

## Multiscale Entropy Analysis of Complex Physiologic Time Series

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There has been considerable interest in quantifying the complexity of physiologic time series, such as heart rate. However, traditional algorithms indicate higher complexity for certain pathologic processes associated with random outputs than for healthy dynamics exhibiting long-range correlations. This paradox may be due to the fact that conventional algorithms fail to account for the multiple time scales inherent in healthy physiologic dynamics. We introduce a method to calculate multiscale entropy (MSE) for complex time series. We find that MSE robustly separates healthy and pathologic groups and consistently yields higher values for simulated long-range correlated noise compared to uncorrelated noise.

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Quantifying the “complexity” of physiologic signals in health and disease has been the focus of considerable attention [1–4]. Such metrics have potentially important applications with respect to evaluating both dynamical models of biologic control systems and bedside diagnostics. For example, a wide class of disease states, as well as aging, appear to degrade physiologic information content and reduce the adaptive capacity of the individual. Loss of complexity, therefore, has been proposed as a generic feature of pathologic dynamics [1,3].

Traditional entropy-based algorithms quantify the regularity (orderliness) of a time series. Entropy increases with the degree of disorder and is maximum for completely random systems. However, an increase in the entropy may not always be associated with an increase in dynamical complexity. For instance, a randomized time series has higher entropy than the original time series, although the process of generating surrogate data destroys correlations and degrades the information content of the original signal.

Diseased systems, when associated with the emergence of more regular behavior, show reduced entropy values compared to the dynamics of free-running healthy systems [3]. However, certain pathologies, including cardiac arrhythmias like atrial fibrillation, are associated with highly erratic fluctuations with statistical properties resembling uncorrelated noise [5–7]. Traditional algorithms will yield an increase in entropy values for such noisy, pathologic signals when compared to healthy dynamics showing correlated ( $1/f$ -type) properties, even though the latter represent more physiologically complex, adaptive states. This inconsistency may be related to the fact that widely used entropy measures are based on single-scale analysis and do not take into account the complex temporal fluctuations inherent in healthy physiologic control systems.

The entropy  $H(X)$  of a single discrete random variable  $X$  is a measure of its average uncertainty. Entropy is calculated by the equation:

$$H(X) = - \sum_{x_i \in \Theta} p(x_i) \log p(x_i). \quad (1)$$

where  $X$  represents a random variable with set of values  $\Theta$  and probability mass function  $p(x_i)$ .

For a time series representing the output of a stochastic process, that is, an indexed sequence of  $n$  random variables,  $\{X_i\} = \{X_1, \dots, X_n\}$ , with set of values  $\Theta_1, \dots, \Theta_n$ , respectively, the joint entropy is defined as

$$H_n = - \sum_{x_1 \in \Theta_1} \dots \sum_{x_n \in \Theta_n} p(x_1, \dots, x_n) \log p(x_1, \dots, x_n), \quad (2)$$

where  $p(x_1, \dots, x_n)$  is the joint probability for the  $n$  variables  $X_1, \dots, X_n$ .

The state of a system at a certain instant,  $X_n$ , is partially determined by its history,  $X_1, X_2, \dots, X_{n-1}$ . However, each new state carries a certain amount of new information. The mean rate of creation of information, also known as the Kolmogorov-Sinai (KS) entropy, is a useful parameter to characterize the system dynamics [8]. Considering that the phase space of a system with  $\mathcal{D}$  degrees of freedom is partitioned into hypercubes of content  $\varepsilon^{\mathcal{D}}$  and the state of the system is measured at intervals of time  $\tau$ , the KS entropy is defined as

$$H_{KS} = \lim_{\tau \rightarrow 0} \lim_{\varepsilon \rightarrow 0} \lim_{n \rightarrow \infty} (H_{n+1} - H_n). \quad (3)$$

Numerically, only entropies of finite order  $n$  can be computed. As soon as  $n$  becomes large with respect to the length of a given time series, the entropy  $H_n$  is underestimated and decays towards zero. Therefore, the KS entropy for “real-world” time series of finite length cannot usually be estimated with reasonable precision.

For the analysis of such typically short, noisy time series, Pincus [9] introduced the approximate entropy

(ApEn) family of parameters, which have been widely used in physiology and medicine [1]. Recently, a modified algorithm, sample entropy (SampEn) [4], has been proposed which has the advantage of being less dependent on the time series length. Such algorithms, however, assign a higher value of entropy to certain pathologic time series that are presumed to represent less complex dynamics than to time series derived from healthy function [3]. One possible reason for obtaining these results may be the fact that these measures are based on a single scale. Both the KS entropy and the related ApEn parameters depend on a function's one step difference (e.g.,  $H_{n+1} - H_n$ ) and reflect the uncertainty of the next new point, given the past history of the series. Therefore, such measures do not account for features related to structure on scales other than the shortest one.

Zhang [10,11] proposed a general approach to take into account the multiple time scales in physical systems. His measure, based on a weighted sum of scale dependent entropies, does, in fact, yield higher values for correlated noises compared to uncorrelated ones. However, since it is based on Shannon's definition of entropy, Zhang's method requires a large amount of almost noise-free data, in order to map a signal to a discrete symbolic sequence with sufficient statistical accuracy. Therefore, it presents obvious limitations when applied to typical physiologic signals that vary continuously and have finite length.

Here we introduce a multiscale entropy technique applicable to the analysis of the biologic time series. We study simulated noises as well as human cardiac interbeat interval time series, the latter representing the output of a major physiologic control system.

Given a one-dimensional discrete time series,  $\{x_1, \dots, x_i, \dots, x_N\}$ , we construct consecutive coarse-grained time series,  $\{y^{(\tau)}\}$ , determined by the scale factor,  $\tau$ , according to the equation:  $y_j^{(\tau)} = 1/\tau \sum_{i=(j-1)\tau+1}^{j\tau} x_i$ ,  $1 \leq j \leq N/\tau$ . For scale one, the time series  $\{y^{(1)}\}$  is simply the original time series. The length of each coarse-grained time series is equal to the length of the original time series divided by the scale factor,  $\tau$ . Here we consider time series with  $3 \times 10^4$  points and coarse-grain them up to scale 20, so that the shortest time series has 1500 points. We then calculate an entropy measure (SampEn) for each coarse-grained time series plotted as a function of the scale factor  $\tau$  [12]. We call this procedure multiscale entropy (MSE) analysis [13].

We first test the MSE method on simulated white and  $1/f$  noises [14]. We find that for scale one, a higher value of entropy is assigned to white noise time series in comparison with  $1/f$  time series. However, while the value of entropy for the coarse-grained  $1/f$  series remains almost constant for all scales, the value of entropy for the coarse-grained white noise time series monotonically decreases, such that for scales  $> 5$ , it becomes smaller than the corresponding values for  $1/f$  noise (Fig. 1). This result is consistent with the fact that, unlike white noise,  $1/f$  noise

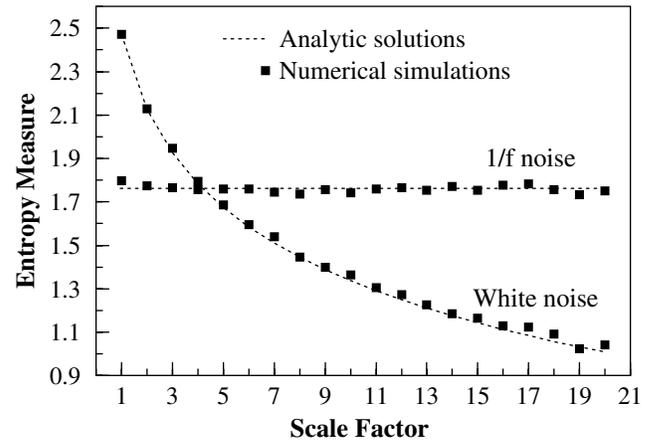


FIG. 1. MSE analysis of Gaussian distributed white noise (mean zero, variance one) and  $1/f$  noise. On the y axis, the value of entropy (SampEn) for the coarse-grained time series is plotted. The scale factor specifies the number of data points averaged to obtain each element of the coarse-grained time series. Symbols represent results of simulations for time series of  $3 \times 10^4$  points [12], and dotted lines indicate analytic results. SampEn for coarse-grained white noise time series, is analytically calculated by the expression  $-\ln \int_{-\infty}^{+\infty} \frac{1}{2} \sqrt{\frac{\tau}{2\pi}} [\operatorname{erf}(\frac{x+r}{\sqrt{2/\tau}}) - \operatorname{erf}(\frac{x-r}{\sqrt{2/\tau}})] e^{-(1/2)x^2\tau} dx$ .  $\tau$  and erf refer to the scale factor and to the error function, respectively.  $r$  is defined in Refs. [4,9,12]. For  $1/f$  noise time series, the analytic value of SampEn is a constant.

contains complex structures across multiple time scales [10,11].

Next, we apply the MSE method to the analysis of selected physiologic time series (Fig. 2). We compare the time series of consecutive heartbeat intervals derived from healthy subjects, patients with severe congestive heart failure [15], and patients with the cardiac arrhythmia, atrial fibrillation. In Fig. 3, we observe three different types of behaviors: (1) The entropy measure for time series derived from healthy subjects increases on small time scales and then stabilizes to a constant value. (2) The entropy measure for time series derived from subjects with congestive heart failure, a life-threatening condition, markedly decreases on small time scales and then gradually increases. (3) The entropy measure for time series derived from subjects with atrial fibrillation monotonically decreases, similar to white noise. Of note, for scale one, atrial fibrillation time series are assigned the highest value of entropy [17], and healthy heartbeat time series are not distinguishable from those of heart failure patients. The largest separation between heart failure patients and healthy subjects is obtained for time scale 5. At the highest scales, the entropy values for the healthy heartbeat fluctuations are significantly higher than those of both pathologic groups.

We also find that the asymptotic value of entropy may not be sufficient to separate time series that represent the output of different dynamical processes. As seen in Fig. 3, for time scale 20, the value of the entropy measure for the

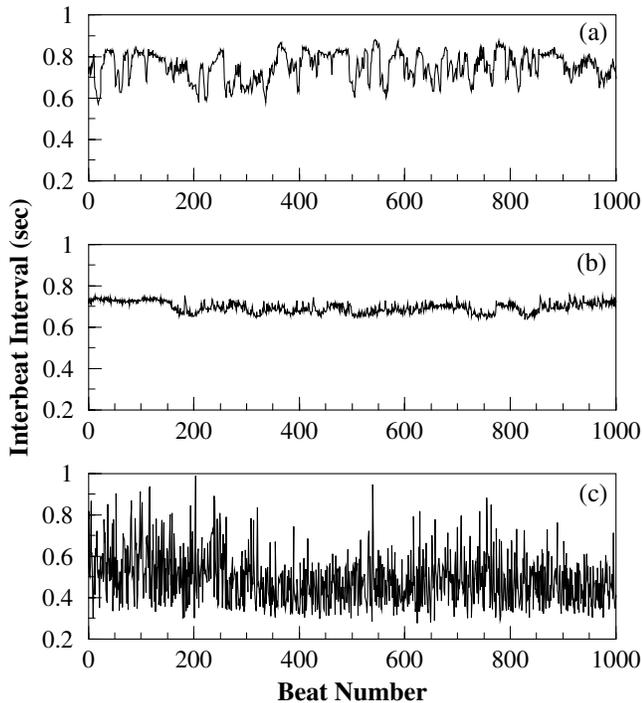


FIG. 2. Representative heartbeat intervals time series from (a) healthy individual (sinus rhythm), (b) subject with congestive heart failure (sinus rhythm), and (c) subject with the cardiac arrhythmia, atrial fibrillation.

heart failure and atrial fibrillation time series is the same. However, these time series represent the output of a very different type of cardiac dynamics (Fig. 2). Therefore, not only the specific values of the entropy measure but also their dependence on resolution need to be taken into account to better characterize a physiologic process.

We further test the MSE algorithm by comparing the heartbeat time series from 20 healthy elderly subjects, 10 males and 10 females (mean age  $\pm$ SD,  $69 \pm 3$  yr), and 20 healthy young subjects, 10 males and 10 females (mean age  $\pm$ SD,  $32 \pm 6$  yr) (Fig. 4). We find that for all time scales, a higher value of entropy is assigned to time series from young subjects, consistent with the hypothesis of loss of complexity with age [3]. Of note, the weakest separation between the two groups occurs for scale one, the only scale studied by traditional entropy metrics. The strongest separation is obtained for time scale 5.

Finally, the MSE algorithm was tested on a set of surrogate data obtained from the heart rate time series of a healthy subject by simple randomization of its data points. The MSE algorithm discriminated the two time series and revealed that the randomized surrogate data was less complex than the original physiologic data. Furthermore, it assigned to the surrogate data set a behavior qualitatively similar to the one already described for white noise time series.

Our findings are of interest from the following perspectives. The long-standing problem of deriving useful mea-

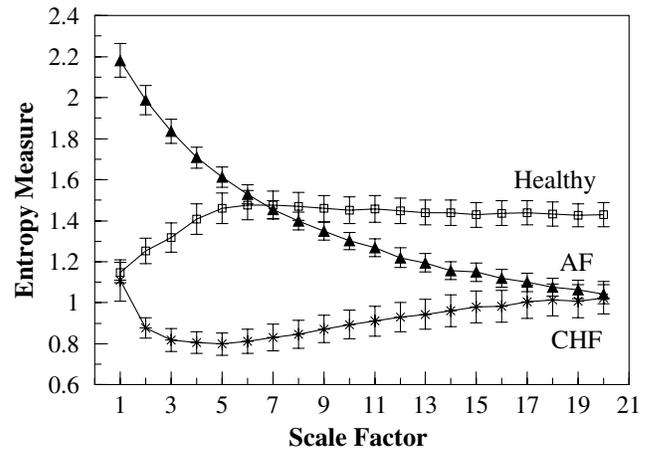


FIG. 3. MSE analysis of interbeat interval time series derived from healthy subjects, subjects with congestive heart failure (CHF), and subjects with atrial fibrillation (AF), as shown in Fig. 2. Values are given as means  $\pm$  standard error [16]. Time series were filtered to remove outlier points due to artifacts and ventricular ectopic beats. The values of entropy depend on the scale factor. For scale one, AF time series are assigned the highest value of entropy, and the values corresponding to healthy and CHF groups completely overlap. For larger scales, e.g., 20, the entropy value for the coarse-grained time series derived from healthy subjects is significantly higher than those for AF and CHF. At this scale, AF and CHF groups become indistinguishable.

asures of time series complexity is germane to analyzing both the output of physical and biologic systems. In this respect, the MSE method appears to yield a more meaningful approach than conventional entropy measurements. MSE is based on the simple observation that complex physical and biologic systems generally exhibit dynamics that are far from the extrema of perfect regularity and complete randomness. Instead, complex dynamics typically reveal structure on multiple spatial and temporal scales. These multiscale features, ignored by conventional entropy calculations, are explicitly addressed in the MSE algorithm.

The MSE algorithm yields consistent findings when applied to assessing the complexity of both (a) simulated correlated and uncorrelated noises and (b) the integrated output of a major physiologic control system (cardiac interbeat intervals) under healthy and pathologic conditions. In particular, we find, in accord with Zhang [10], that correlated ( $1/f$ ) noise has a higher complexity level than uncorrelated (white) noise when multiple time scales are taken into account (Fig. 1). We also find that pathologic dynamics associated with either increased regularity/decreased variability [Fig. 2(b)] or with increased variability due to loss of correlation properties [Fig. 2(c)] are both characterized by a reduction in complexity. This finding is compatible with the unifying concept that physiologic complexity is fundamentally related to the adaptive capacity of the organism, which requires integrative,

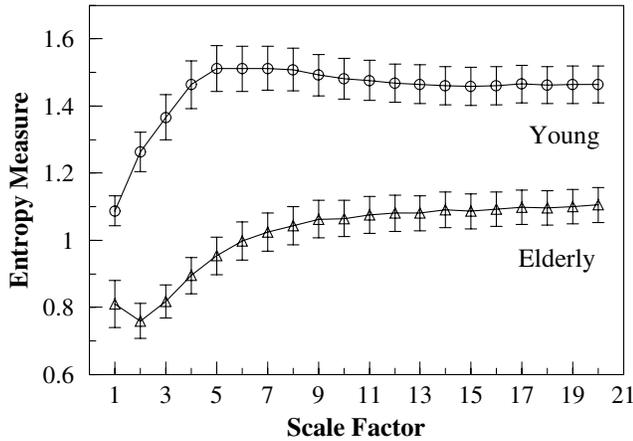


FIG. 4. MSE analysis of the cardiac interbeat time series derived from healthy young subjects and healthy elderly subjects. Values are given as means  $\pm$  standard error [16]. For all time scales, the values of entropy for coarse-grained time series obtained from elderly subjects are significantly ( $p < 0.005$ ; Student's  $t$ -test) lower than those from young subjects. The poorest separation between groups is obtained for scale one, indicating the importance of calculating entropy over different scales.

multiscale functionality. In contrast, disease states (Fig. 3), as well as aging (Fig. 4), may be defined by a sustained breakdown of long-range correlations and loss of information [18]. Finally, we note that the MSE method has potential applications to studying a wide variety of other physiologic and physical time series data.

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