Feasibility of Linear Parametric Estimation of Dynamic Information Measures to assess Physiological Stress from Short-Term Cardiovascular Variability*

Riccardo Pernice, Gabriele Volpes, Jana Cernanova Krohova, Michal Javorka, Alessandro Busacca, and Luca Faes, *Senior Member, IEEE*

***Abstract*— Extensive efforts have been recently devoted to implement fast and reliable algorithms capable of assessing the physiological response of the organism to physiological stress. In this study, we propose the comparison between model-free and linear parametric methods as regards their ability to detect alterations in the dynamics and in the complexity of cardiovascular and respiratory variability evoked by postural and mental stress. Dynamic entropy (DE) and information storage (IS) measures were calculated on three physiological time-series, i.e. heart period, respiratory volume and systolic arterial pressure, on 61 healthy subjects monitored in resting conditions as well as during head-up tilt and while performing a mental arithmetic task. The results of the comparison suggest the feasibility of DE and IS measures computed from different physiological signals to discriminate among resting and stress states. If compared to the model-free algorithm, the faster linear method appears to be capable of detecting the same (or even more) statistically significant variations of DE or IS between resting and stress conditions, being thus in perspective more suitable for the integration within wearable devices. The computation of entropy indices extracted from multiple physiological signals acquired through wearables will allow a real-time stress assessment on people during daily-life situations.**

I. Introduction

In recent years, an increasing interest has been reported in the literature towards the study of the physiological response of the organism to mental and postural stress, aimed at characterization of the complex behavior of the autonomic nervous system (ANS), also given the number of diseases that are associated with stress [1]. A common method of analysis employs an assessment of the beat-to-beat dynamics of cardiovascular variables from finite-length time-series that quantify these variables over time. Among such variables, the most important and widely studied is heart rate variability (HRV) which is typically assessed from R-R intervals (RRI) of electrocardiogram (ECG) recordings [2]. Time-series of about 5 minutes (300 beats) are usually examined, being this duration recognized as a standard for HRV analyses (short-term HRV) thanks to the good trade-off between practical purposes (duration of recordings under steady state conditions) and the information contained for the assessment of cardiovascular control [2]. Moreover, HRV and autonomic system are strongly affected by several coexisting control mechanisms, which involve the influence of respiration and systolic blood pressure contributions [3].

Short-term cardiovascular time series are typically analyzed making use of time-domain, frequency-domain or information-theoretic measures [4]. The latter have attracted an ever growing interest allowing to reliably assess ANS complexity and regularity, as well as to investigate the nature of the interaction between biosignals [2]–[4]. In particular, dynamic entropy (DE) and information storage (IS) are two measures able to respectively quantify the information contained in the dynamics of a time series and its regularity [5]. However, information-theoretic measures are usually computationally more costly than time- or frequency domain indices or than correlation-based approaches [6]. For this reason, the main efforts in recent years have been devoted to the implementation of algorithms presenting, at the same time, a reduced computational cost and an acceptable loss of precision in entropy estimation [5].

In this paper, a comparison between two estimation methods for information-theoretic measures, i.e. a non-linear model-free estimator based on nearest neighbor analysis and a linear parametric estimator, is presented in order to assess the degree of agreement, taking into account as well their computational costs. In a previous work, we compared conditional entropy measures calculated starting from RRI time series [7]. Here, we expand such investigation studying DE and IS on multiple time-series (RR, respiratory and systolic blood pressure) for a more complete assessment of strengths and limitations of the two approaches. The final aim is to identify the method allowing the best trade-off between ability to monitor the response to stress and computational costs.

II. Materials and Methods

A. Experimental protocol

The study has been carried out on 61 healthy subjects (37 female, 24 male, age 17.5 ± 2.4 years), all normotensive and within the normal range of body mass index (19-25 kg m^{-2}) [1]. Data were acquired in four physiological conditions: (i) a baseline resting phase (R_1) lasting 15 min with the subjects lying in supine position; (ii) a head-up tilt (T) phase of 8 min

* R.P. is supported by the Italian MIUR PON R&I 2014-2020 AIM project no. AIM1851228-2. L.F. is supported by the Italian MIUR PRIN 2017 project 2017WZFTZP "Stochastic forecasting in complex systems" and Italian MIUR PON project "4FRAILTY - Sensoristica intelligente, infrastrutture e modelli gestionali per la sicurezza di soggetti fragili" (MIUR D.D. 1735 13/07/2017). J.C.K. and M.J. are supported by grants VEGA 1/0200/19 and VEGA 1/0283/21.

R. Pernice, G. Volpes, A. Busacca and L. Faes are with the Department of Engineering, University of Palermo, 90128 Palermo, Italy (corresponding author e-mail: luca.faes@unipa.it).

J. Cernanova Krohova and M. Javorka are with the Dept. of Physiology and the Biomedical Center Martin, Comenius University in Bratislava, Jessenius Faculty of Medicine, Martin, Slovakia.

obtained tilting the motorized table to 45° to evoke mild orthostatic stress; (iii) a second supine resting phase (R_2) lasting 10 min; (iv) a 6-min mental arithmetic (M) test during which the subjects were asked to perform mentally (without verbalization) quick mathematical operations to evoke mental stress. Physiological signals acquired synchronously on the subjects consisted of (i) ECG recorded through a horizontal bipolar thoracic lead (CardioFax ECG-9620, NihonKohden, Japan), (ii) continuous arterial blood pressure recorded on the finger through the volume-clamp method (Finometer Pro, FMS, Netherlands), and (iii) respiratory volume signal acquired using thoracic and abdominal belts via respiratory inductive plethysmography (RespiTrace 200, NIMS, USA). The sampling rate of all the acquired signals was 1 kHz. Further details on the experimental protocol can be found in [1]. All the procedures were approved by the Ethical Committee of the Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia and all the participants signed a written informed consent.

B. Time series extraction

The time-series measured from the acquired signals consisted of stationary segments covering a duration of 300 heartbeats, extracted at least 2 min after the start of each physiological condition to avoid transition effects. R-R time series (RR) were extracted from the ECG signal as the temporal distance between the n-th and (n+1)-th QRS apexes [4], while the respiratory signal (RESP) was sampled at the onset of each RR interval and the systolic arterial pressure (SAP) was computed as the maximum value of blood pressure signal within a given RR interval [1]. All the time series have been normalized to zero mean and unit variance before computing the entropy measures.

C. Entropy measures

Considering a stationary stochastic process X, let us denote as X_n and $\boldsymbol{X}_n^m = [X_n X_{n-1} \cdots X_{n-m+1}] = [X_n\, \boldsymbol{X}_{n-1}^{m-1}]$ the variables describing one single state of the process and the collection of m states. The entropies of these variables are defined as [5]:

$$H(X_n) = -\boldsymbol{E}[\log p\,(x_n)] \tag{1a}$$

$$H(\boldsymbol{X}_n^m) = -\boldsymbol{E}[\log p\,(x_n, x_{n-1}, \dots, x_{n-m+1})] \tag{1b}$$

where $\boldsymbol{E}[\cdot]$ is the expectation operator and $p(\cdot)$ the probability density. The measure in (1a) quantifies the 'static' information contained in one single state of the stationary process, while the measure in (1b) reflects the 'dynamic' information content in m states of the process. The second measure, which we denote as dynamic entropy, $DE(X) = H(\boldsymbol{X}_n^m)$, is related to the entropy rate of the process defined as $\lim_{m\to\infty} \frac{1}{m} H(\boldsymbol{X}_n^m)$. The two measures are related to the information storage (IS), quantifying the amount of information carried by the present that can be explained by the past history of the process [8]:

$$IS(X) = I(X_n; \boldsymbol{X}_{n-1}^{m-1}) = H(X_n) + H(\boldsymbol{X}_{n-1}^{m-1}) - H(\boldsymbol{X}_n^m) \tag{2}$$

where $I(\cdot;\cdot)$ denotes mutual information; eq. (2) holds exactly if X is a Markov process of order m-1. The information storage is an important measure of the regularity of a stochastic process [5].

In this work, we estimate DE and IS starting from a time series $x = \{x_1, \dots, x_N\}$ of length N, considered as a realization of the process X. The first considered estimation method (herein referred as *knn*) is a non-parametric approach using nearest neighbor metrics, which exploits the intuitive notion that the local probability density around a data point is inversely related to the distance between the point and its neighbors [5]. With this approach, the DE can be estimated, computing distances between m-dimensional patterns extracted from the time series as realizations of $\boldsymbol{X}_n^m$, as [5]

$$DE_{knn}(X) = -\psi(k) + \log(N-m) + m\langle log\epsilon_{n,k}\rangle, \tag{3}$$

where $\epsilon_{n,k}$ denotes twice the distance between the n-th realization of $\boldsymbol{X}_n^m$ and its k-th nearest neighbor, k is the number of neighbors counted, $\langle\cdot\rangle$ denotes average over the N-m+1 realizations, and $\psi(\cdot)$ is the digamma function; note that distances are computed using the maximum norm. On similar grounds, and using a distance-projection approach that compensates for estimation bias, the IS is estimated as [5]:

$$IS_{knn}(X) = \psi(k) + \log(N-m) - \langle\psi(n_x) + \psi(n_{\mathbf{x}})\rangle, \tag{4}$$

where n_x and $n_{\mathbf{x}}$ are the number of patterns whose distance from the n-th realizations of X_n and of $\boldsymbol{X}_{n-1}^{m-1}$, respectively, is smaller than $\epsilon_{n,k}$, with $\epsilon_{n,k}$ as in (3).

The second estimation method (herein referred as *lin*) follows a linear parametric approach relying on the fact that many real-word data tend to the Gaussian distribution. For a stationary Gaussian process, entropies can be computed exactly from the covariance matrices of the variables sampling the process. Specifically, given that the entropy of a d-dimensional variable $\boldsymbol{W}$ is $H(\boldsymbol{W}) = 0.5\log(2\pi e)^d\,|\Sigma_{\boldsymbol{W}}|$, where $|\Sigma_{\boldsymbol{W}}|$ is the determinant of the covariance matrix of $\boldsymbol{W}$, the utilization of this relation in (1b) and (2) leads to estimate the DE and IS as:

$$DE_{lin}(X) = \frac{1}{2}\log(2\pi e)^m\,\left|\hat{\Sigma}_{\boldsymbol{X}_n^m}\right|, \tag{5}$$

$$IS_{lin}(X) = \frac{1}{2}\log\frac{\hat{\Sigma}_{X_n}\left|\hat{\Sigma}_{\boldsymbol{X}_{n-1}^{m-1}}\right|}{\left|\hat{\Sigma}_{\boldsymbol{X}_n^m}\right|}, \tag{6}$$

where $\Sigma_{X_n} = \sigma_X^2$ is the variance of X and the covariance estimates $\hat{\Sigma}$ are obtained with the Blackman-Tukey estimator.

In agreement with previous works on short-term cardiovascular variability [4], the dimension of the vector variables used for dynamic analysis was set to m=2. The number of neighbors for the *knn* estimator was set to k=10 [4].

D. Statistical analysis

For both *knn* and *lin* methods, the entropy measures described in the previous subsection were computed on the three time series (RR, RESP and SAP) extracted on the 61 subjects for each of the four phases (R_1, T, R_2 and M). For carrying out the statistical analyses, parametric tests were used since the hypothesis of normality of the distribution of each measure was not rejected according to the Anderson-Darling test for almost all the analyzed time-series. For each entropy measure (DE or IS) and estimator (*knn* or *lin*), the Student t-test was used to compare the distributions obtained in a stress condition (i.e., T or M) with those relevant to the corresponding resting state (R_1 or R_2). The same test was applied to compare the distributions of DE or IS obtained with the two estimators given the experimental condition. All tests were performed assuming p=0.05 as the probability that the null hypothesis of equal mean is true.

III. Results

A. Entropy measures

Figures 1 to 3 depict, for each physiological time series (RR, RESP and SAP), the distributions of DE (panels a) and IS (panels b) across the 61 subjects assessed in the four conditions (R_1, T, R_2 and M) using *knn* (grey boxplots) and *lin* (white boxplots) estimators.

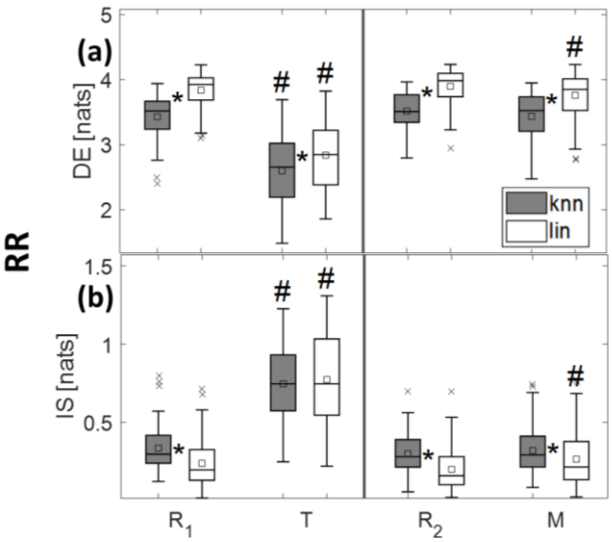

Figure 1. Boxplot distributions of (a) DE and (b) IS indexes computed on RR time series during rest (R_1, R_2) and stress (T, M) conditions, using *knn* (gray) and *lin* (white) estimators. Statistical tests: #, p<0.05 R_1 vs T and R_2 vs M; *, p<0.05 *knn* vs *lin*.

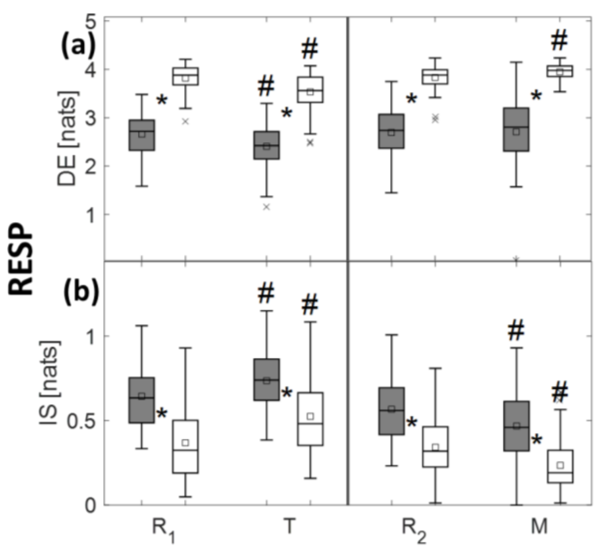

Figure 2. Boxplot distributions of (a) DE and (b) IS indexes computed on RESP time series during rest (R_1, R_2) and stress (T, M) conditions, using *knn* (gray) and *lin* (white) estimators. Statistical tests: #, p<0.05 R_1 vs T and R_2 vs M; *, p<0.05 *knn* vs *lin*.

Analyses have been focused on assessing the statistically significant differences between rest and stress conditions (R_1 vs T and R_2 vs M) and between estimators at a given condition. The investigation carried out on RR time series (Fig. 1) evidenced, for both estimators, a decrease of DE and an increase of IS after postural stress elicitation. The linear estimator detected also a reduction of DE and an increase of IS during mental stress. Analyzing RESP time series (Fig. 2), both estimators evidenced a decrease of DE and an increase of IS during tilt and an increase of IS during mental stress, while only the linear estimator detected higher DE during mental arithmetic. As regards the SAP time series (Fig. 3), an increase of DE and a lower IS were observed during mental stress by both estimators, while an increased IS after the orthostatic maneuver was detected by using the linear estimator.

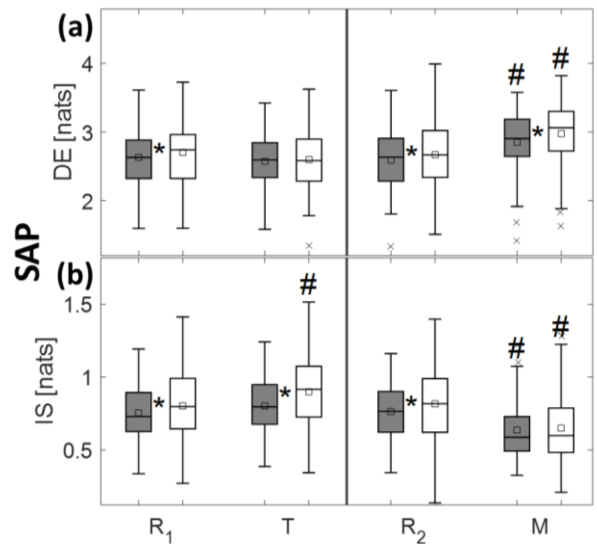

Figure 3. Boxplot distributions of (a) DE and (b) IS indexes computed on SAP time series during rest (R_1, R_2) and stress (T, M) conditions, using *knn* (gray) and *lin* (white) estimators. Statistical tests: #, p<0.05 R_1 vs T and R_2 vs M; *, p<0.05 *knn* vs *lin*.

The comparison between the two estimators computed on RR time series (Fig. 1) evidenced that the linear method produces higher estimates of DE and lower estimates of IS (except during postural stress). These differences were emphasized and always statistically significant for the RESP time series (Fig. 2). On the contrary, trends indicating higher estimates of both DE and IS obtained using the linear estimator were observed for the SAP time series (Fig. 3), with statistical significance reached during R_2 and M for DE and during R_1, T and R_2 for IS.

B. Computational cost

The average computation time of the entropy measures on 732 iterations (3 time series in 4 different physiological conditions for the 61 subjects) was about 0.36 ms per iteration for the linear estimator, compared to 10.9 ms per iteration of the k-nearest method, i.e. around two orders of magnitude lower. Such computational times were obtained on a notebook equipped with an Intel Core i5-2410M CPU (2.3 GHz with Turbo Boost up to 2.9 GHz), 8 GB RAM, 256 GB SSD, Windows 10, MATLAB R2019b. These results are in line with those obtained in an our previous work [7] in which we only compared computational time of *lin* and *knn* conditional entropy measures on RR time series.

IV. Discussion

The decrease of the information contained in the RR time series and the increase of its regularity during orthostatic stress are in agreement with previous findings achieved calculating static entropy and conditional entropy on RR time series [1], [9] and confirm that heart period dynamics are strongly affected by postural stress, with a significant reduction in complexity. The increased regularity during tilt reflects a widely known behavior of heart rate variability due to an activation of the sympathetic nervous system and inhibition of parasympathetic nervous system activity, which have a regularizing effect on the cardiac dynamics [9]. The increased regularity may be also related to the reduced information transfer from RESP to RR reported in [3]. The analyses on RESP time series indicate higher IS during orthostatic stress and lower IS during mental stress; similar results were found respectively in [9] and [1], and could be related to the increased tidal volume and slightly lower breathing rate during tilt and to the increased breathing rate during mental arithmetic. Postural stress does not affect SAP time-series dynamics; on the other hand, an increased DE and a reduced regularity is observed during arithmetic test. This may be ascribed to cortical mechanisms related to mental stress eliciting the changes in the patterns of autonomic activation following a cognitive load, including vasomotor reactions that are reflected in SAP variations [1], [3].

The analyses were also aimed at comparing the two estimators for each measure, time series and condition. With regard to RR variability, the linear estimator returned lower estimates of DE and higher estimates of IS, reflecting respectively lower information content and higher predictability of the time series. These findings suggest the presence of non-linear dynamics in HRV time series at rest and during mental stress; the only exception to these trends, i.e. the distribution of IS during postural stress, agrees with previous findings showing that the strength of nonlinear dynamics in HRV is reduced during tilt in young people [10]. The lower information content and higher regularity were observed even more evidently for the RESP time series in all conditions, confirming previous work highlighting that respiration is a strongly non-linear process [11].

Analyzing all the results, it is worth noting that all the statistical differences identified by the *knn* method are also detected by the linear one, with the advantage of a strong reduction of the computational times. Moreover, the linear estimator reports some changes that are in contrast not shown using the model-free approach; while this result could be exploited in practical application to augment the discriminative capability of entropy measures, it may be somewhat misleading as it can be due to non-linear dynamics which are present in the phenomenon but are not taken properly into account by the *lin* estimator.

V. Conclusion

Our results document the viability to exploit combined dynamic entropy and information storage measures computed on different physiological time series to discriminate among resting state and physiological challenges (orthostatic stress, cognitive load). This observation confirms the practical importance of synchronously acquiring several biosignals from different body locations (and not just one) using wearable systems, exploiting the so-called network physiology approach [6], [12].

Moreover, our analyses highlighted the feasibility to employ a faster and less power and time-consuming method to compute entropy measures exploiting a linear Gaussian approximation. This could have practical implications and pave the way to the implementation of the linear algorithms for DE and IS estimation within the firmware of mobile or wearable devices or within fitness or medical apps for smartphones or smartwatches, to allow a real-time assessment of the stress level of people during daily-life situations [13], [14]. Another future activity should foresee the investigation on the application of the entropy measures on shorter HRV time series, i.e. the so-called “ultra short-term HRV”, even easier to acquire using wearable devices, in order to assess their reliability if compared to short-term gold standard [15].

References

[1] M. Valente *et al.*, “Univariate and multivariate conditional entropy measures for the characterization of short-term cardiovascular complexity under physiological stress,” *Physiol. Meas.*, vol. 39, no. 1, p. 14002, 2018.

[2] F. Shaffer and J. P. Ginsberg, “An Overview of Heart Rate Variability Metrics and Norms,” *Front. public Heal.*, vol. 5, p. 258, Sep. 2017.

[3] J. Krohova *et al.*, “Multiscale Information Decomposition Dissects Control Mechanisms of Heart Rate Variability at Rest and During Physiological Stress,” *Entropy* , vol. 21, no. 5. 2019.

[4] R. Pernice *et al.*, “Comparison of short-term heart rate variability indexes evaluated through electrocardiographic and continuous blood pressure monitoring,” *Med. Biol. Eng. Comput.*, vol. 57, no. 6, pp. 1247–1263, 2019.

[5] H. Azami, L. Faes, J. Escudero, A. Humeau-Heurtier, and L. E. V Silva, “Entropy Analysis of Univariate Biomedical Signals: Review and Comparison of Methods.”

[6] R. Pernice *et al.*, “Multivariate Correlation Measures Reveal Structure and Strength of Brain–Body Physiological Networks at Rest and During Mental Stress,” *Front. Neurosci.*, vol. 14, p. 1427, 2021.

[7] R. Pernice *et al.*, “A validity and reliability study of Conditional Entropy Measures of Pulse Rate Variability*,” in *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2019, pp. 5568–5571.

[8] W. Xiong, L. Faes, and P. C. Ivanov, “Entropy measures, entropy estimators, and their performance in quantifying complex dynamics: Effects of artifacts, nonstationarity, and long-range correlations,” *Phys. Rev. E*, vol. 95, no. 6, p. 62114, Jun. 2017.

[9] L. Faes *et al.*, “Multiscale information storage of linear long-range correlated stochastic processes,” *Phys. Rev. E*, vol. 99, no. 3, p. 32115, Mar. 2019.

[10] L. Faes *et al.*, “Comparison of methods for the assessment of nonlinearity in short-term heart rate variability under different physiopathological states,” *Chaos An Interdiscip. J. Nonlinear Sci.*, vol. 29, no. 12, p. 123114, Dec. 2019.

[11] V. Bari *et al.*, “Nonlinear effects of respiration on the crosstalk between cardiovascular and cerebrovascular control systems,” *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.*, vol. 374, no. 2067, p. 20150179, 2016.

[12] M. Zanetti *et al.*, “Information Dynamics of the Brain, Cardiovascular and Respiratory Network during Different Levels of Mental Stress,” *Entropy* , vol. 21, no. 3. 2019.

[13] A. Kumari and R. Singh, “Evaluation of Work-Related Stress Amongst Industrial Workers,” in *Advances in Manufacturing and Industrial Engineering*, 2021, pp. 315–328.

[14] M. Umair, N. Chalabianloo, C. Sas, and C. Ersoy, “HRV and Stress: A Mixed-Methods Approach for Comparison of Wearable Heart Rate Sensors for Biofeedback,” *IEEE Access*, vol. 9, pp. 14005–14024, 2021.

[15] R. Castaldo, L. Montesinos, P. Melillo, C. James, and L. Pecchia, “Ultra-short term HRV features as surrogates of short term HRV: a case study on mental stress detection in real life,” *BMC Med. Inform. Decis. Mak.*, vol. 19, no. 1, pp. 1–13, 2019.