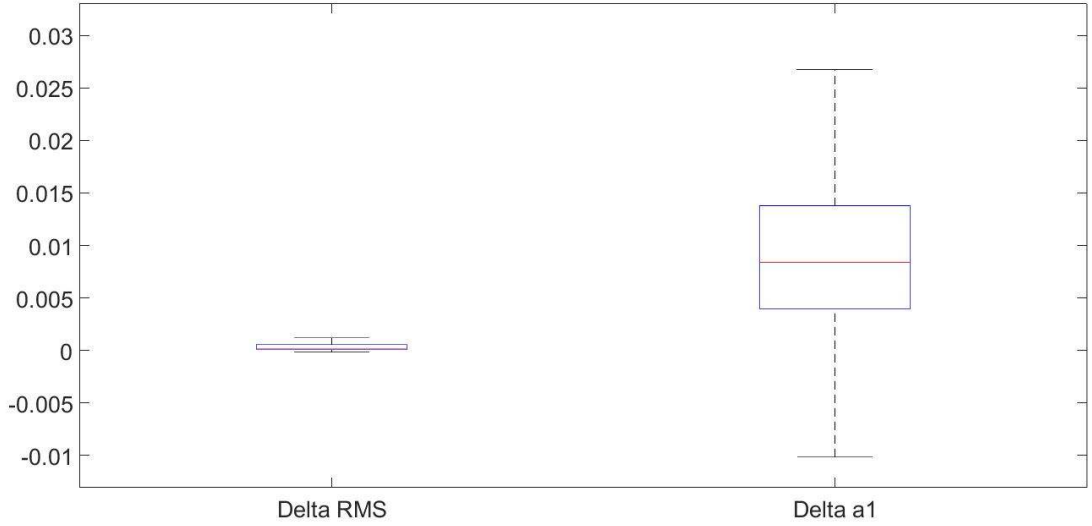

Fig. 1. Boxplot of the difference (delta) between RMSSD and a1ApEn for the reconstructed RR series and the original ones

Table 4. Correlation of HRV/C estimators with heart rate

	Pearson correlation coefficient	P-value
SDNN	-0.65	.000
RMSSD	-0.58	.000
a1ApEn	-0.42	.02
LF	-0.53	.002
HF	-0.41	.02
VHF	*-0.32*	*.09*
nuLF	0.77	.000
nuHF	-0.37	.04
nuVHF	0.59	.000

a1ApEn shows a decrease in the transition between rest and low intensity exercise (Tables 3 and 4). Therefore, our results are in contrast to what is described for plain Approximate Entropy as well as for Sample Approximate Entropy.

Due to the strong correlations with heart rate, the HRV estimators as well as a1ApEn turn out to be correlated among each other. Therefore, the a1ApEn estimator of complexity gives a result more in line with those from variability analysis. On the other hand, if the complexity estimator under investigation would simply tell the same story that the variability estimators already tell, it would be much more of a redundant index than a complementary tool.

The next sections show that the estimator a1ApEn addresses different information in relation to variability estimators.

Table 5. Comparison between estimators from the original and reconstructed R-R intervals

	SDNN		RMSSD		a1ApEn	
	Original	**rR-R**	**Original**	**rR-R**	**Original**	**rR-R**
	0.015	0.015	0.008	0.008	0.193	0.209
	0.044	0.044	0.028	0.028	0.236	0.249
	0.019	0.019	0.009	0.010	0.186	0.211
	0.083	0.083	0.098	0.098	0.310	0.330
	0.037	0.037	0.036	0.036	0.272	0.309
	0.161	0.161	0.196	0.197	0.339	0.354
	0.022	0.022	0.015	0.015	0.235	0.253
	0.066	0.066	0.063	0.063	0.282	0.320
	0.012	0.012	0.007	0.007	0.254	0.253
	0.132	0.132	0.155	0.155	0.368	0.347
	0.038	0.038	0.035	0.035	0.315	0.307
	0.045	0.045	0.037	0.037	0.266	0.286
	0.030	0.030	0.017	0.017	0.215	0.223
	0.067	0.067	0.062	0.062	0.238	0.276
	0.036	0.036	0.024	0.024	0.254	0.248
	0.058	0.058	0.048	0.048	0.281	0.292
	0.031	0.031	0.015	0.016	0.180	0.208
	0.078	0.078	0.042	0.043	0.189	0.210
	0.016	0.016	0.009	0.009	0.216	0.226
	0.090	0.090	0.105	0.105	0.240	0.323
	0.009	0.009	0.004	0.005	0.212	0.222
	0.068	0.068	0.071	0.071	0.313	0.311
	0.033	0.033	0.025	0.025	0.218	0.266
	0.060	0.060	0.048	0.048	0.257	0.302
	0.019	0.019	0.009	0.009	0.201	0.207
	0.042	0.042	0.039	0.039	0.268	0.292
	0.024	0.024	0.012	0.012	0.193	0.220
	0.058	0.058	0.038	0.039	0.260	0.271
	0.038	0.038	0.031	0.031	0.269	0.267
	0.031	0.031	0.019	0.019	0.199	0.254
Grand mean	0.049	0.049	0.044	0.044	0.249	0.268
Δ		0.0E+00		1.6E-04		1.9E-02
P-value		.74		.000		.000

Δ: Difference between the grand means from the reconstructed rR-R intervals and the original ones. P-value: paired t-test between original and reconstructed series

3.2 Inverse Fourier Transform with Phase Shuffling

Table 5 shows the results for SDNN, RMSSD and a1ApEn from the original R-R series (that can be found in Table 2 as well) and those from the reconstructed R-R series by iFFT with phase shuffling. Frequency bands do not take part in this analysis since they are exactly the same in the original and in the reconstructed series. In fact, SDNN, being the square root of variance, which is also preserved by the procedure, is presented only for illustrative purposes. As it can be checked out in Table 5, SDNN from the original and the rR-R series are the same.

Both RMSSD and a1ApEn are affected by phase shuffling, and both present an increase due to the procedure. This reveals that the original time-series have a certain organization that is disrupted despite the preservation of the original frequencies.

RMSSD and a1ApEn have dissimilar ranges. Therefore, in order to compare which one suffered more due to the temporal disorganization caused by the phase shuffling, we normalized the values from each estimator (in Table 5) by the Euclidian norm, using the 60 values from a given estimator (30 from the original and 30 from the rR-R series). Fig. 1 illustrates, graphically, the impact of phase shuffling in RMSSD and a1ApEn for the normalized data. In these data, the grand means for RMSSD and a1ApEn in the original and in the reconstructed series are, respectively: 0.091, 0.092, 0.122, 0.132.These represent differences of $3.3x10^{-4}$ for RMSSD and $9.6x10^{-3}$ for a1ApEn, shown in Fig. 1. Obviously, the P-values for the normalized data are the same as those in Table 5. As it can be seen, temporal disorganization had a more pronounced effect, almost 30 times greater, over a1ApEn than over RMSSD.

These results, once again, indicate that the a1ApEn estimator is in line with variability estimators but accesses some diverse features of the cardiac control.

3.3 The Scaling Profile

Table 6 presents the correlations of the three indicators (Min, Mean, Max) with vector size during rest and walking. Each line corresponds to the result of one of the 15 volunteers. Some important results must be pointed out. Firstly, the majority of the scaling profiles in Table 6 have perfect matches with patterns of non-bounded random numbers shown in Table 1. Secondly, none of the scaling profiles in Table 6 that do not have a perfect match with those in Table 1 presents a pattern compatible with any of the patterns from bounded random or deterministic maps. In fact, the profiles in Table 6 that do not match NbRN profiles have at least two criteria of NbRN and one or zero criterion of BnRN or deterministic maps.

Therefore, the scaling profile of the complexity estimator a1ApEn clearly indicates that the cardiac control operates as a pseudo-random system, irrespectively of the metabolic demand (in the range here studied). These results confirm a preliminary analysis of our group [19] and are aligned with recent results and interpretations about cardiac control [24–27].

Table 6. Correlations of the indicators with vector size

REST			WALK		
Min	**Mean**	**Max**	**Min**	**Mean**	**Max**
0	-	-	0	-	-
0	-	-	0	-	-
+	-	-	0	-	-
0	-	-	0	-	-
+	0	-	0	-	-
0	-	-	0	-	-
+	0	-	0	-	-
0	-	-	0	-	-
0	-	-	0	-	-
0	0	-	0	-	-
0	-	0	0	-	-
-	-	-	0	-	-
0	-	-	0	-	-
+	-	-	-	-	0
0	-	-	-	-	-

Coding as in Table 1

4. CONCLUSION

a1ApEn is an estimator of what is generally called as complexity of a time-series. Previously, we showed its adequacy as a measure of the temporal organization of several prototypical processes. These studies were conducted using artificially (*in machina*) generated time-series. Nevertheless, it lacked a validation in empirically obtained series and this is what we addressed in the present work. We choose to study heart rate variability because there are many estimators of it, and these estimators have a somehow known behavior. As we show here, a1ApEn adequately

estimates complexity of heart rate control and adds information beyond those gave by the usual HRV estimators. Therefore, a1ApEn is a valid tool to study real time-series.

ETHICAL APPROVAL

The experimental was approved by the Comissão de Ética - Instituto de Biociências (CEUA-IB/ CAAE: 34609214.6.0000.5464) and each volunteer gave informed consent.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pincus SM, Huang W. Approximate entropy: Statistical properties and applications, Commun. Stat. - Theory Methods. 1992;21:3061–3077.
DOI: 10.1080/03610929208830963.
2. Pincus SM. Assessing serial irregularity and its implications for health. Ann. N. Y. Acad. Sci. 2001;954:245–267.
DOI: 10.1111/j.1749-6632.2001.tb02755.x
3. Castiglioni P, Di Rienzo M. How the threshold "r" influences approximate entropy analysis of heart-rate variability, Comput. Cardiol. 2008;561–564.
DOI: 10.1109/CIC.2008.4749103
4. Santos BT, Martins RA, Natali JES, Rodrigues VH, Marques FS, Chauí-Berlinck JG. Consistency in approximate entropy given by a volumetric estimate. Chaos, Solitons & Fractals. 2009;42:322–334.
DOI: 10.1016/j.chaos.2008.12.002
5. Chon K, Scully CG, Lu S. Approximate entropy for all signals. IEEE Eng. Med. Biol. Mag. 2009;28:18–23.
DOI: 10.1109/MEMB.2009.934629
6. Lu S, Chen X, Kanters JK, Solomon IC, Chon KH, Automatic selection of the threshold value R for approximate entropy. IEEE Trans. Biomed. Eng. 2008;55:1966–72.
DOI: 10.1109/TBME.2008.919870
7. Natali JES, Chaui-Berlinck JG. Area 1 of Approximate entropy as a fast and robust tool to address temporal organization. Br. J. Appl. Sci. Technol. 2016;13:1–11.
DOI: 10.9734/BJAST/2016/22726
8. TASK FORCE, Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur. Heart J. 1996;17: 354–81.
Available:http://www.ncbi.nlm.nih.gov/pubmed/8737210
(Accessed May 29, 2014)
9. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. Front. Psychol. 2014;5:1–19.
DOI: 10.3389/fpsyg.2014.01040
10. Tulppo MP, Hughson RL, Mäkikallio TH, Airaksinen KE, Seppänen T, Huikuri HV. Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. Am. J. Physiol. Heart Circ. Physiol. 2001;280:H1081-7.
DOI: 11179050
11. Schmitt DT, Ivanov PC. Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: A new mechanistic picture of cardiac control in healthy elderly. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2007;293:R1923–R1937.
DOI: 10.1152/ajpregu.00372.2007
12. Ivanov PC, Nunes Amaral LA, Goldberger AL, Havlin S, Rosenblum MG, Struzik ZR, Stanley HE. Multifractality in human heartbeat dynamics. Nature. 1999;399: 461–465.
DOI: 10.1038/20924
13. Guzzetti S, Borroni E, Garbelli PE, Ceriani E, Della Bella P, Montano N, Cogliati C, Somers VK, Mallani A, Porta A. Symbolic dynamics of heart rate variability: A probe to investigate cardiac autonomic modulation. Circulation. 2005;112:465–470.
DOI:10.1161/CIRCULATIONAHA.104.518449
14. Lewis MJ, Short AL. Sample entropy of electrocardiographic RR and QT time-series data during rest and exercise. Physiol. Meas. 2007;28:731–44.
DOI: 10.1088/0967-3334/28/6/011

15. Bailon R, Laguna P, Mainardi L, Sornmo L. Analysis of heart rate variability using time-varying frequency bands based on respiratory frequency, in: 2007 29th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE. 2007;6674–6677.
DOI: 10.1109/IEMBS.2007.4353891
16. Bailón R, Mainardi L, Orini M, Sörnmo L, Laguna P. Analysis of heart rate variability during exercise stress testing using respiratory information. Biomed. Signal Process. Control. 2010;5:299–310.
DOI: 10.1016/j.bspc.2010.05.005
17. Peçanha T, Bartels R, Brito LC, Paula-Ribeiro M, Oliveira RS, Goldberger JJ. Methods of assessment of the post-exercise cardiac autonomic recovery: A methodological review, Int. J. Cardiol. 2017;227:795–802.
DOI: 10.1016/j.ijcard.2016.10.057
18. Pincus SM. Approximate entropy as a measure of system complexity. Proc. Natl. Acad. Sci. U. S. A. 1991;88:2297–2301.
DOI: 10.1073/pnas.88.6.2297
19. Natali J, Starzynski P, El-Dash I, Luccia T, El-Dash V, Chaui-Berlinck J. Size-related properties of area1 of approximate entropy to characterize time-series organization. Br. J. Appl. Sci. Technol. 2016;18:1–16.
DOI: 10.9734/BJAST/2016/29596.
20. Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. Eur. J. Appl. Physiol. 2003;90:317–325.
DOI: 10.1007/s00421-003-0953-9
21. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC. Power spectrum analysis of heart rate fluctuations: A quantitative probe of beat-to-beat cardiovascular control. Science. 1981;80:213:220–222.
22. Phillips B, Jin Y. Effect of adaptive paced cardiolocomotor synchronization during running: A preliminary study. J. Sport. Sci. Med. 2013;12:381–387.
23. Tulppo MP, Mäkikallio TH, Takala TE, Seppänen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am. J. Physiol. 1996;271:H244-52.
Available:http://www.ncbi.nlm.nih.gov/pubmed/8760181
24. Dvir H, Zlochiver S. Stochastic cardiac pacing increases ventricular electrical stability - A computational study. Biophys. J. 2013;105:533–542.
DOI: 10.1016/j.bpj.2013.06.012
25. Dvir H, Zlochiver S. The interrelations among stochastic pacing, stability, and memory in the heart. Biophys. J. 2014; 107:1023–1034.
DOI: 10.1016/j.bpj.2014.07.004
26. Dai S, Keener JP. Using noise to determine cardiac restitution with memory. Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys. 2012;85:1–10.
DOI: 10.1103/PhysRevE.85.061902
27. Armour JA. Potential clinical relevance of the “little brain” on the mammalian heart. Exp. Physiol. 2008;93:165–176.
DOI: 10.1113/expphysiol.2007.041178

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