Multiscale Fuzzy Entropy Analysis of Balance: Evidences of Scale-Dependent Dynamics on Diabetic Patients With and Without Neuropathy

Alessandro Mengarelli, *Member, IEEE*, Andrea Tigrini, *Member, IEEE*, Federica Verdini, *Member, IEEE*, Rosa Anna Rabini, and Sandro Fioretti, *Member, IEEE*

Abstract— Postural control is usually assessed by examining the fluctuations of the center of pressure (COP). Balance maintenance is based on sensory feedback and neural interactions, deployed over multiple temporal scales and producing less complex outputs with aging and disease. This paper aims to investigate postural dynamics and complexity on diabetic patients, since diabetic neuropathy (DN) affects the somatosensory system and impairs postural steadiness. A multiscale fuzzy entropy (MSFEn) analysis, over a wide range of temporal scales, was performed on COP timeseries during unperturbed stance in a group of diabetic individuals without neuropathy and two groups of DN patients, with and without symptoms. A parameterization of the MSFEn curve is also proposed. A significant loss of complexity was recognized for the medial-lateral direction in DN groups with respect to non-neuropathic population. For the anterior-posterior direction, symptomatic DN group showed a lowered sway complexity for longer time scales with respect to non neuropathic and asymptomatic patients. The MSFEn approach and the related parameters highlighted that the loss of complexity might be attributed to different factors depending on sway direction, i.e. related to the presence of neuropathy along the medial-lateral axis and to a symptomatic state on the anterior-posterior direction. Results of this study support the use of the MSFEn for gaining insights into balance control mechanisms for diabetic patients, in particular when comparing non neuropathic with neuropathic asymptomatic patients, whose identification by posturographic analysis would be of great value.

Index Terms— Multiscale entropy, fuzzy entropy, diabetes, center of pressure, neuropathy.

I. INTRODUCTION

HUMAN upright stance maintenance is only deceptively a straightforward task, being instead the eventual outcome of a process involving multiple sensory feedback integration and direct neural regulation, together with a partial reliance on the passive mechanical properties of muscles and ligaments [1]. Degradation of postural stability is one of the first signs of impairment due to aging and disease [2], [3], [4], with a jeopardized capability of adapting the balance response to environmental and internal demands, leading to a higher risk of falls and related concerns [2].

The instrumented static posturography still remains the favorite way to investigate quiet standing [1], [2], [5], being a relatively simple experimental setup, suitable for clinical settings [2]. Further, it does not represent a physical challenging task, being thus suitable for elderly and pathological individuals [6], [7], [8]. Moreover, the sources of disturbance are mainly internal and can be referred as a whole to the upright stance mechanical characteristics [1], [3]. Thus, unperturbed posture analysis can provide insights about the ultimate goal of the balance control system, i.e. to stabilize an intrinsically unstable system [1].

In posturographic investigations, two fundamental quantities are taken into account, namely the body center of mass (COM) displacement and the center of pressure (COP) fluctuations. Despite it is well acknowledged that they are strictly related [1], [3], [9], actually COM and COP mirror quite different balance features. The former represents an actual movement that can be estimated but not directly measured [1], whereas the latter reflects the torque exerted at the lower limb joints, which is the result of descending motor commands acting through skeletal muscles [3]. Hence, the COP encompasses information relative to the balance regulation, partially dependent on mechanical properties but mainly governed by the nervous system [1], [5]. Therefore, investigating the COP trajectory has a key role in gaining insights about the neural schemes of postural control [5], [10], [11], [12] and for a better comprehension of the development and adverse outcomes of diseases affecting balance [2], [4].

During quiet standing, the time course of the COP exhibits a strongly erratic and non stationary behavior [13], [14] but

traditional stabilometry methods provide parameters related to amplitude, temporal, and frequency content of the COP, thickening its entire trajectory into a single scalar-valued index [4], [5]. These quantities have a narrow perspective, since they reflect only specific characteristics of balance maintenance [5] and cannot account for the inner dynamics of COP timeseries [13], [14], [15]. A number of studies has been thereby devoted to the analysis of temporal and structural patterns of sway, exploring its fractal and correlation properties by different descriptors and stochastic models [12], [16]. Other approaches adopted a deterministic paradigm, extracting nonlinear indexes related to variability, stability, and repeatability of COP patterns [14], [15], [17], whereas other studies dealt with the chaotic behavior of such data [13]. However, biological timeseries can hardly be viewed as purely deterministic or stochastic, being instead the result of a combination of the two components [12], [18].

A further way for investigating COP dynamics, without assuming any underlying model, is the quantification of repeatability and regularity of sway through entropy measures [19], [20], [21], [22], which reflect the rate of occurrence of different patterns within the data series [18], [23]. However, entropy measures give maximized outputs for uncorrelated random data, e.g. white noise, and assign the lowest value to totally predictable signals, e.g. periodic waves, whilst neither of them encompasses structurally complex content, i.e. meaningful patterns enclosing information about the underlying dynamics [18], [24]. Furthermore, entropy measures operate on each data point given the earlier one, i.e. on a single scale, and thus the information related to scales different from the shortest one cannot be fully captured [18], [23]. However, the functions of a physiological system are deployed through the interactions between different control dynamics, across multiple spatial and temporal scales [18], [25].

In order to deal with these issues, the multiscale entropy (MSEn) was proposed [18], [26]. Basically, the MSEn performs an entropy analysis over multiple time scales, providing a measure of the complexity of a timeseries rather than only straightforward quantification of its regularity [18], [27]. The MSEn has been widely employed for treating biological series and it was applied to the COP displacement in order to gain insights about the adverse effects on postural control of diseases affecting the neural system [6], [8] and of aging and frailty as well [25], [28], [29]. Although many evidences indicate that the balance control process operates with different temporal dynamics [5], [12], [13], [14], [24], few studies investigated COP fluctuations over relatively large time scales [6], [8]. Further, when wider scales were considered, this was joined to prolonged and unconstrained postural tasks, not easily feasible for elderly or pathological patients [7].

Among the diseases that affect stance maintenance, type-2 diabetes is one of the most widespread, in particular within the older adults population [30], [31]. Neuropathy is a common complication recognizable in almost 50% of diabetic individuals [4], impairing peripheral sensory perception [32], [33]. Diabetic neuropathy is an acknowledged factor which negatively impacts on balance control, leading to a degraded

stability during static and dynamic stance [10], [11], [30] and a higher risk of fall [31], [34], which might be shared also with diabetic subjects without neuropathy [35], [36]. This motivated a number of studies devoted to the evaluation of postural features of diabetic individuals, mainly through traditional measures [4], [35], [37] whereas few efforts were devoted to explore nonlinear and stochastic features of COP time evolution [22], [34] and no previous works dealt with the diabetic postural sway in terms of its complexity over multiple time scales. The latter may provide clues about the breakdown of physiological functions and systems interactions governing balance stability [24]. Hence, such approach appears of interest in this context, since diabetes impairs mostly the somatosensory system, with a possible involvement also of the vestibular one [10], [35] and a decline in the integration of the sensory feedback information is expected [10], [11].

This study aimed to investigate the complexity of balance control in three groups of diabetic patients, i.e. affected by non neuropathic diabetes, asymptomatic, and symptomatic neuropathic diabetes, analyzing COP data collected during static posture trials through a MSEn approach, in order to explore complex dynamics deploying over large temporal scales. As a measure of regularity for the multiscale analysis, the Fuzzy entropy (FEn) was used. This represents an entropy metric yet employed for biological signals [22], [38], [39] and whose embedding in a MSEn framework was applied to EEG and gait timeseries [40], [41] but not to human sway data.

II. METHODS

Data belonging to forty-three patients affected by type-2 diabetes mellitus were retrospectively analyzed [4]. Eighteen subjects were affected by symptomatic neuropathy (NSD group), eight suffered asymptomatic neuropathy (NAD group) and seventeen were non neuropathic (NND group). Average values for age and body mass index were 71 ± 5 years and 27.4 ± 3.6 $\frac{kg}{m^2}$ for the NND group; 69 ± 8 years and 30.8 ± 4.2 $\frac{kg}{m^2}$ for the NAD group; 67 ± 10 years and 28.4 ± 4.6 $\frac{kg}{m^2}$ for the NSD group. Each patient performed two posture trials standing barefeet on a dynamometric force plate (Kistler 9281) and each trial lasted 120 s. More details of the experimental setup are reported in [4].

A. Multiscale Entropy

The MSEn was introduced as a method to calculate entropy over multiple time scales [18], [26]. The MSEn is based on entropy computation, integrating a coarse-graining procedure of the original timeseries, which allows to observe dynamics that may exist over different temporal scales. Given a N-length timeseries $\mathbf{x}(n)$ and an integer scale factor τ, consecutive coarse-grained timeseries are computed by dividing the original timeseries into non overlapping windows of length τ. Each element of a coarse-grained timeseries is obtained averaging the samples of the original series $\mathbf{x}_i$ within each considered window:

$$z_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x(i) \quad \left(1 \leq j \leq \frac{N}{\tau}\right) \quad (1)$$

where $z_j^{(\tau)}$ is the jth element of the coarse grained timeseries and $x(i)$ is the ith element of $\mathbf{x}_i$. For $\tau = 1$, the corresponding coarse-grained timeseries $\mathbf{z}^{(1)}$ is equal to the original time-series. The length of each $\mathbf{z}^{(\tau)}$ is $\frac{N}{\tau}$. Then, the selected entropy measure is computed for each coarse-grained time series and considered as a function of the scale factor τ.

In this study the fuzzy entropy was used as complexity index for the MSEn analysis. Broadly speaking, the FEn represents a statistic for quantifying the rate of regularity of a N-length data series, by measuring the probability that m-length subseries, with $m < N$, which are similar within a certain threshold value, remain similar also for $m + 1$. Note that m is the distance of points to be compared, defining the length of each embedding vector and the temporal resolution of the analysis [27], [42]. The FEn was proposed by [39] and the pivotal difference with respect to the other entropy measures, such as the sample entropy (SEn), lies in the function used for assessing similarity. Indeed, for the SEn the Heaviside step function is used [39] whereas the FEn employs an exponential function, that allows to obtain the maximum of the self-similarity, avoiding abrupt changes in similarity values [39]. Given a N-length timeseries $\mathbf{x}(n)$, $(N-m)$ embedding vectors are constructed as:

$$\mathbf{y}_i^m = \left[x_i, x_{i+k}, \ldots, x_{i+(m-1)k} \right] \quad (2)$$

where x_i is the ith sample of the original timeseries and k is an integer time-lag, representing a scaling factor for embedding vector computation. Each embedding vector thus contains m samples of the original timeseries, taken at a distance of k samples. In this study, k was chosen equal to 1, in order to avoid loss of information about COP temporal dynamics [23], [27]. For each $\mathbf{y}_i^m$ the correlation sum is computed as follows:

$$C_i^m(r, n) = \frac{1}{N-m-1} \sum_{j=1, j \neq j}^{N-m} \exp \left(-\frac{(\mathscr{D}_{i,j}^m)^n}{r} \right) \quad (3)$$

$\mathscr{D}(\cdot)$ is a metric for measuring the distance between $\mathbf{y}_i^m$ and all the remaining $N-m-1$ embedding vectors. In this study, the Chebyshev distance has been used [39]. The FEn computation depends on three parameters: the first one is the embedding dimension m, whereas the other two are the width (r) and the gradient (n) of the exponential function, that define a similarity boundary within which neighboring points must fall for contributing to $C_i^m(r, n)$. Then, the $N-m$ correlation sums defined for each $\mathbf{y}_i^m$ are summed up, obtaining $\Gamma_m(r, n)$:

$$\Gamma_m(r, n) = \frac{1}{N-m} \sum_{i=1}^{N-m} C_i^m(r, n) \quad (4)$$

The same procedure is then repeated for $m + 1$ and the FEn is eventually computed in the following way:

$$\text{FEn}(m, r, n) = -\ln \left(\frac{\Gamma_{m+1}(r, n)}{\Gamma_m(r, n)} \right) \quad (5)$$

When dealing with entropy-based analysis, setting the embedding dimension m equal to 2 represents the most common choice for physiological signals [26], [39], [40], [42], also if COP timeseries are investigated. This is related to the

need for having at least 10^m data samples in order to obtain a reliable entropy computation [19]. Thus, $m = 2$ allows a more detailed description of the process dynamics with respect to $m = 1$, limiting at the same time the large data lengths required for $m \geq 3$ [39]. To be noted, this choice results the most common one also when COP timeseries are investigated [6], [7], [27] and appears quite independent from the sampling rate, since also for a wide range of recording frequencies an embedding of 2 was still reported [25], [27], [29], [43], [44]. This denotes that, within a MSEn approach, the information on different time scales is retrieved by construction from the coarse graining process and the m value showed to be instead a function of data logistics, i.e. number of data samples [27]. Hence, this aspect has to be carefully considered, since the last coarse-grained timeseries, i.e. that corresponding to the higher scale factor, must contain itself enough samples for ensuring a proper entropy computation. In passing, different m values for COP analysis showed to not affect the outcomes when comparing multiple groups, leading only to an expected variation of the entropy numerical value [21]. However, establishing the best embedding for COP time course analysis was far beyond the scope of this study and further work is requested for addressing this issue, in particular when physiological timeseries are considered, due to their heterogeneous characteristics which prevent rough generalizations [22], [27], [39].

For a MSEn analysis, the r value is a fraction (unitless) of the timeseries standard deviations and it is commonly set between 0.1 and 0.2 [7], [27], but higher values were considered for human sway data [20]. However, since r can be viewed also as a threshold to filter out timeseries glitches [42], it should be small enough to prevent information loss but too low r values could lead to an undesired influence of noise [23], [39]. In what follows, the unitless value of r itself is reported rather than the product $r \times SD$, as common practice in related works [18], [21], [27], [43]. The same considerations hold for the gradient (n) of the exponential function in FEn computation [39]. In addition, FEn was originally developed as a single-scale complexity measure [39] but its validity in recognizing the correct amount of complexity on multiple time scales remains a still discussed issue [40], [41].

The latter aspect led to a preliminary evaluation of the multiscale fuzzy entropy (MSFEn) for distinguishing between different signals with known levels of complexity, over large time scales. Hence, MSFEn has been tested on a set of synthetic signals, with known stochastic and deterministic behaviors (see Appendix A). MSFEn resulted able to recognize processes characterized by different dynamics and in particular showed to be reliable in distinguish different levels of complexity also for large scale factor, being thus suitable for the following analyses.

B. Parameters Selection

The parameters selection for MSFEn computation was based on the criterion proposed in [39], where the variability of the entropy measure was evaluated for different r and n. In order to obtain a parameters selection not biased by the properties of human sway data to be further analyzed,
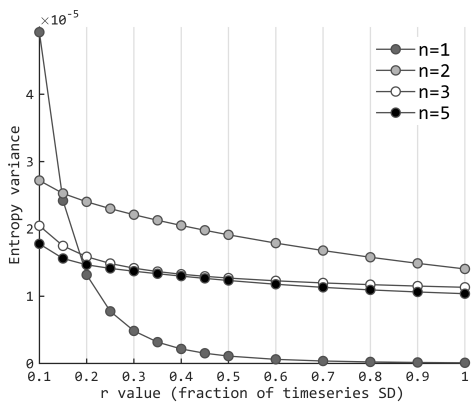
Fig. 1.   Average variance of MSFEn computed on 30 random walk signals according with the r and n parameters of the exponential function. The embedding dimension was $m = 2$.

Fig. 2.   Power spectral density represented on a log-log scale for COP component in the anterior-posterior direction for a representative subject.

synthetic signals have been considered. The COP trajectory can be modeled as a random walk process [12] and 30 different random walk processes of length $N = 10^4$ were generated. The average variance of MSFEn was evaluated for $r \in [0.1, 0.2, \ldots, 1]$ and $n \in [1, 2, 3, 5]$, with τ from 1 to 100. For $n \geq 2$, the variability of entropy value was poorly affected by the r values (Fig. 1), which instead was strongly reduced if $n = 1$. For $r \geq 0.5$ and $n = 1$ the entropy variability showed an almost constant trend, being the lowest among the other n values. Therefore, for MSFEn computation, $r = 0.5$ and $n = 1$ were chosen. Incidentally, the selection of a r value greater than those commonly used for MSEn analyses (between 0.1 and 0.2) agrees with what was reported in [20], where $r = 0.3$ was employed for SEn analysis on human sway data.

C. Data Processing and Analysis

Kinetic data were acquired at 100 Hz, resulting in 12000 data samples and COP trajectories in both anterior-posterior (AP) and medial-lateral (ML) directions were considered. COP data were low-pass filtered at 20 Hz, for removing high-frequency artifacts [6]. Then, since the non-stationarity of COP data can affect the reliability of an entropy-based analysis [14], [20], each timeseries was checked in order to assess the presence of low-frequency trends [28]. The latter identify long-range correlated processes [20] for which the power spectrum follows a decaying power law of the type $P(f) \propto \frac{1}{f^\beta}$.

Both COP components showed a clear linear fit in the log-log PSD representation (Fig. 2), which is a reliable sign of long-term correlations [20]. It has been suggested that computing the increment of COP timeseries can contribute in reducing data correlations [20], [45], since a long-term correlated process upon increment becomes anti-correlated [45]. However, this procedure could alter the complexity characteristics of data [45]. Thus, long-term correlation was removed by detrending COP data through a high-pass filter (4th order Butterworth digital filter). The cut-off frequency was chosen according to [7] as ten times the lowest possible frequency in the data (0.008 Hz).

MSFEn was computed on both COP components, coarse graining the timeseries according to (1) with the integer scale
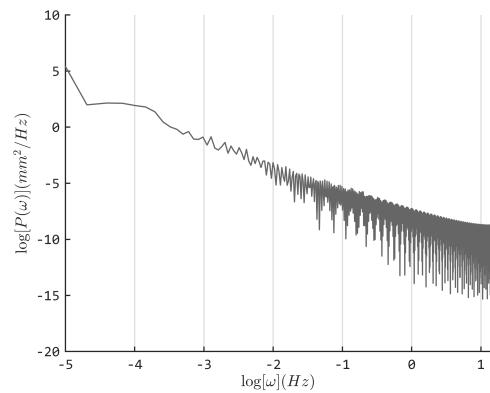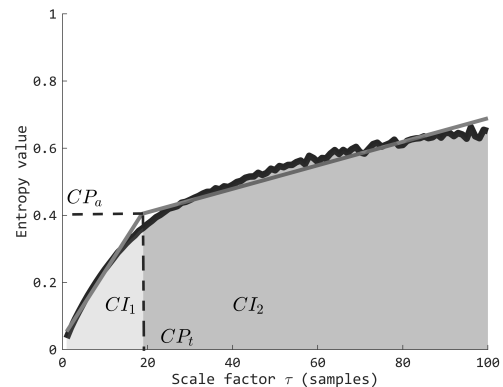

Fig. 3.   Graphical representation of the parameters computed on the MSEn curve (black line). Fitting lines are reported in gray. CP_t indicates the temporal change point, obtained as the scale factor in correspondence of the intersection point between the fitting lines, whereas the CP_a is the entropy value in correspondence of the CP_t. CI_1 and CI_2 represent the two areas of the MSEn curve in which the CP_t divides the total area CI.

factor τ from 1 to 100. Since the τ value itself is independent from experimental variables as the sampling rate and data collection time, in order to ease the comparison with different studies the scale factor will be reported also as time scale [24]. Then, the area under the curve was computed for each MSFEn trace, representing the complexity index (CI) [6], [7], [8]. The MSFEn curve presents two distinct epochs characterized by a different rate of change of entropy value and thus the initial and final parts were linearly interpolated in order to detect the time scale where the complexity shifts from a growing rate to a quasi-stationery rate (Fig. 3). Hereafter the latter time scale is indicated as the temporal change point (CP_t) and the entropy value in correspondence of the CP_t as the amplitude change point (CP_a). Further, since the CI thickens in a single index all the considered time scales, providing a poorly timely located measure of complexity, also the CIs encompassing the time scales ranging from 1 to CP_t (CI_1) and from CP_t up to the last time scale (CI_2) were computed (Fig. 3). Note that MSEn values and related parameters are without physical unit, since entropy is a function of the data series probability distribution [23] and its final value (see Eq. (5)) is the ratio of the same quantity computed for m and $m + 1$. The normality of data distributions for each population and each sensory
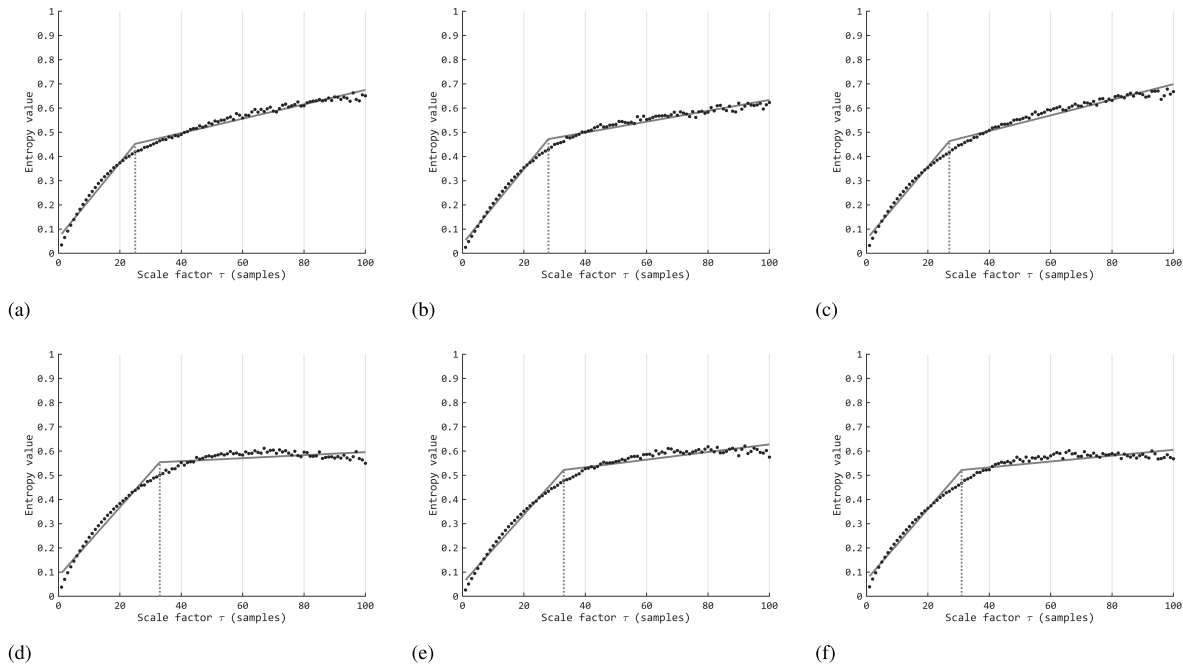
Fig. 4. MSFEn curves of the center of pressure in the AP (a, b, c) and ML (d, e, f) directions for a representative NND (a, d), NAD (b, e), and NSD (c, f) patient. Black dots represent FEn values for each scale. Linearly interpolated lines are indicated by solid gray lines whereas vertical dashed line divides small and large scale areas.

condition was established by the Kolmogorov-Smirnov test. Differences between groups were evaluated by the one-way ANOVA and Kruskal-Wallis test in case of gaussian and non gaussian distributed data, followed by Tukey's *post hoc* test. Significance was set at 5%.

III. RESULTS

The MSFEn curves for three representative patients belonging to NND, NAD, and NSD groups are reported in Fig. 4, for anterior-posterior and medial-lateral COP components. The parameters computed on the MSFEn curves for the three populations are reported in Fig. 5.

The CI, CI_1, and CP_a parameters resulted not significantly different between the three groups in the AP direction whereas in the ML direction NND population showed a significantly ($p<0.01$) higher CI with respect to NAD and NSD (Fig. 5(a), 5(b), and 5(d)). No significant differences were detected between NAD and NSD groups for the above mentioned parameters. The CI_2 parameter remained significantly higher ($p<0.01$) in the NDD population for the ML component of COP and it showed significant differences also for the AP component (Fig. 5(c)), where NSD group presented a lower CI_2 value with respect to NND and NAD groups ($p<0.01$). Between the latter two groups, no significant differences were observed for CI_2. Finally, CP_t exhibited no significant differences between groups for the AP or ML components of COP (Fig. 5(e)).

IV. DISCUSSION

A. Non Neuropathic (NND) and Neuropathic (NAD and NSD) Patients: Medial-Lateral Sway

The CI on the ML direction was significantly lower for both groups affected by neuropathy (NAD and NSD) if compared

with the NND group and this holds also whether CI_1 and CI_2 are considered (Fig. 5). This finding matches with the marked ML instability observed in diabetic subjects [46], suggesting that the neuropathy itself, irrespective of the presence of symptoms, is the main factor affecting balance along the ML axis. Incidentally, a lower complexity on ML direction was reported also for elderly and patients affected by neurological disorders [47]. The significant differences obtained on the ML direction could reflect the enhanced role of the hip joint for controlling balance and an increase of the sensitivity towards the ML sway information in diabetic patients with neuropathy [30], [31], [37]. Indeed, the latter primarily affects peripheral areas [32] and the postural information available at the ankle level becomes degraded [33], leading the subject to rely more on a balance control focused around the hip [30], [37].

In addition, the balance control on the ML direction, based on the trunk orientation in space, heavily depends on sensory information provided by the vestibular system [30], [37]. When a somatosensory loss occurs, as happens for diabetic neuropathy [32], an increase of the sensitivity and the dependence toward the vestibular information is expected [10]. The lower CI obtained for NAD and NSD populations with respect to NND (Fig. 5(a)) could thereby be partially attributed also to the presence of vestibular dysfunctions, which have been often associated with diabetes, in symptomatic and asymptomatic patients [36]. It is interesting to note that Novak et al. [48] investigated also diabetic COP traces with the stabilogram diffusion function (SDF) [12], reporting that patients showing white matter hyperintensities (WMHs) had less correlated and more stochastic fluctuations over the long-term region for the ML sway [48]. These findings appear in agreement with the lower CI of NAD and NSD groups
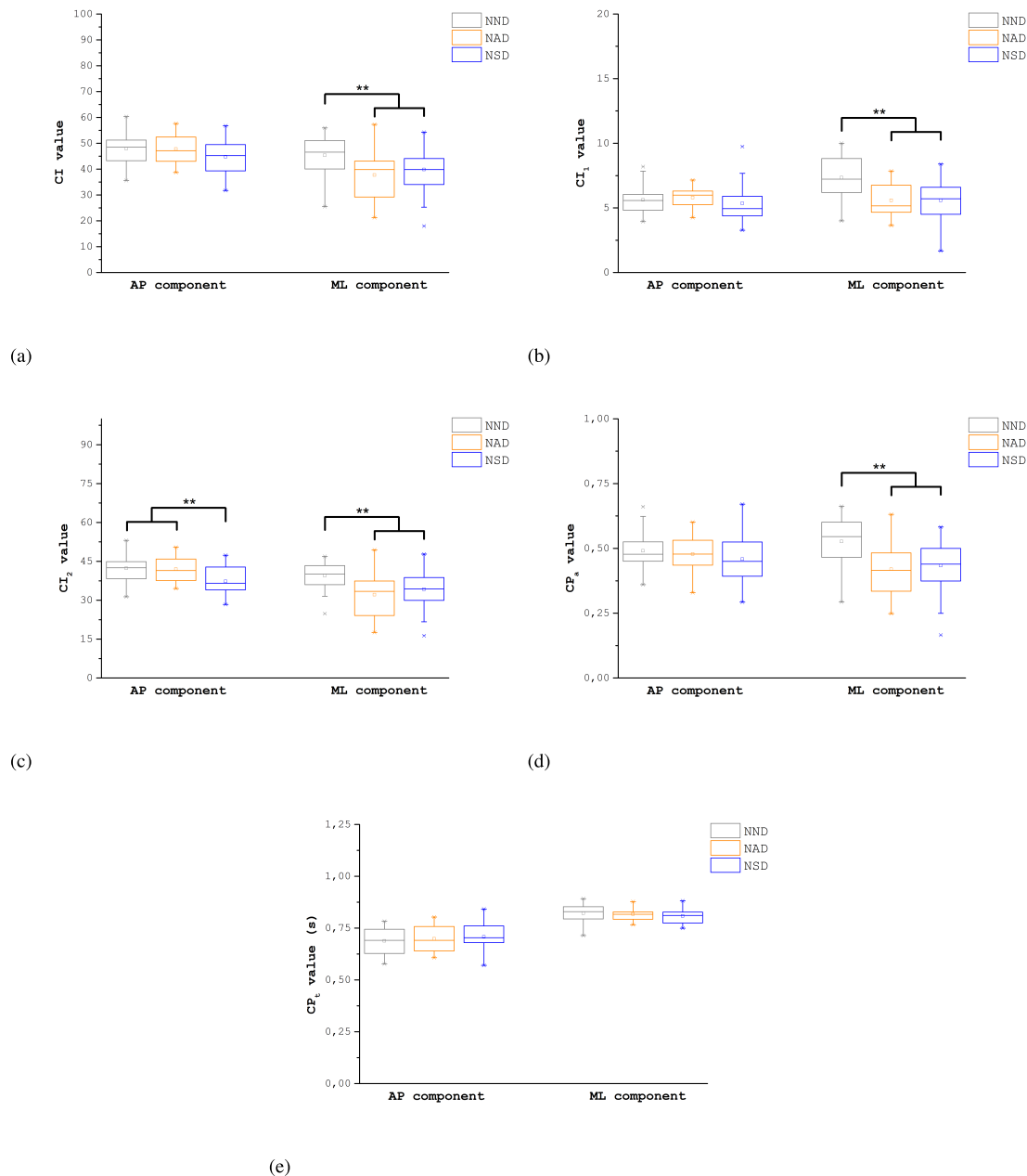
(a)

(b)

(c)

(d)

(e)

Fig. 5. Boxplots of the parameters extracted from the MSFEn curve for both COP components and the three groups. Double asterisk symbol denotes statistically significant differences with $p<0.01$.

and in particular for the CI_2 index (Fig. 5(c)), since the latter encompasses time scales larger than 1 s, where a balance control driven by sensory feedback information is assumed to take place [12].

Furthermore, a more random behavior of the ML sway in diabetic patients with respect to healthy controls was observed for the short-term region of the SDF [34], matching with the lower complexity recognized over the smaller time-scales, identified by CI_1 (Fig. 5(b)). Indeed, a lowered complexity, combined with an increase of irregularity, has been reported for many different physiological data with compromised functions [18], [26], [29]. This is coherent with the *loss of complexity* paradigm, that postulates a lowered complexity of the

output of a physiological system when a functions' breakdown occurs, due to aging or disease [6], [18]. The diminished ML complexity of NAD and NSD populations thereby reflects a reduced capability to cope with balance demands under free-running conditions, relying on few and repeatable postural patterns with a limited physiological adaptability. This aspect appears to be unrelated to the neuropathy symptoms insurgence, since no differences were detected between NAD and NSD groups (Fig. 5). In passing, this can comply also with the interpretation that a lower regularity mirrors a more efficient control, since higher entropy values and complexity were reported when the visual sensory feedback is available [6], [17], [20] and thus the subject can rely on the full information

about the environment, fully exploiting its own automatic strategies for maintaining balance.

Reading the present results under the foregoing theoretical framework underlines the additional value provided by a MSEn analysis, compared with a single scale entropy investigation. The latter method gives a measure of regularity [23], i.e. the more a signal exhibits uncorrelated structures, the higher is the assigned entropy value [18]. Instead, a MSEn analysis offers a measure of complexity, which is minimized for perfectly ordered or completely unpredictable series, since both of them do not enclose complex structures [26]. This can account for the apparent discrepancies with the results obtained when balance is investigated with a single scale entropy approach. For instance, young adults showed the lowest entropy value among elderly and elderly fallers, who in turn had the highest entropy for all the tested balance conditions [19], [21]. Actually, a higher entropy reflects an enhanced irregularity on a single time scale, which likely mirrors a poorer and less structured balance control of fallers with respect to non-fallers and young adults [21]. Instead, a loss of physiological complexity becomes evident with a MSEn approach for diseases affecting balance capabilities [6], [8], [29], possibly related also to a less automatic and efficient control, due to the need for increasing awareness-based mechanisms devoted to keep upright stance. Although the relations between COP complexity, regularity, and postural regulation dynamics is still object of investigation [15], [24], [47] and merits further studies for gaining additional insights, present outcomes confirm that a multiple scale approach should be adopted when the matter of interest is to address the long-term dynamics of a physiological system and structural complexity.

An increased sway is a known feature of neuropathic individuals, being a marker of a degraded postural control [30], [31], [34], [35], but an increased postural sway associated to a poor complexity content of COP fluctuations was reported [29]. This is not in contrast with the lowered complexity observed for the neuropathic patients (NAD+NSD) in the ML direction (Fig. 5), since the complexity is not necessarily coupled with spatial and geometrical properties of a timeseries. A larger sway for neuropathic patients can therefore be related to the need for counteracting the somatosensory deficit, by raising the minimum amount of sway required to ease perception [30]. Indeed, a certain amount of postural sway, termed *exploratory sway*, is required for easing the upright stance maintenance by exploring towards the spatial limits of stability [30]. Thus, the exploratory sway in neuropathic patients could occur in a poorer complex way, being more irregular and less arranged and preventing to fully develop a proper postural control. This is supported also by the higher risk of falling in diabetic subjects [34]. Although this hypothesis deserves to be further investigated, it is remarkable that also in this case the ML sway dynamics appear of primary importance.

Present findings confirm the role of the ML COP component for the diabetic balance control and the merit of not limiting the analysis to the AP direction alone [30], [35], [37]. In addition, a symptomatic state does not appear to affect the complexity of the ML postural sway, since a significantly lower complexity in both neuropathic groups was recognized with respect to NND patients but all the CI indexes showed similar values for NAD and NSD groups (Fig. 5). This aspect appears of particular importance, indicating that the complexity of the medial-lateral sway is able to highlight significant differences between NND and NAD groups, revealing signs of neuropathy even without a symptomatic state of the disease.

B. Asymptomatic (NND and NAD) and Symptomatic (NSD) Patients: Anterior-Posterior Sway

In the AP direction, a significant lower CI_2 was observed in symptomatic patients (NSD) with respect to those without symptoms (NND+NAD, Fig. 5(c)). A possible interpretation of this finding might refer to the impairment of group II spindle fibers, suited to detect the low frequency body sway around the ankle joint in the AP direction [49]. As reported in [11], postural instability due to neuropathy depends on what kind of spindle fibers are affected and, for diabetic neuropathy, abnormal balance sway arises only when group II fibers are degraded [11], [49]. Hence, the lower complexity of symptomatic patients (NSD group) could mirror the impairment of the above cited spindle fibers, whose functionality could be worsened when the neuropathy manifests a symptomatic state. However, this hypothesis warrants further investigation, focused on the degree of fibers degradation for symptomatic and asymptomatic neuropathy.

Furthermore, different sensory inputs are related to different frequency bands of human sway spectrum and the somatosensory feedback control is deployed within the $0.5-1$ Hz band [50]. Since for each group the CP_t resulted about 0.7 s (Fig. 5(e)), CI_2 spans roughly the $25 \leq \tau \leq 100$ interval, encompassing the frequency content from ~ 1.3 to ~ 0.3 Hz. Hence, CI_2 accounts for the complexity of the stance control which relies on the feedback information provided by the somatosensory system, degraded by a symptomatic state of the disease. In this case a less complex postural sway appears to be related to the insurgence of symptoms, rather than the presence of the neuropathy itself. Accordingly, between patients without neuropathy (NND) and those with neuropathy but without symptoms (NAD) no significant differences have been observed (Fig. 5(c)). Instead, the similar values of CI_1 between groups (Fig. 5(b)) may indicate no dysfunctions in the way the central nervous system governs stance maintenance, since this is recognizable on frequencies above 1 Hz [50] and thus for $\tau < 30$, agreeing with the fact that type-2 diabetes affects mainly peripheral pathways [30], [31].

Interpreting CI_2 as an indicator of the complexity of balance related to the integration of afferent sensory information is in agreement with [12], which reported a closed-loop neuromuscular regulation, on the long-term region of the SDF. Furthermore, the latter exhibits an anti-persistence behavior [12] and the higher value of CI_2 (Fig. 5) agrees with the lower stochasticity of this SDF region, mirroring a more tightly regulation of balance, due to afferent sensory feedback. This is highlighted also by the almost constant level of complexity for scales $>CP_t$ (Figs. 3 and 4), which indicates that new structured information is present across multiple time scales [18]. The deployment over large time scales of a stance control

driven by neural integration of sensory inputs is supported also by Yamamoto et al. [5], who indicated that high frequency components of body sway account for the biomechanics of stance, whereas slow oscillations reflect postural strategies governed by neural activity. In addition, the short-term region of the SDF [12] exhibited a more stochastic and random behavior with respect to the long-term region and these two regions are separated by a critical time of ~ 1 s [12]. This aligns with the low complexity for small time scales measured by CI$_1$ (Fig. 5), where an open-loop neuro-muscular control of balance is advocated, characterized by persistence [12].

The CP$_t$ resulted the only parameter without significant differences between groups (Fig. 5(e)) for either COP components. Such CP$_t$ value (~ 0.7 s) is very close to the time between peaks ($MT \sim 0.6$ s) of the sway density plot (SDP) proposed by Baratto et al. [3]. MT depends on stance biomechanics and resulted pathology independent [3], in agreement with present results. In particular, MT is related to the rate of production of postural commands, aimed at avoiding fall [3]. Thus, it appears reasonable that CP$_t$ defines two MSEn regions (CI$_1$ and CI$_2$), with higher complexity for time scales $\geq$CP$_t$, where active balance regulation is deployed.

Outcomes provided by the proposed MSFEn parameterization hence agree with those reported in previous studies, regarding the scaling laws governing COP time course. However, the MSEn was originally designed for assessing the complexity of a data series, overcoming the often misleading equivalence between irregularity and complexity [18] and being able to describe dynamical properties not identified by other statistics, as the detrended fluctuation analysis (DFA) [26]. Thus, albeit MSFEn offers some advantages, such as the absence of preliminary assumptions on the scaling regimes, needed by the SDF [51], and the continuous and convex fuzzy function that avoid abrupt changes in similarity assessment, sometimes observed for the DFA [52], further studies are required for assessing the relationship between present findings and those provided by other timeseries analysis tools regarding COP fractal and scaling properties, also by a numerical viewpoint.

In summary, a less complex postural sway on the anterior-posterior direction seems to be related to the symptomatic state of the disease, rather than the presence of the neuropathy itself. Significant differences were observed only for long time scales (CI$_2$), which account for the somatosensory feedback control of balance, and no differences arose if only the common CI index is considered. Furthermore, only posture trials in eyes open condition were analyzed, for which structural measures showed no predictive power [4]. This underlines the value of the proposed MSEn curve parameterization (Section II-C) and, in general, of investigating structural regularity of balance data over long time scales.

V. CONCLUSION

This study confirmed the value of a MSEn analysis for human sway data, pointing out the additional merit of considering a large scale factor, since it allows to observe balance dynamics related to different feedback control information. In particular, the loss of complexity on ML sway seemed to
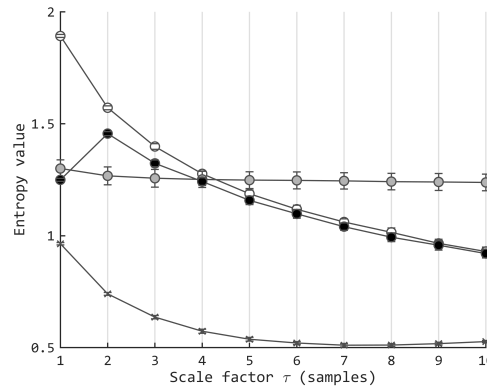

Fig. 6. Average values ($\pm$ SD) of MSFEn of white noise (circle), $\frac{1}{f}$ noise (square), logistic map (dot) and sine wave (asterisk).

reflect the presence of neuropathy itself rather than a symptomatic state, whereas on AP direction it appeared linked to the presence of symptoms, affecting somatosensory feedback. These findings could be useful for helping the detection of diabetic neuropathy, in order to enact therapeutic strategies for avoiding or limiting the symptomatic development of the disease.

Possible directions for future work include the assessment of whether the MSEn-based parameters proposed in this study can be valuable in clinical settings, by using them for a computer-aided classification of different stages of diabetes. In this view, further studies should be devoted to investigate whether the present MSEn parameters would be able to characterize functional loss also in different pathological populations.

APPENDIX A
SUITABILITY OF MSFEn OVER LARGE SCALE FACTORS

Here is reported the analysis for assessing the suitability of FEn to be used within a multiscale framework, encompassing large scale factors. Firstly, the MSFEn was applied to a set of synthetic signals with different levels of complexity, as in [42].

The selected signals were white noise (WN), $\frac{1}{f}$ noise, logistic map (LOGMAP) and sine wave (SW). WN is a gaussian distributed uncorrelated random signal, whereas $\frac{1}{f}$ noise is a multiscale correlated signal, whose power spectral density falls off at 10 dB per decade. LOGMAP is a chaotic deterministic signal, generated as:

$$x(i+1) = \alpha \cdot x(i) \cdot [1 - x(i)] \qquad (A.1)$$

with $\alpha = 4$. The SW was constructed by adding white noise to a sinusoidal waveform [41]. For each signal, a total of 30 timeseries were generated, made by 10^4 samples. Then, MSFEn was computed on each synthetic signal, and the corresponding average entropy values were plotted with a scale factor from 1 to 10 (Fig. 6).

The MSFEn correctly recognized a decreasing complexity for WN, which mirrors the absence of complex structures for large time scales, while the almost constant value for the $\frac{1}{f}$ noise indicates that new information is present across multiple scales [18]. Further, MSFEn detected a lower degree
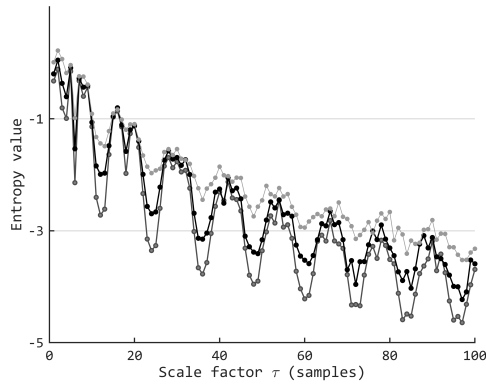
Fig. 7. MSFEn of MIX signal for different p values. Dark gray line indicates $p = 0.05$, black line refers to $p = 0.10$ and light gray line stands for $p = 0.20$. Entropy values are plotted in logarithmic scale for a better visualization.
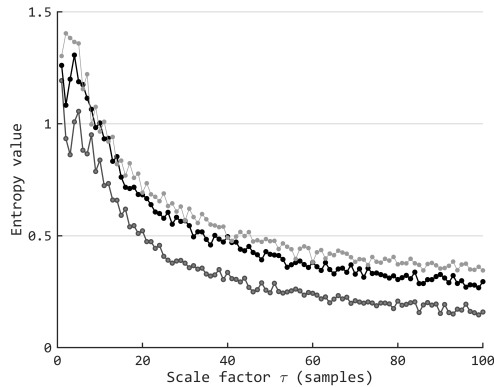

Fig. 8. MSFEn of Henon map for different β values. Dark gray line indicates $\beta = 0.84$, black line refers to $\beta = 0.88$ and light gray line stands for $\beta = 0.92$.

of irregularity for the LOGMAP with respect to WN and $\frac{1}{f}$ noise [42], assigning the lowest complexity to the SW (Fig. 6), which represents a totally predictable signal, without any complex pattern.

In order to assess whether MSFEn can recognize different levels of complexity over large time scales, it was applied to two additional synthetic signals: the MIX process and the Henon map. Realizations of both processes, characterized by different levels of regularity, can be obtained by a proper parameter selection. The MIX signals is a corrupted deterministic process:

$$MIX(p) = (1 - z) \cdot x + z \cdot y \qquad (A.2)$$

where x is a sinusoidal waveform of period 12 generated as in [42], y is a gaussian distributed variable within the set $[-\sqrt{3}, \sqrt{3}]$ and z is a random variable which is 1 with probability p and 0 with probability $1 - p$. By definition, the higher is p the less the MIX process is regular and repeatable. The Henon map represents a chaotic dynamical process [38], defined as:

$$\begin{cases} x(i + 1) = \beta \cdot y(i) + 1 - 1.4 \cdot x^2(i) \\ y(i + 1) = 0.3 \cdot \beta \cdot x(i) \end{cases} \qquad (A.3)$$

where increasing values of β lead to chaos dynamics characterized by more complex attractor.

Three signals of 10^4 samples were generated for MIX signal and Henon map, with slightly different levels of complexity: for the MIX signals p was chosen as 0.05, 0.10, and 0.20, whereas for the Henon map β was 0.84, 0.88, and 0.92. Then MSFEn was computed with a 1-100 scale factor τ.

For each considered scale factor, the MSFEn assigned an increasing entropy value for MIX signal and Henon map characterized by increasing complexity, i.e. for higher p and β values (Figs. 7 and 8). Despite the limited variations in terms of complexity of MIX signal and Henon map, MSFEn correctly recognized different complexity structures, resulting in higher entropy values for higher p and β parameters (Figs. 7 and 8). Incidentally, MSFEn was able to detect the periodic behavior of the MIX signal, being the sudden falls of complexity in correspondence of the signal period (Fig. 7). It is noteworthy that the latter feature holds also for each considered scale factor, larger than those considered by [42], thus strengthening the suitability of MSFEn over multiple time scales.

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