On multiscale entropy analysis for physiological data

Ranjit A. Thuraisingham, Georg A. Gottwald*

School of Mathematics and Statistics, University of Sydney, NSW 2006, Australia

Abstract

We perform an analysis of cardiac data using multiscale entropy as proposed in Costa et al. [Multiscale entropy analysis of complex physiological time series, Phys. Rev. Lett. 89 (2002) 068102]. We reproduce the signatures of the multiscale entropy for the three cases of young healthy hearts, atrial fibrillation and congestive heart failure. We show that one has to be cautious how to interpret these signatures in terms of the underlying dynamics. In particular, we show that different dynamical systems can exhibit the same signatures depending on the sampling time, and that similar systems may have different signatures depending on the time scales involved. Besides the total amount of data we identify the sampling time, the correlation time and the period of possible nonlinear oscillations as important time scales which have to be involved in a detailed analysis of the signatures of multiscale entropies. We illustrate our ideas with the Lorenz equation as a simple deterministic chaotic system.

1. Introduction

Over the past years, interest has risen in applying methods and concepts from nonlinear dynamics to problems in physiology. This is evidenced by several focus issues on cardiology and nonlinear dynamics [1–5]. It has been proposed that the normal heartbeat is associated with complex nonlinear dynamics and chaos [6–8]. This has opened new avenues to use methods from nonlinear dynamics as diagnostic tools for the analysis of physiological data for certain heart trouble [9–11]. Moreover, physicists and mathematicians have been inspired by the wealth of interesting physiological problems to develop new tools and methods.

One such problem in cardiology is to extract information from a given set of heart rate data about the health status of a given patient. This is obviously of great clinical importance for diagnostics. One aim is to find early signs of cardiac arrhythmias. These are often precursors for fatal malfunctions such as ventricular fibrillation. Cardiovascular disease is the main cause of death in the industrialized world, and ventricular fibrillation is the most common route to death for patients with cardiac conditions. Early detection of these possibly fatal heart conditions allows for preventive drug management, application of radio-frequency ablation, or the use of an implantable defibrillators.

---

*Corresponding author.

E-mail address: gottwald@maths.usyd.edu.au (G.A. Gottwald).

It is widely believed that a healthy heart is characterized by chaotic heart rate time series whereas the intermittent appearance of periodicities in heart data is associated with the onset of congestive heart failure [12]. The naive picture behind this is that a chaotic heart which generically involves a multitude of spatial and temporal scales is more adaptive and can react better to external changes of its input. The occurrence of regularity in heart data as observed with certain heart trouble is often associated with the emergence of re-entrant spiral waves whose rotation frequency dominates the inter-beat intervals. This is a consequence of the heart being an excitable medium (see Ref. [13] for an overview on cardiac arrhythmias).

There have been several approaches coming from nonlinear dynamics to identify signatures in heart data (see for example, Ref. [14] for an overview). The inevitable presence of noise forbids to use traditional measures of chaoticity such as Lyapunov exponents (see Ref. [15] for an overview on nonlinear time series methods). Amongst the ones used to measure complexity in physiological data are entropy methods which are mostly based on symbolic dynamics [16–20], methods based on recurrence plots [21] and methods analyzing the multiscale powerlaws of the length distribution of low-variability periods in heartbeat dynamics [22]. In a recent paper [1], a new entropy based measure of complexity, the multiple scale entropy (MSE), was introduced. The authors applied their new complexity measure to distinguish between young healthy hearts and congestive heart failure. Moreover, they were able to distinguish atrial fibrillation from healthy hearts. The former is associated with erratic fluctuations similar to uncorrelated noise [23,24]; the latter with fluctuations stemming from an underlying chaotic deterministic dynamics. They key to their method lies in a multiscale approach. We explain their method in the next section and reproduce their results for real clinical heart data in Section 3. However, we will show in Section 4, that care has to be taken when interpreting the signatures of their complexity measure and drawing conclusions about possible deterministic dynamics. We show that the signatures depend on the ratio of the sample time τ_s of the time series, the correlation time τ_c and the period of possible nonlinear oscillations τ_p.

2. Multiscale entropy

The concept of entropy has been widely used to quantify complexity. Traditional entropy definitions such as the Shannon-entropy or the Kolmogorov–Sinai entropy characterize the gain of information and measure disorder and uncertainty. The Kolmogorov–Sinai entropy h_{KS} measures the exponential rate at which information is obtained. In principle, Pesin's identity [25] which states that the sum of all positive Lyapunov exponents forms an upper bound for h_{KS} makes this entropy attractive to characterize complexity. However, its definition requires an infinite data series with infinitely accurate precision and resolution [26]. This is never the case in experimental data. Entropy-based complexity measure designed to deal with short and noisy time series were recently introduced. Based on the so-called *approximate entropy* introduced in Ref. [27], and its modification, the *sample entropy* [28], a multiscale entropy has been introduced and successfully applied to physiological data [1]. We note that the term 'multiscale entropy' is also used in a different context in image processing [29].

The multiscale entropy is based on the application of *approximate entropy* [27] or *sample entropy* [28]. We will therefore briefly review both of these entropies. For a good review on the connection between these measures of entropy and their historic connection see Ref. [30]. Given a time series $\{X_i\} = \{x_1, x_2, \ldots, x_N\}$ of length N, one can define m-dimensional sequence vectors $y^{(m)}(i) = \{x_i, x_{i+1}, \ldots, x_{i+m-1}\}$. Two vectors $y^{(m)}(i)$ and $y^{(m)}(j)$ are called similar if their distance $d(i,j) = \max\{|x(i+k) - x(j+k)| : 0 \leqslant k \leqslant m-1\}$ is smaller than a specified tolerance level δ. For each of the $N - m + 1$ vectors $y^{(m)}(i)$ the number of similar vectors $y^{(m)}(j)$ is determined by measuring their respective distances. Let $n_i^{(m)}$ be the number of vectors similar to $y^{(m)}(i)$. The relative frequency to find a vector $y^{(m)}(j)$ which is similar to $y^{(m)}(i)$ within a tolerance level δ is given by

$$C_i^{(m)}(\delta) = \frac{n_i^{(m)}}{N - m + 1}. \tag{2.1}$$

To define an entropy-like quantity we look at the relative frequency of the logarithm of $C_i^{(m)}(\delta)$. Under the hypothesis of stationarity we obtain

$$H_N^{(m)}(\delta) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \log C_i^{(m)}(\delta). \tag{2.2}$$

The mean rate of creation of information can now be defined as

$$h_{approx}(\delta,m) = \lim_{N\to\infty} [H_N^{(m)}(\delta) - H_N^{(m+1)}(\delta)], \tag{2.3}$$

or equivalently using ergodicity

$$h_{approx}(\delta,m) = \lim_{N\to\infty} \frac{1}{m} H_N^{(m)}(\delta). \tag{2.4}$$

In the evaluation of $h_{approx}(\delta,m)$ the vectors $y^{(m)}(i)$ are allowed to selfmatch. This results in a biased statistics. Therefore, the sample entropy $h_{sample}(\delta,m)$ was introduced [28] which avoids self matching in the above described procedure.

As in the Kolmogorov–Sinai entropy, both sample and approximate entropy, provide a measure for the information increase over one step from $m \to m + 1$. To be able to resolve complexity on scales larger than this smallest scale, multiscale entropy was introduced [1]. Here the entropy is calculated not directly by comparing $y^{(m)}(i)$, but instead new coarse grained vectors $v^{(m)}(i,\tau)$ which are sequence vectors constructed from a coarse grained averaged time series $\{v_j(\tau)\}$

$$v_j(\tau) = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leqslant j \leqslant N/\tau,$$

where $\tau = 1, 2, 3, \ldots$. Note that $v_j(1) = x_j$. For nonzero τ the original time series $\{X_i\}$ is segmented in N/τ coarse grained sequences with each segment being of length τ. For each segment the mean value $v_j(\tau)$ is calculated which now constitute the coarse grained time series $\{v_j(\tau)\}$. From this time series now the m-dimensional sequence vectors $y^{(m)}(i,\tau)$ are built as before.

The coarse graining introduces smoothing and decorrelation of the vectors. Now, the multiscale entropy can be defined as the sample (or approximate) entropy for the new vectors defined by using $v_j(\tau)$ instead of x_i.

Both, *sample entropy* and *approximate entropy* involve two free parameters, the sequence length m and the tolerance level δ. Their output measures the likelihood that two sequences of length m stay close to each other at the next step within a tolerance level δ. If the output is zero, then consecutive sequences are identical. Obviously, as δ decreases the two entropies increase as it will be harder to find consecutive sequences which are close within the prescribed δ-tolerance level. The proposed measures are therefore no absolute measures.

In our analysis we used $m = 2$ and $\delta = 0.15\sigma$ where σ is the standard deviation of the original time series. For a discussion on optimal choices for m and δ, see Ref. [33].

In Ref. [31], it was noted that by introducing the scale parameter τ and the associated process of averaging, the variation of the data decreases with increasing τ. However, the tolerance level δ is assumed to be fixed for all scales τ and is not adjusted to the standard deviation of the coarse-grained data at each scale, which implies that the standard deviation of a given data set decreases with increasing scale τ. When δ is fixed for all scales, one is also measuring the standard deviation and not just entropy. However, as pointed out in Ref. [32] the τ-independent tolerance level δ which is determined as a percentage of the standard deviation of the original time series, exactly avoids that the differences in entropy are caused by differences in standard deviations. Moreover, there does not exist a universal relationship between entropy and standard deviation. The relationship between the two depends on the correlation properties. For example, differences in standard deviation cannot be used to clearly distinguish between young healthy and patients with congestive heart failure [32]. In Ref. [32] a simple example is given whereby a periodic signal with variance σ_p and a random signal with variance σ_r are considered. The entropy of the periodic signal is always smaller than that of the random signal even if $\sigma_p \gg \sigma_r$. In Section 4, we show that this statement depends on the relationship between the correlation time of the random signal, the period of the periodic signal and the sample time.

3. Analysis of cardiac data using multiscale entropy

In this section, we reproduce the analysis of Ref. [1]. We use data provided in Ref. [34] which consist of consecutive heartbeat intervals (R–R intervals) derived from young healthy patients, patients with congestive heart failure and patients with atrial fibrillation. The results are depicted in Fig. 1 and show distinctive signatures for all three different cases. The signatures were obtained by using MSE and subsequent averaging over all patients. For the averaging of the healthy heart signals and the congestive heart failure data we used 15 data sets each. For the atrial fibrillation we had only one case. The time series were filtered to remove spurious outliers.

The differences in the MSE signature are striking. However, we note that we also found cases of congestive heart failure with a signature of a young healthy heart. Moreover, although the differences between the three groups is striking for their averages, we found that MSE is not a reliable diagnostic tool for individual patients. The MSE-signatures of individual patients are very hard to associate with the signatures of their averages. However, we note that the authors of Ref. [1] stress in Ref. [36] that MSE is rather a detector of complexity than a diagnostic tool. The question of whether MSE can be used as a diagnostic tool to discriminate between healthy and pathological patients had been discussed in Refs. [35,36].

In Ref. [35], it is argued that the (averaged) signature of multiscale entropy for elderly healthy patients is similar to the (averaged) signature of patients with congestive heart failure, and hence multiscale entropy is not a good diagnostic tool for cardiac conditions. In a rebuttal [36], the authors argue that the purpose of multiscale entropy is rather to quantify complexity than to provide a diagnostic tool. Fluctuations of aging and of pathological systems show a lesser degree of complexity when compared with healthy systems. The underlying hypothesis is—as mentioned in the introduction—that a healthy physiological system needs to exhibit processes which run on several different time scales to be able to adapt to an ever changing environment. It is in this sense that complexity is a sign of health. Multiscale analysis is able to quantify the degree of complexity as argued in Ref. [36]; in Ref. [30] multiscale analysis is applied to binary DNA sequences and synthetic computer codes to quantify complexity. In Ref. [36], it is stressed that complexity rather than irregularity is investigated using multiscale entropy. This allows to discriminate between atrial fibrillation and congestive heart failure. In Ref. [36] it is argued that increased irregularity is not necessarily associated with increased complexity. In the next section, we extend this point and show that one has to be careful with drawing any conclusions from multiscale entropy on any dynamical properties such as irregularity or regularity, and certain a priori knowledge on the dynamical time-scales involved is needed to draw conclusions. In the spirit of Ref. [36], we see multiscale analysis as a general tool to study complexity. The next
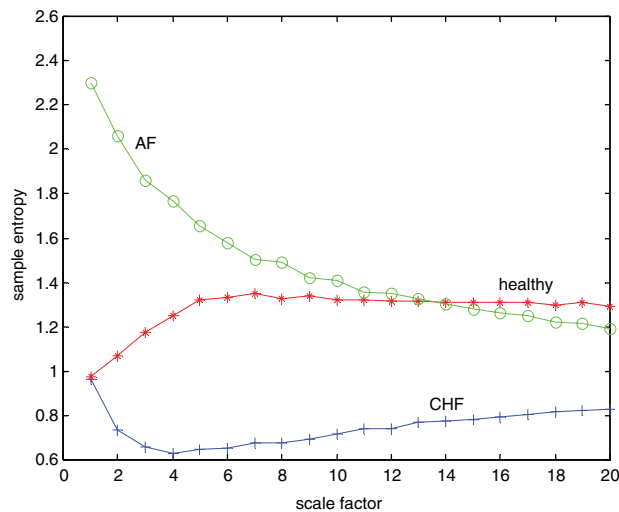

Fig. 1. Plot of the multiscale signature for young healthy hearts (stars), atrial fibrillation (circles) and congestive heart failure (crosses).

section looks at general aspects of multiscale entropy analysis and pitfalls in the interpretation of signatures and conclusions about complexity.

4. Validity of the multiscale entropy method for the interpretation of physiological data

In this section, we investigate the interpretation of the signatures of the multiscale entropy of heart data given in Ref. [1]. It was suggested that the signature for atrial fibrillation is associated with white noise data and an underlying stochastic dynamics. In contrast, the signature of young healthy hearts was associated with underlying chaotic dynamics. The signature of congestive heart failure was believed to originate from the occurrence of regularity in the dynamics.

We show that such one-to-one correspondence between signatures and the underlying dynamics producing such signatures cannot be made, and care has to be taken when interpreting signatures of multiscale entropy. To interpret signatures, it is necessary to have a clear idea about the following three different time scales involved: the sample time τ_s of the time series, the correlation time τ_c of the data, and the period of possible nonlinear oscillations τ_p.

To illustrate our argument we use data from numerical simulations of the Lorenz system

$$\dot{x} = \sigma(y - x),$$

$$\dot{y} = rx - y - xz,$$

$$\dot{z} = xy - bz. \tag{4.1}$$

To assure that the dynamics has settled down to their respective regular or chaotic attractors, we always allow for a transient before sampling a data set. We can measure the correlation length τ_c by computing the autocorrelation function of a data set, and the period τ_p by detecting peaks in the Fourier spectrum of a time series. Note that $\tau_p = \infty$ if no such peaks are present.

We first concentrate on systems without any regularity. By that we mean either purely random data or chaotic dynamics without any prevalent nonlinear frequencies. In Fig. 2a, we show the result for a purely random data set. The time series consists of white noise data. The resemblance with the signature for atrial fibrillation is evident (compare with Fig. 1). The monotonic decrease of entropy as a function of the scale factor τ is due to the averaging involved in the calculation of the multiscale entropy. The larger the τ, the more consecutive data points are averaged. As the average is constant (zero in our case) the entropy will decrease due to the law of large numbers.

However, a similar picture can be obtained by analyzing a data set which originates from the Lorenz system with parameters resulting in chaotic dynamics. A finite correlation time τ_c is typical for such chaotic dynamics. If the sampling time τ_s is chosen such that $\tau_s \gg \tau_c$, measurements or samplings cannot resolve the deterministic chaoticity exhibiting a finite correlation length. Instead the resulting time series appears to be uncorrelated and yields a signature similar to the δ-correlated white-noise data as can be seen in Fig. 2b.

If, however, the sampling is done at a rate with $\tau_s \ll \tau_c$, the time series can resolve the finite correlation and we see indeed the signature of a young healthy heart as in Fig. 1. In Fig. 3, we show the result for the same parameters as in Fig. 2b but now for a smaller sampling rate. The initial increase in entropy with increasing scale factor τ can be explained by noting that increasing the scale factor, i.e., averaging consecutive τ data points, is an effective decorrelation of a data set with a finite correlation time τ_c. This results in an increase of disorder and entropy. For larger scale factors the entropy has to decrease inevitably as discussed above for the purely random case.

We now look at chaotic dynamics which involve prevalent nonlinear frequencies with finite periods τ_p. These frequencies can be detected in a Fourier spectrum. We show examples of such Fourier spectra in Fig. 4.

The local signature of the multiscale entropy for a time series of a chaotic system with prevalent frequencies depends crucially on the ratio of the scale associated with the regular periodic part, τ_p, and the time scale associated with the chaotic dynamics, τ_c. In Fig. 5, we show a sketch of the two extreme cases, $\tau_p \gg \tau_c$ and $\tau_p \ll \tau_c$. Note that the autocorrelation time τ_c of a signal depends on its sample time τ_s.
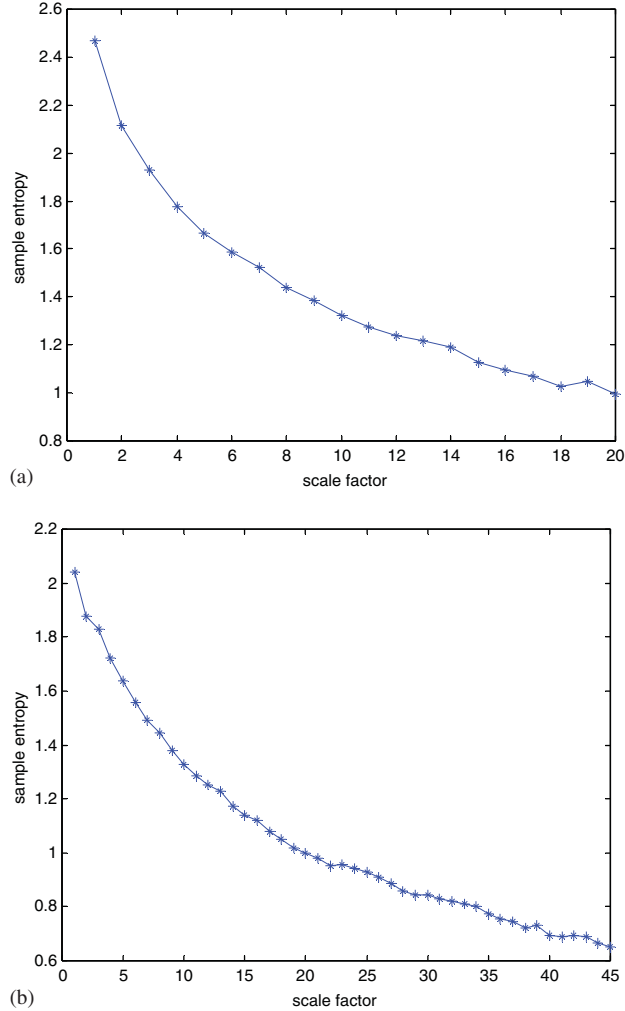
Fig. 2. (a) Plot of the multiscale entropy for a purely random data set. The time series consists of data drawn from a white-noise distribution with a variance of 1, (b) plot of the multiscale entropy for the Lorenz system with $r = 28$, $\sigma = 10$ and $b = \frac{8}{3}$. A time series of 4.5×10^3 data points has been used with a total time length of 4.5 t.u. The time scales are $\tau_c = 0.3$ t.u. and $\tau_s = 3.0$ t.u.

The signature of regular dynamics is a dip of the multiscale entropy for certain values of the scale factor τ, whereas the 'local' signature of chaotic dynamic is an increase of the multiscale entropy. The difference of the two cases depicted in Fig. 5 in MSE becomes clear if we recollect that the coarse graining factor τ smoothes the signal by averaging. In the case $\tau_p \gg \tau_c$ this averaging simply results in smoothing over the 'fast' finite correlation part of the dynamics resulting in a smoother more regular signal. In this case, we expect a dip in MSE with initial increasing τ. However, in the case $\tau_p \ll \tau_c$, the only effect of increasing τ is to decorrelate the finite τ_c signal, and no initial dip can be observed. The occurrence or nonoccurrence of the initial dip in MSE is linked to the two competing effects of increasing the coarse graining factor τ; namely the effect of decorrelation, leading to an increase of MSE, and the effect of smoothing leading to a decrease in MSE if τ_c is small enough.

In the case $\tau_p \gg \tau_c$ we obtain indeed a signature resembling the signature of congestive heart failure (compare with Fig. 1). In Fig. 6, we show results for the Lorenz system with $r = 213$, $\sigma = 10$ and $b = \frac{8}{3}$ which yield the Fourier spectrum in Fig. 4. For these parameters we have $\tau_p = 0.5$ t.u. and $\tau_c = 0.08$ t.u.

The influence of the sample time τ_s on the signature of the multiscale entropy can be understood by looking at the sketch in Fig. 5a. Increasing τ_s will decorrelate the chaotic component which is correlated on the fast
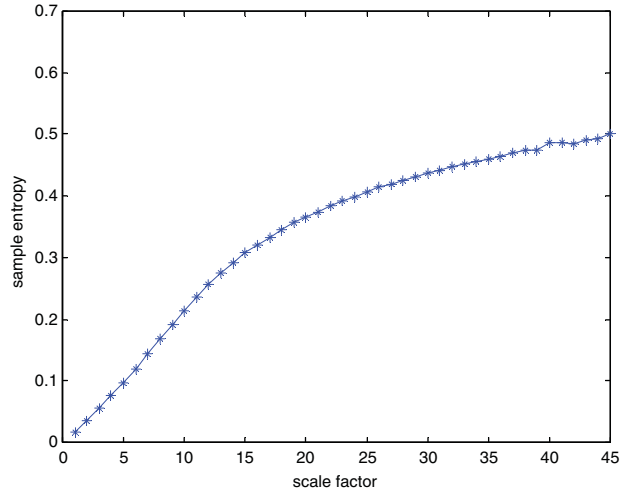
Fig. 3. Plot of the multiscale entropy for the Lorenz system with $r = 28$, $\sigma = 10$ and $b = \frac{8}{3}$. A time series of 4.5×10^3 data points has been used with a total time length of 4.5 t.u. and $\tau_s = 0.001$ t.u.
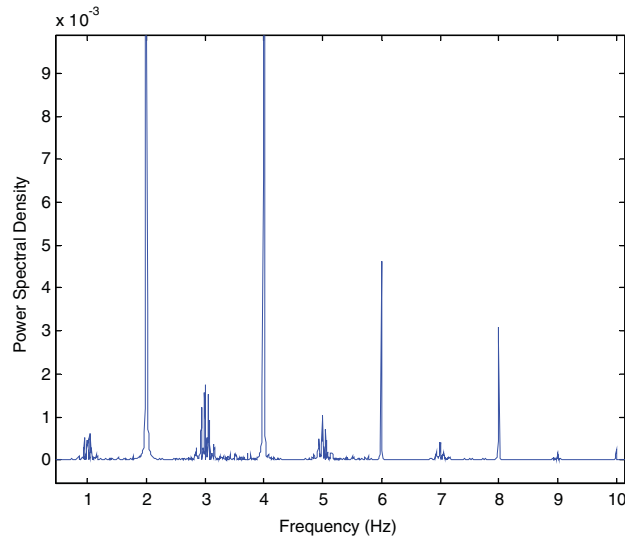

Fig. 4. Fourier spectrum of a time series of the Lorenz system with $r = 213$, $\sigma = 10$ and $b = \frac{8}{3}$. The maximal peak corresponds to $\tau_p = 0.5$ t.u.

time scale τ_c. However, increasing τ_s will not affect the regular slow time scale part of the regular component (if τ_s is moderate).

We note that the characteristic decrease of the multiscale entropy for small τ is strongly dependent on the sampling time τ_s for noisefree data. The inclusion of δ-correlated noise yields a more pronounced dip (see Fig. 6).

5. Summary

The paper is an attempt to model and understand the MSE of cardiac data. This is carried out using electro cardiogram data and the Lorenz model. We have revisited the analysis of physiological cardiac data by means of multiscale entropy proposed in Ref. [1]. Signatures of the multiscale entropy for the three cases of young
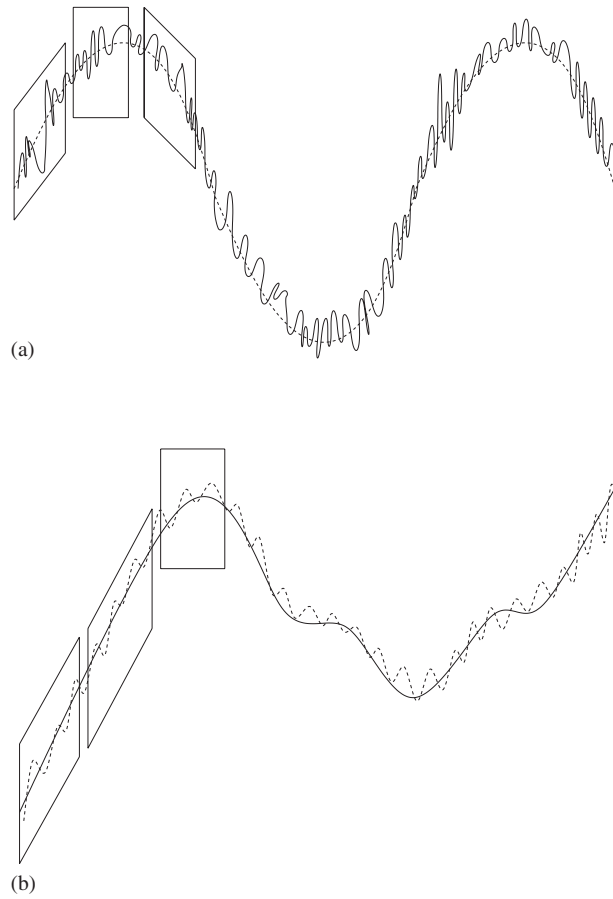
(a)

(b)

Fig. 5. Sketch of a time series which involves a finite frequency and a finite correlation length. The regular part is depicted in dashed lines, the chaotic part in solid lines. The boxes are of length τ and indicate the segmentation of the signal by smoothing over τ: (a) the case where $\tau_p \gg \tau_c$, (b) the case where $\tau_p \ll \tau_c$.
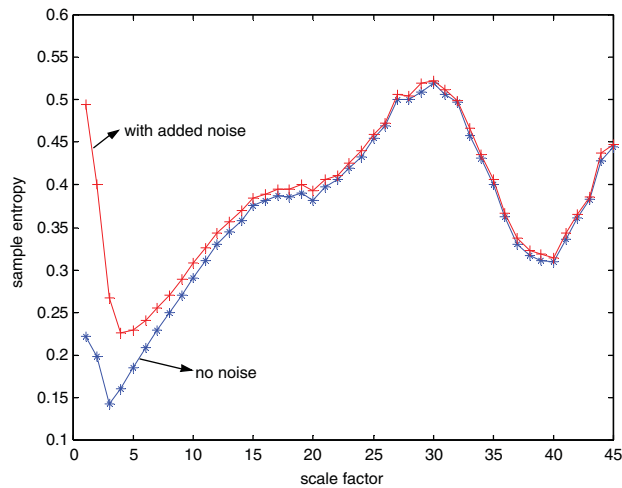

Fig. 6. Plot of the multiscale entropy for the Lorenz system with $r = 213$, $\sigma = 10$ and $b = \frac{8}{3}$. Lower curve: noise free data. $\tau_p = 0.5$ t.u., $\tau_c = 0.08$ t.u. and $\tau_s = 0.00402$. Upper curve: Gaussian noise with variance 2.89 has been added as measurement noise to the data.

healthy hearts, atrial fibrillation and congestive heart failure were identified. We discussed the interpretation of these signatures.

By studying the Lorenz equation as a simple deterministic chaotic system, we showed that for a dynamical system the MSE signature one obtains from a time series depends on the sampling time interval, the correlation time and the period of oscillation, if any frequencies are present. For example, sampling rate can cause decorrelation, suppress periodicities, thus effects the observed MSE signature.

This sounds a bell of caution to the reader to be wary of drawing definite conclusions about the nature of the underlying dynamical system from the MSE signature of a sampled time series without detailed knowledge of the different time scales involved. The degree of complexity depends crucially on the time scales under consideration.

Chaotic time series with and without nonlinear frequencies yield the same MSE signature as a purely white noise signal if the sampling time is greater than the correlation time and the period of possible nonlinear frequencies. In the case where the correlation time in the sampled data is much greater than the sampling time (and periods of possible nonlinear frequencies are at least smaller than the correlation time) coarse graining will cause the sample entropy to increase initially due to decorrelation before it begins to decrease according to the law of averages. The MSE signature of the young healthy heart shows such a behaviour, suggesting the presence of complex long time correlations. However, we note that in the case of cardiac data which is a time series of the interbeat intervals, the sampling time interval obviously cannot be varied.

Whether periodicities in a chaotic signal result in the MSE signature of congestive heart failure depends crucially on the relation between the correlation time τ_c and the period τ_p. Only if $\tau_c \ll \tau_p$ we can find the dip in multiscale entropy which was found to be an indication for loss of complexity and the appearance of regularity in congestive heart failure [1]. However, the finite correlation does not necessarily have to come from a deterministic chaotic system but could as well be some noise with finite correlation time.

In conclusion, similar to the fact that when a time series is constructed on the succession of the same Mahler symphony, the resulting time series may look complex on short intervals whereas the actual signal is periodic [37]. In the same way, we have to be careful when we draw conclusions from time series analysis about the underlying dynamics.

In a recent paper [30], which had been published after our submission, the authors address similar issues to ours. In Ref. [30] the influence of uncorrelated noise and sample frequency on multiscale entropy is investigated. In addition to our work in Ref. [30] also the influence of outliers within a given data set on multiscale entropy is investigated. However, we note that the definition of sample time in their work and in our work is different. Whereas sample time in Ref. [30] is used to define the accuracy by which Holter monitor data are collected to produce R–R interval data series, we use sample time to denote the sampling interval of the data set which is being directly analyzed (note that there is no freedom in choosing different sampling times according to our definition for R–R interval data). Whereas changes in the sampling time of the data series to be analyzed and its ratio to the correlation time and possible present regular frequencies were found here to be of great importance, changes in sample frequency as defined in Ref. [30] were not important.

The study on the influence of noise in Ref. [30] is limited to uncorrelated noise and does not address the connection between the correlation time of the noise and the correlation time of the deterministic system or the period of the embedded regular dynamics.

References

[1] M. Costa, A.L. Goldberger, C.-K. Peng, Multiscale entropy analysis of complex physiological time series, Phys. Rev. Lett. 89 (2002) 068102.
[2] Spotlight issue on chaos in the cardiovascular system, Cardiovasc. Res. 31 (1996).

[3] Focus issue: fibrillation in normal ventricular myocardium, Chaos 8 (1998).

[4] Focus issue: mapping and control of complex cardiac arrhythmias, Chaos 12 (2002).

[5] Special issue on the heart, Chaos, Solitons Fractals 13 (2002) 1579–1762.

[6] A.L. Goldberger, Is the normal heartbeat chaotic or homeostatic?, News Physiol. Sci. 6 (1991) 87–91.

[7] F.X. Witkowski, K.M. Kavanagh, P.A. Penkoske, R. Plonsey, M.L. Spano, W.L. Ditto, D.T. Kaplan, Evidence for determinism in ventricular fibrillation, Phys. Rev. Lett. 75 (1995) 1230–1233.

[8] G. Sugihara, W. Allan, D. Sobel, K.D. Allan, Nonlinear control of heart rate variability in human infants, Proc. Natl. Acad. Sci. USA 93 (1996) 2608–2613.

[9] T.A. Denton, G.A. Diamond, R.H. Helfant, S. Khan, H. Karagueuzian, Fascinating rhythm: a primer on chaos theory and its application to cardiology, Am. Heart. J. 120 (1990) 1419–1440.

[10] J.E. Skinner, A.L. Goldberger, G. Mayer-Kress, R.E. Ideker, Chaos in the heart: implications for clinical cardiology, Biotechnol. 8 (1990) 1018–1024.

[11] A.L. Goldberger, Nonlinear dynamics for clinicians: chaos theory, fractals and complexity at the bedside, Lancet 347 (1996) 1312–1314.

[12] C.-S. Poon, C.K. Merrill, Decrease of cardiac chaos in congestive heart failure, Nature 389 (1997) 492–495.

[13] D.J. Cristini, L. Glass, Introduction: mapping and control of complex cardiac arrhythmias, Chaos 12 (2002) 732–739.

[14] C.D. Wagner, P.B. Persson, Chaos in the cardiovascular system: an update, Cardiovasc. Res. 40 (1998) 257–264.

[15] H. Kantz, T. Schreiber, Nonlinear Time Series Analysis, second ed., Cambridge University Press, Cambridge, 2004.

[16] J. Kurths, A. Voss, A. Witt, P. Saparin, H.J. Kleiner, N. Wessel, Quantitative analysis of heart rate variability, Chaos 5 (1995) 8–94.

[17] A. Voss, J. Kurths, H.J. Kleiner, A. Witt, N. Wessel, P. Saparin, K.J. Osterziel, R. Schurath, R. Dietz, The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death, Cardiovasc. Res. 31 (1996) 419–433.

[18] N. Wessel, A. Voss, J. Kurths, A. Schirdewan, K. Hnatkova, M. Malik, Evaluation of renormalised entropy for risk stratification using heart rate variability data, Med. Biol. Eng. Comput. 38 (2000) 680–685.

[19] N. Wessel, C. Ziehmann, J. Kurths, U. Meyerfeldt, A. Schirdewan, A. Voss, Short-term forecasting of life-threatening cardiac arrhythmias based on symbolic dynamics and finite-time growth rates, Phys. Rev. E 61 (2000) 733–739.

[20] N. Wessel, H. Malberg, U. Meyerfeldt, A. Schirdewan, J. Kurths, Classifying simulated and physiological heart rate variability signals, Comput. Cardiol. 29 (2002) 133–135.

[21] N. Marwan, N. Wessel, U. Meyerfeldt, A. Schirdewan, J. Kurths, Recurrence-plot-based measures of complexity and their application to heart-rate-variability data, Phys. Rev. E 66 (2002) 026702.

[22] M. Säkki, J. Kalda, M. Vainu, M. Laan, The distribution of low-variability periods in human heartbeat dynamics, Physica A 338 (2004) 255–260.

[23] J. Hayano, F. Yamasaki, S. Sakata, A. Okada, S. Mukai, T. Fujinami, Spectral characteristics of ventricular response to atrial fibrillation, Am. J. Physiol. 273 (1997) H2811–H2816.

[24] W. Zeng, L. Glass, Statistical properties of heartbeat intervals during atrial fibrillation, Phys. Rev. E 54 (1996) 1779–1784.

[25] Ya.B. Pesin, Characteristic Lyapunov exponents and smooth ergodic theory, Russ. Math. Surveys 32 (1977) 55.

[26] J.R. Dorfman, An Introduction to Chaos in Nonequilibrium Statistical Mechanics, Cambridge University Press, Cambridge, 1999.

[27] S.M. Pincus, Approximate entropy as a measure of system complexity, Proc. Natl. Acad. Sci. USA 88 (1991) 2291–2301.

[28] J.S. Richmann, J.R. Moorman, Physiological time series analysis using approximate entropy and sample entropy, Am. J. Physiol. Heart Circ. Physiol. 278 (2000) H2039.

[29] J.L. Starck, F. Murthag, A. Bijaoui, Image Processing and Data Analysis, Cambridge University Press, Cambridge, 1998.

[30] M. Costa, A.L. Goldberger, C.-K. Peng, Multiscale entropy analysis of biological signals, Phys. Rev. E 71 (2005) 021906.

[31] V.V. Nikulin, T. Brismar, Comment on multiscale entropy analysis of complex physiological time series, Phys. Rev. Lett. 92 (2004) 089803.

[32] M. Costa, A.L. Goldberger, C.-K. Peng, Reply to [31], Phys. Rev. Lett. 92 (2004) 089804.

[33] D.E. Lake, J.S. Richmann, M.P. Griffin, J.R. Moorman, Sample entropy analysis of neonatal heart rate variability, Am. J. Physiol. Heart Circ. Physiol. 283 (2002) R789–R797.

[34] MIT-BIH Normal Sinus Rhythm Database, BIDMC Congestive Heart failure database and MIT-BIH Atrial Fibrillation Database available at http://www.physionet.org/physiobank/database/#ecg.

[35] N. Wessel, A. Schirdewan, J. Kurths, Comment: intermittently decreased beat-to-beat variability in congestive heart failure, Phys. Rev. Lett. 91 (2003) 119801.

[36] M. Costa, A.L. Goldberger, C.-K. Peng, Reply to [35], Phys. Rev. Lett. 91 (2003) 119802.

[37] P.E. Rapp, T. Schmah, Complexity measures in molecular psychiatry, Mol. Psychiatry 1 (1996) 408–416.