Refined Generalized Multivariate Multiscale Fuzzy Entropy: a Preliminary Study on Multichannel Physiological Complexity during Postural Changes

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***Abstract*—We propose a novel approach to characterize the complexity of multivariate physiological processes over multiple time scales, which hereinafter we call Refined Generalized Multivariate Multiscale Fuzzy Entropy (ReGeM-MFE). In this preliminary study, we evaluate the effectiveness of this methodology in discerning different levels of complexity in Autonomic Nervous System (ANS) dynamics during active stand-up, considering a bivariate process comprising heart rate variability and blood pressure variability series. Results show that, using mean- and variance-based ReGeM-MFE throughout different coarse-graining steps, it is possible to statistically discern the resting and stand-up conditions. Compared with the previously proposed Refined Composite Multivariate Multiscale Fuzzy Entropy, we demonstrate that the proposed ReGeM-MFE consistently outperforms this metrics.**

***Index Terms*—Complexity, Multivariate Multiscale Entropy, Generalized Multiscale Entropy, Fuzzy Entropy, Autonomic Nervous System, Heart Rate Variability, Blood Pressure.**

I. Introduction

The concept of system complexity derives from the analysis of nonlinear dynamics in physical processes. Complexity in physiological systems intrinsically arises from their intricate structures and interactions with other systems [1]. Entropy measures have been widely used to quantify complexity in heartbeat and brain dynamics, being able to discern between age, gender, and a numerous amount of cardiovascular and/or neurodegenerative diseases [1]–[4]. Particularly, such states have been mostly associated with a loss of physiological complexity [1]–[4].

Popular entropy algorithms are the Approximate and Sample Entropy (SampEn) [5], [6], as well as their multiscale version (known as Multiscale Entropy, MSE) [7] devised to account for multiple dynamics at different scale resolution and long-range correlations. MSE was successfully used to quantify complexity of signals in many fields, e.g., financial time series, seismic time series and of course, physiological signals [8]–[11]. The multiscale approach relies on two main steps: a coarse-graining process to compute the scaled time series and the application of SampEn algorithm. The traditional coarse-graining process comprises dividing the original signal into non-overlapping segments, and compute the mean value of the samples within each window [7]. Recently, a generalized version of MSE using also other moments than the mean has been proposed [12], showing good performances also for a variance-based MSE_{σ^2} .

Another limitation of traditional SampEn-based approaches is the dependence from parameters such as the threshold value r accounting for the count of embedded vectors [13]. Standard choices fix this threshold as the 15-20% of the series standard deviation [6]. Nevertheless, in the frame of a multiscale entropy calculation, if r is kept constant for all the scaled series, some dynamical patterns of the process generating the physiological series could be neglected [14], [15]. To this extent, Valencia *et al.* proposed a Refined Multiscale Entropy approach where the r threshold was changed as per the standard deviation of each scaled time series [15]. Moreover, Fuzzy Entropy [16] and its multiscale version were also proposed to overcome the parameter selection and data length dependence of SampEn [17]. In fact, the similarity of different dynamical states is fuzzily defined on the basis of an exponential function, rather than the Heaviside function.

Furthermore, methodological advances in estimating physiological complexity have been directed towards the study of multichannel recordings, aiming to better understand the entangled dynamics underlying a multivariate physiological system. A former approach estimating entropy in multichannel data refers to multivariate MSE [18], followed by the so-called multivariate multiscale permutation entropy [19], and the recently proposed Refined Composite Multivariate Generalized Multiscale Fuzzy Entropy (RCmvMFE) [20]. Note that RCmvMFE uses a coarse-graining technique for multivariate analysis, with fuzzy rules for estimating similarity of phase space vectors [20].

Nevertheless, RCmvMFE coarse-graining procedures employs overlapping vectors in time, which might bias the actual entropy estimation. Moreover, the dimension of the embedded vectors in the multivariate phase space reconstruction is estimated through the sum of the dimensions associated with each series dynamics, therefore possibly resulting in an overestimation of the actual phase space dimension. To overcome these limitations, here we propose a Refined Generalized Multivari-

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ate Multiscale Fuzzy Entropy (ReGeM-MFE), implementing a coarse-graining procedure with non-overlapping time vectors and a novel estimation of the multivariate phase space. The proposed ReGeM-MFE embeds the features of RCmvMFE regarding the fuzzyness and correction of the threshold r throughout different scale factors.

We test ReGeM-MFE using two different coarse-graining processes based on the mean and variance of the multivariate physiological input (ReGeM-MFE$_\mu$ and ReGeM-MFE$_{\sigma^2}$), and validate this novel approach in discerning two different states of ANS activation. Specifically, we study combined cardiovascular and diastolic blood pressure variability during supine resting state and active stand-up. Note that latter upright state is associated with a cardiac sympathetic activation, vagal withdrawal, and a significantly complexity reduced then resting state [21], [22].

Experimental protocol and subject recruitment are described in Section II, together with the proposed ReGeM-MFE algorithm and the statistical analysis methods. Results are reported in Section III, and Discussion and Conclusions follow in Section IV.

II. Materials and Methods

A. Subject Recruitment, Experimental Protocol, and Acquisition set-up

Data were gathered from the well-known publicly available repository Physionet [24]. Extensive details on the experimental protocol are reported in [22], [23]. Briefly, ten healthy volunteers (five males) with no sign of cardiovascular diseases were recruited in a postural change study. Individual subjects' information is reported in Table I.

Table I
Subject information

Subjects ID	Gender	Age (years)	Height (cm)	Weight (kg)
12726	M	28	170	64
12734	M	30	165	64
12744	M	28	180	100
12754	F	26	160	61
12755	M	32	192	83
12814	F	27	165	56
12815	F	22	185	73
12819	F	28	155	55
12821	F	32	173	77
13960	M	34	183	83
		28.7 $\pm$ 1.2	172.8 $\pm$ 4.0	70.6 $\pm$ 4.5

ECG signal and blood pressure were acquired throughout the experiment by means of a standard ECG monitor system (BIOPAC MP System) and a non-invasive blood pressure monitoring device (2300 FINAPRES BP monitor). ECG signals were recorded following the lead II configuration, while blood pressure was acquired non-invasively at the second phalanx of the left middle finger.

The experimental protocol comprised six postural changes:

- two stand-ups;
- two rapid head-up tilt (75°over 2 seconds);
- two slow head-up tilt (75°over 50 seconds).

The six postural changes were randomized among subjects and each of them lasted three minutes, being separated by five minutes of resting state in a supine position.

The experimental procedure was approved by the Advisory Board of the MIT-MGH General Clinical Research Center and the MIT's Committee on the Use of Humans as Experimental Subjects. From the ECG and blood pressure signals, heart rate variability (HRV) and diastolic blood pressure variability (DBPV) series were extracted (details on the extraction of fiducial points and artefact identification and correction are in [25]). Then, a shape-preserving piecewise cubic interpolation at the standard rate of 4 Hz was applied to both series. In this preliminary endeavour, stand-up and precedent resting sessions are considered for further analyses.

B. The proposed Refined Generalized Multivariate Multiscale Fuzzy Entropy (ReGeM-MFE$_\mu$ and ReGeM-MFE$_{\sigma^2}$)

As a multiscale entropy algorithm, the proposed ReGeM-MFE relies on a coarse-graining procedure of the input series.

Standard coarse-grained time series are constructed from the original series by averaging the data points within non-overlapping windows at scale β [7]. Given a c-variate time series $\mathbf{Y} = \{y_{k,b}\}_{b=1}^{L}$, where $k = 1, ..., c$ and L is the length of the series, each element of the coarse-grained series ${}^{\mu}\chi_{k,i}^{(\beta)}$ is calculated as follows:

$$ {}^{\mu}\chi_{k,i}^{(\beta)} = \frac{1}{\beta} \sum_{b=(i-1)\beta+1}^{i\beta} y_{k,b} \tag{1} $$

considering $1 \leq i \leq \left\lfloor \frac{L}{\beta} \right\rfloor = N$ and $1 \leq k \leq c$. The length of each coarse-grained time series is equal to the length of the original time series divided by β.

As reported in the Introduction, a generalized multiscale entropy analysis employing moments other than the mean has been proven effective in characterizing multiscale complexity of physiological systems [12]. Accordingly, MSE$_\mu$ may describe the main coarse graining process, whereas MSE$_{\sigma^2}$ may complement the complexity estimation by using second moments, i.e., the variance, as follows:

$$ {}^{\sigma^2}\chi_{k,i}^{(\beta)} = \frac{1}{\beta} \sum_{b=(i-1)\beta+1}^{i\beta} (y_{k,b} - {}^{\mu}\chi_{k,i}^{(\beta)})^2 \tag{2} $$

where $1 \leq i \leq \left\lfloor \frac{L}{\beta} \right\rfloor = N$ and $1 \leq k \leq c$. The proposed ReGeM-MFE$_n$ starts from one of the two aforementioned coarse-graining processes (based on $n \equiv \mu$ and $n \equiv \sigma^2$), applied to the normalized channels of a c-variate physiological process.

If the embedding dimension and the time delay of the c-variate multivariate process are $[m_1, m_2, ..., m_c]$ and $[\tau_1, \tau_2, ..., \tau_c]$, respectively, the ReGeM-MFE multivariate embedded vectors are defined as follows:

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$$Z_{\mathbf{M}}(i) = [\Xi(\chi_{1,i}, \chi_{2,i}, ..., \chi_{c,i}), \Xi(\chi_{1,i+\tau}, \chi_{2,i+\mathbf{T}}, ..., \chi_{c,i+\mathbf{T}}), ..., \Xi(\chi_{1,i+(\mathbf{M}-1)\mathbf{T}}, \chi_{2,i+(\mathbf{M}-1)\mathbf{T}}, ..., \chi_{c,i+(\mathbf{M}-1)\mathbf{T}})] \quad (3)$$

where Ξ represents the median value of the samples, $\mathbf{M} = max(m_1, m_2, ..., m_c)$ and $\mathbf{T} = max(\tau_1, \tau_2, ..., \tau_c)$.

As in [20], [26], ReGeM-MFE employs a fuzzy function $\Gamma(d, r)$ which allows to account for the pairs of vectors at a distance larger than the standard fixed r. The ReGeM-MFE fuzzy function for a given fuzzy power f_c (usually set equal to 2) can be expressed as [20]:

$$\Gamma(d, r) = e^{\frac{-d^{f_c}}{r}} \quad (4)$$

considering a distance d between vectors computed as the maximum absolute difference of their corresponding scalar components. Furthermore, in order to prevent the influence of the reduced variance of the coarse-grained series at higher scales, the threshold r changes according to the scale factor β: $r = 0.20 \times std(^{n}\Psi^{(\beta)})$, where $^{n}\Psi^{(\beta)}$ is the vector given by the median values between the scaled channels. The selection of the coefficient 0.20 used in the calculation of r is common in the literature [31].

Then we define a global quantity:

$$\Lambda^{\mathbf{M}}(r) = \frac{1}{(N-\nu)} \sum_{i=1}^{N-\nu} \frac{\sum_{j=1, i\neq j}^{N-\nu} e^{(\frac{-(d[Z_{\mathbf{M}}(i), Z_{\mathbf{M}}(j)])^{f_c}}{r})}}{N-\nu-1} \quad (5)$$

where $\nu = \mathbf{T} \times \mathbf{M}$.

Extending the dimensionality from $\mathbf{M}$ to $\mathbf{M}+\mathbf{1}$, ReGeM-MFE is finally computed as follows:

$$\text{ReGeM} - \text{MFE}(\mathbf{Y}, \beta, \mathbf{T}, \mathbf{M}, \mathrm{r}) = -ln(\frac{\Lambda^{(\mathbf{M}+1)}(r)}{\Lambda^{\mathbf{M}}(r)}) \quad (6)$$

In this study we set $\mathbf{M} = 2$ and $\mathbf{T} = 1$, taking into consideration that these are the parameter values usually employed for the univariate entropy estimation for the HRV and DBPV series [27].

C. Statistical analysis

Statistical analyses were performed for μ-coarse graining from 1 to 5, and σ^2-coarse graining from 2 to 5 considering ReGeM-MFE estimates during the last two minutes of resting state, and the first two minutes of stand-up after the transition phase. Likewise, estimates of RCmvMFE were evaluated for comparison reasons.

From the trends of ReGeM-MFE and RCmvMFE, an overall complexity index (CI) [11], [13], [28] quantifying the area under the curve of the entropy level as a function of the scale factor β, was also calculated.

Wilcoxon non-parametric test was used to compare the two conditions (resting vs. stand-up) with null hypothesis of equal median between samples. Of note, the use of such non-parametric tests was justified by the non-gaussian distribution of samples as demonstrated by a Shapiro-Wilk procedure.

III. Experimental Results

Figure 1 shows estimates of ReGeM-MFE$_\mu$ and RCmvMFE$_\mu$ computed over the first five scale factors during resting state and stand-up conditions. At each scale factor, median ReGeM-MFE$_\mu$ was higher during the supine resting condition, while showing a significant decrease during stand-up. Estimates of RCmvMFE$_\mu$, however, overlap at $\beta = 4, 5$ with trends of higher complexity associated with stand-up conditions.

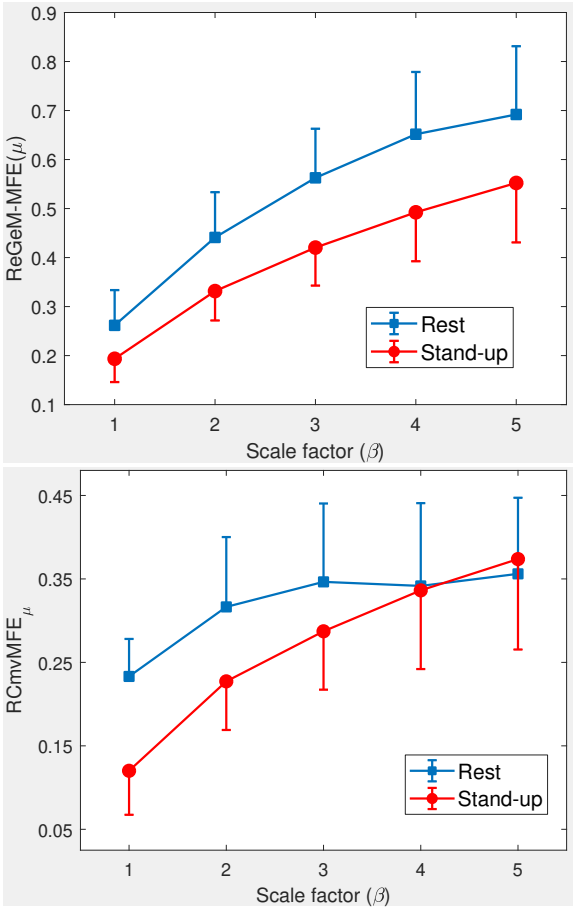

Figure 1. Median and median absolute deviation (MAD) of the ReGeM-MFE$_\mu$ (top) and RCmvMFE$_\mu$(bottom) values computed during stand-up and previous resting state sessions.

Table II
P-VALUES OF WILCOXON STATISTICAL TEST APPLIED TO REGEM-MFE$_\mu$ AND RCMVMFE$_\mu$ VALUES CALCULATED IN THE STAND-UP PHASES AND IN THE CORRESPONDING PREVIOUS RESTING STATE SESSIONS.

	Rest vs. Stand-up	
	ReGeM-MFE$_\mu$	*RCmvMFE$_\mu$*
β=1	**0.0004**	**0.0002**
β=2	**0.0007**	**0.0013**
β=3	**0.0028**	**0.0137**
β=4	**0.0072**	0.0930
β=5	**0.0276**	0.4553
CI	**0.0036**	**0.0090**

Bold indicates significant p-values ($p < 0.05$)

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Table II shows p-values from Wilcoxon statistical tests computed while comparing rest vs. stand-up conditions at each scale for the ReGeM-MFE$_\mu$ and RCmvMFE$_\mu$ metrics. CI metrics are shown as well. Estimates of ReGeM-MFE$_\mu$ are associated with statistically significant differences at each scale factor, as well as for CI, whereas estimates of RCmvMFE$_\mu$ are associated with not significant results ($p > 0.05$) at scales $\beta = 4, 5$. Furthermore, 5 out of the 6 ReGeM-MFE$_\mu$ estimates are associated with a more significant p-value than the corresponding RCmvMFE$_\mu$.

Figure 2 shows estimates of ReGeM-MFE$_{\sigma^2}$ and RCmvMFE$_{\sigma^2}$. In this case, supine resting state conditions were characterized by higher complexity than stand-up using both algorithms.

Table III shows the p-values from Wilcoxon statistical tests computed for ReGeM-MFE$_{\sigma^2}$ and RCmvMFE$_{\sigma^2}$ samples. Both approaches statistically discriminated the two conditions at all scales, as well as with CI. Nevertheless, 4 out of 5 p-values associated with ReGeM-MFE$_{\sigma^2}$ estimates are one order of magnitude lower than the corresponding RCmvRFE$_{\sigma^2}$, whereas at $\beta = 2$ the difference goes from $p = 0.0001$ for ReGeM-MFE$_{\sigma^2}$ to $p = 0.03$ for RCmvRFE$_{\sigma^2}$.

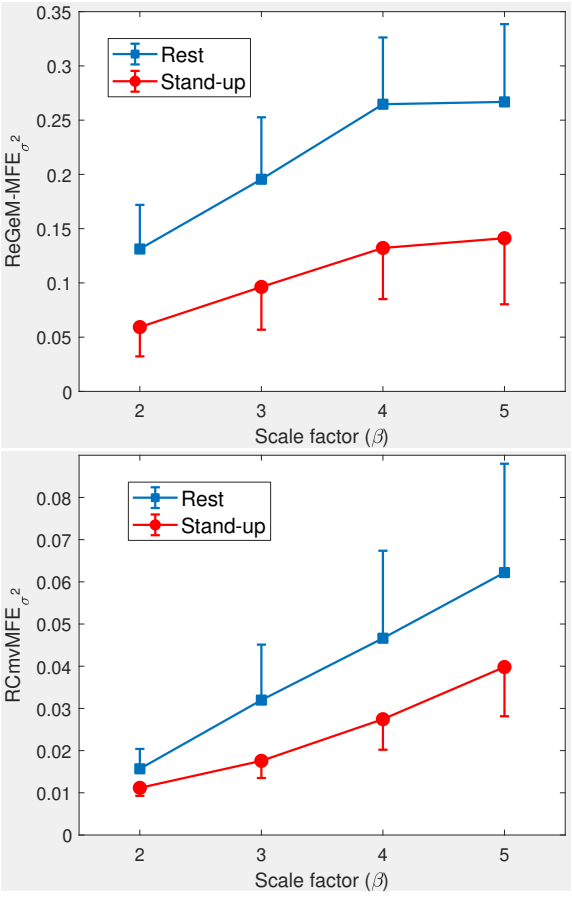

Figure 2. Median and median absolute deviation (MAD) of the ReGeM-MFE$_{\sigma^2}$ (top) and RCmvMFE$_{\sigma^2}$(bottom) values computed during stand-up and previous resting state sessions.

Table III
P-VALES OF WILCOXON STATISTICAL TEST APPLIED TO REGEM-MFE$_{\sigma^2}$ AND RCMVMFE$_{\sigma^2}$ VALUES CALCULATED IN THE STAND-UP PHASES AND IN THE CORRESPONDING PREVIOUS RESTING STATE SESSIONS.

	Rest vs. Stand-up	
	ReGeM-MFE$_{\sigma^2}$	*RCmvMFE$_{\sigma^2}$*
β=2	**0.0001**	**0.0304**
β=3	**0.0002**	**0.0028**
β=4	**0.0001**	**0.0028**
β=5	**0.0004**	**0.0022**
CI	**0.0036**	**0.0028**

Bold indicates significant p-values ($p < 0.05$)

IV. DISCUSSION AND CONCLUSIONS

This preliminary study introduces ReGeM-MFE as a novel signal processing methodology to describe complex physiological multivariate-multiscale dynamics using fuzzy rules and moments other than the first-order. Our method allows to characterize both short and long-range correlations in ANS dynamics within (multiscale) and between (multivariate) different autonomic signs.

We took inspiration from previously defined fuzzy entropy algorithms and, especially, Refined Composite Multivariate Generalized Multiscale Fuzzy Entropy (RCmvMFE) [20] because of the significant reliability in dealing with short-time series, low dependence on free parameters, and computational efficiency. Starting from the generalized version of MSE [12], we proposed ReGeM-MFE$_\mu$ and ReGeM-MFE$_{\sigma^2}$ considering first- and second-order moments of the coarse-grained series. Both indices embed a scale-dependent radius r in a fuzzy function that measures the match degree of the state space vectors. The proposed methodology also employs a novel estimation procedure of such embedded vectors in the multivariate phase-space reconstruction, taking into account the non-parametric central tendency of the multivariate scaled series.

We tested ReGeM-MFE indices in a landmark experimental setup eliciting sympathovagal changes after postural changes [22]–[24], considering bivariate series including HRV and DBPV during resting state and active stand-up condition.

Results clearly indicate that the proposed ReGeM-MFE$_\mu$ and ReGeM-MFE$_{\sigma^2}$ indices consistently outperform RCmvMFE estimates at all considered scales as demonstrated by Wilcoxon non-parametric statistics. Nonetheless, we cannot exclude different performance at higher scales, which in this preliminary study were limited to 5 because of the protocol length (2 minutes).

Results confirms that the the cardiovascular system, considered as a multivariate system, is associated with a significantly reduced complexity level during postural changes than in resting state [21], [29]. These effects of orthostatic stress on cardiovascular dynamics are known to be the result of a vagal withdrawal, with reduced complexity levels associated to different degrees of postural changes [21]. Note also that the relationship between sympathovagal changes and multiscale entropy analysis of HRV has been recently studied in rats, demonstrating that higher sympathetic drive tends to reduce HRV complexity [29]. In fact, experimental results in ani-

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mal models associated sympathetic influences to the scaling properties of heartbeat dynamics, and vagal influences to the complexity levels [30].

In conclusion, our findings suggest that the proposed ReGeM-RFE approach can be considered a promising tool for the multiscale complexity analysis of ANS considered as a multivariate system. Future works will progress in validating this method with further experimental protocols and multivariate synthetic data, as well as in extending the applications to other multivariate systems than the cardiovascular (e.g., brain-brain and brain-heart interactions).

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