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The multiscale entropy: Guidelines for use and interpretation in brain signal analysis

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HIGHLIGHTS

- We provide an intuitive explanation of MSE, its application and interpretation.
- Both simulated and empirical data are used.
- We show how the properties of a signal are reflected in the MSE curves.
- MSE captures linear and nonlinear autocorrelations.
- The use of complementary methods helps in preventing misleading interpretations.

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ABSTRACT

Background: Multiscale entropy (MSE) estimates the predictability of a signal over multiple temporal scales. It has been recently applied to study brain signal variability, notably during aging. The grounds of its application and interpretation remain unclear and subject to debate.
Method: We used both simulated and experimental data to provide an intuitive explanation of MSE and to explore how it relates to the frequency content of the signal, depending on the amount of (non)linearity and stochasticity in the underlying dynamics.
Results: The scaling and peak-structure of MSE curves relate to the scaling and peaks of the power spectrum in the presence of linear autocorrelations. MSE also captures nonlinear autocorrelations and their interactions with stochastic dynamical components. The previously reported crossing of young and old adults' MSE curves for EEG data appears to be mainly due to linear stochastic processes, and relates to young adults' EEG dynamics exhibiting a slower time constant.
Comparison with existing methods: We make the relationship between MSE curve and power spectrum as well as with a linear autocorrelation measure, namely multiscale root-mean-square-successive-difference, more explicit. MSE allows gaining insight into the time-structure of brain activity fluctuations. Its combined use with other metrics could prevent any misleading interpretations with regard to underlying stochastic processes.
Conclusions: Although not straightforward, when applied to brain signals, the features of MSE curves can be linked to their power content and provide information about both linear and nonlinear autocorrelations that are present therein.

1. Introduction

Multiscale entropy (MSE) has been used lately as a complexity measure for neuroimaging signals (for examples see Escudero et al., 2006; McIntosh et al., 2008, 2014; Sleimen-Malkoun et al., 2015; Yang et al., 2013). The purpose behind its use is to evaluate

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the structure of variability of such signals across multiple temporal scales. Costa et al. (2002, 2005), who introduced first this method and used it with biological signals, relate the degree of complexity of a time series to the existence of long-range temporal correlations. In brain signals, assessing the presence of temporal relationships over different scales is of interest as it provides important information about network dynamics (Heisz et al., 2012; Lopes da Silva, 2013; Stam, 2005). In this context, MSE is thought to inform about the relative contribution of local and global (long-range) information processing in the brain (McIntosh et al., 2014; Mizuno et al., 2010; Vakorin et al., 2011). Specifically, in M/EEG studies, the structure of variability at short time scales, or high frequencies, has been linked to local neural population processing, whereas variability at longer time scales, or lower frequencies, has been linked to large-scale network processing (McIntosh et al., 2014; Mizuno et al., 2010; Vakorin et al., 2011). This view was supported by the presence of (anti-)correlations between the changes of MSE values at short and long time scales with various measures of local and distributed entropy or functional connectivity, respectively (McDonough and Nashiro, 2014; McIntosh et al., 2014; Vakorin et al., 2011). This link between high/low frequencies and spatial scales of neuronal processing could be considered as more of a neurophysical than neurophysiological nature. Indeed, frequencies in different bands and across bands are associated with communication and information processing across spatial scales within the brain network. Synchronization and desynchronization, as well as its transient and multi-frequency organization capture the network's information flow and can be measured via cross-frequency coupling (CFC) (Jirsa and Müller, 2013). Although the existence of different types of CFC (such as phase-to-power or power-to-frequency) renders communication analysis highly nontrivial, the association of long-range communication with lower frequencies (delta, theta and alpha) and short-range communication with higher frequencies (beta and gamma) can be intuitively understood on the basis of error propagation, in which the absolute value of variance has more detrimental effects upon faster oscillations. Furthermore, despite the fact that MSE appears to have promising applications to distinguish amongst populations, as young and older groups, and task conditions, as rest and task conditions, (see Sleimen-Malkoun et al., 2015 for an overview and an example), it is not evident how to interpret the features of MSE profiles beyond concluding that one signal is more or less "entropic" for shorter or longer time scales than the other. It is also neither evident how to explicitly relate MSE profiles with underlying brain dynamics and neurophysiological processes. Indeed, given the widely accepted functional significance of the dynamic formation and dissolution of local and global brain networks for cognitive processes (Schnitzler and Gross, 2005; Sporns, 2011; Varela et al., 2001), it is relevant to shed some light on the relationship between MSE's time scales and the frequency content of brain signals, as well as the presence of (non)linear correlations therein. Clarifying these issues would render the use and interpretation of MSE more intuitive and provide a more precise picture of the network extent of the underlying processes. In current literature, only very few studies explicitly explored these aspects. For instance, Bruce et al. (2009) reported a correlation between the single scale entropy metric and the power spectrum (PS) namely a negative correlation with delta power and a positive one with beta. The authors even concluded that changes in single scale entropy reflect changes in spectral content rather than changes in regularity. Later studies using MSE attempted to relate entropy at different time scales to changes in the frequency content of the underlying signal, suggesting that fast and slow frequencies relative power were associated with MSE values for fine and coarser time scales, respectively (McIntosh et al., 2014; Mizuno et al., 2010; Vakorin and McIntosh, 2012; Vakorin et al., 2011). On the other hand, the issue of MSE being a measure of nonlinear changes in the brain has been less investigated. For example, Park et al. (2007) have presented MSE as a means to evaluate the nonlinear structure of brain dynamics without, however, establishing any empirical link in that regard.

Technically, MSE is an extension of the sample entropy (SampEn) algorithm (Richman and Moorman, 2000) using a temporal coarse-graining procedure (Costa et al., 2002, 2005). It aims at evaluating the variability of biological signals across a range of temporal scales. SampEn as a measure has been developed to quantify the structure of variability of a time series in terms of its regularity (or inversely, irregularity) or predictability over time through the identification of reproducible patterns. Higher values of SampEn being indicative of lesser predictability, or what it is commonly referred to as more complexity. The added temporal coarse-graining procedure in MSE consists of downsampling successively the original signal by applying a moving average filter with nonoverlapping windows of increasing length for increasing time scales (see Section 2); in the frequency domain this acts as a low-pass filter (Govindan et al., 2007; Kaffashi et al., 2008; Valencia et al., 2009). On the one hand, such a coarse-graining procedure alleviates the signal from linear effects between consecutive samples, like those associated with observational noise at short time scales, thereby MSE can evaluate the remaining correlations of possibly nonlinear deterministic nature (Govindan et al., 2007; Kaffashi et al., 2008; Vakorin et al., 2011; Valencia et al., 2009). On the other hand, as the coarse-graining modifies the frequency content of the signal, it renders the relationship between MSE and other multiscale variability measures, such as PS, less evident. To help gain insight into this latter issue, and to guide the application and interpretation of MSE on brain signals, in the present study we systematically investigate how the scaling and peak structure of PS as well as the (non)linearity[1] of a time series are reflected in the MSE curve, in comparison with the other measures. This is achieved by analyzing numerically simulated phenomenological examples of stochastic and oscillatory processes with different levels of nonlinearity at given frequency spectra, in addition to experimental EEG data. In order to demonstrate the ability of MSE to evaluate nonlinear autocorrelations in addition to linear ones, we compare it to a multiscale measure of linear autocorrelations that we introduce, which we refer to as the multiscale root-mean-square-successive-difference (MRMSSD). This method applies the root-mean-square-successive-difference (RMSSD) algorithm over a range of scales obtained through coarse-graining. The "single scale" RMSSD has been widely used to assess temporal variability of heart-rate (Berntson et al., 2005; Owen and Steptoe, 2003), and more recently in neuroimaging data (Samanez-Larkin et al., 2010). In the light of the obtained results, we discuss the implications of our systematic investigations on functional processing in the brain.

The remainder of this paper is organized as follows. Section 2 provides an overview of our approach as well as of the SampEn and MSE algorithms. In Section 3, our results demonstrate the close relationship between MSE, PS and MRMSSD. We investigate the scaling properties of the tested signals and provide rules of thumb for relating the peak (and possibly the slope) of MSE curves with the frequency content of a signal. Finally, in Section 4, we discuss to what degree there is complementarity or redundancy of information between MSE and the PS, as well as the implications of our results for linking SampEn values at short and long time

[1] By nonlinearity in time series, we refer to the existence of nonlinear autocorrelations, i.e., to the existence of relationships in the signal with itself of a nonlinear functional form at some time scales. The process generating this kind of signal could be described by a Langevin equation (Langevin, 1908), and such nonlinearities result from nonlinear terms (i.e., of higher than first order), either in the deterministic or in the stochastic functions.