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Short communication

Multi-scale transitions of fuzzy sample entropy of RR-intervals and their phase-randomized surrogates: A possibility to diagnose congestive heart failure

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ABSTRACT

Heart rate variability (HRV) is the variability of consecutive cardiac inter-beat intervals (RR-intervals or RR-signals). It contains features that are essential indicators for the health of a human being. Recently, researchers have investigated the usefulness of non-linear dynamics to gain insight on temporal relationships within the RR-signals. Sample entropy and fuzzy sample entropy (fSEn) are variables reflecting the non-linear dynamics of HRV. However, previous studies have only rarely considered that the information of a signal might be encoded in its phase. In this article, we define and quantify complexity of a signal by the part of regularity caused by the non-random aspect of the phase of a signal.

The purpose of the study is to show that information about the control of HRV is largely encoded in the phase of the Fourier transformed signal and its complexity can be quantified using the multi scale transition (MST) of fSEn of RR-signals and their phase-randomized surrogates. This may allow classifying individual participants with congestive heart failure from healthy controls.

The results show distinct differences in the biphasic MST transitions between controls and patients suffering from congestive heart failure. The differences of normalized fSEn of surrogates minus fSEn of the RR-signal show a clear first, fast response lasting about 3–4 s followed by a long lasting trend. The sum of these differences in the fast response trend represent a feature variable that allowed classifying patients and controls with a high sensitivity of 87% and a high specificity of 89%. The relationship to neural control of the HRV can now be investigated with variables that reflect the regularity and complexity of the HRV using the information that is encoded in the phase of the Fourier transformed RR-signal and is not resolved by the classical, power spectra based HRV analysis.

1. Introduction

Heart rate variability (HRV) is the variability of consecutive cardiac inter-beat intervals (RR-intervals or RR-signals), which is an essential indicator of the health in human being. In some laboratories HRV is used to monitor the fitness of athletes while in a clinical environment it is generally used to assess cardiac diseases [1]. To a great extent the HRV is controlled by the autonomous nervous system (ANS) [2]. To differentiate between parasympathetic and sympathetic activity of the ANS, generally a *power spectral analysis* (PSD) is performed [3]. More recently, researchers have investigated the usefulness of non-linear dynamics to gain further insights on temporal relationships within a biological signal [4,5].

One of the approaches was to use measures of entropy [6] to assess regularity, complexity and long range correlation of HRV signals. The entropy in the context of the information theory is defined as: "the measure of the average uncertainty in the random variable" and is usually presented in bits [7]. To approximate the entropy for a signal with a finite length, different algorithms have been proposed [8,9]. Among the recent measures, the approximate entropy [10] the sample entropy (SEn) [11] and the fuzzy entropy (fSEn) [12,13] are the most commonly used. The SEn is defined as the natural logarithm of the conditional probability that when two m point sequences are similar within a tolerance matching r, they remain similar after adding the next point. The m point sequences are taken from the signal at intervals indicated by a scale, where scale*dt (dt is the sampling rate of the resampled RR-signal) represents the time between consecutive points in the rescaled RR-signal.

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Using the entropy measures, it was shown that the complexity of RR-signal decreases with aging and disease. These measures however suffered from limited interpretability [14–16]. As cardiac health plays a critical role to overall wellbeing of individuals, it is important to understand the controlling mechanism involved in regulating HRV more thoroughly. To achieve this objective more intuitive and interpretable measures are required.

Theoretically, a signal with no HRV, thus constant RR-intervals, has fSEn = 0, which implies that it is regular and carries no information. In contrast, in a completely randomly permuted HRV signal in which the probability density function of the signal is preserved [14], no regularity can be observed and therefore no further information other than the amplitude of the fluctuations is available. In all other intermediate scenarios, the signal is neither completely random nor regular. Thus, there must be some physiological mechanism that introduces the structure (a complex structure) into the RR-signal in these intermediate scenarios. Complexity is not yet well defined however, sometimes it is defined as the richness in data over multiple scales [11]. However "richness" is not an easily measurable quantity. Oppenheim [17] has shown that the information that makes an image recognizable is predominantly present in the phase of the Fourier transformed image. In this article we define the complexity as follows:

Complexity is the property of the signal that results in a non-random structure in the phase of a Fourier transformed signal.

Therefore, the complexity of the RR-signal at different scales can be assessed by measuring the difference between the normalized fSEn (nfSEn) of the RR signal and the normalize fSEn of the phase surrogate of the RR signal ($nfSEn_{sur}$) for a given scale. The fSEn of nsr-persons and chf-patients was normalized by dividing the calculated fSEn by the corresponding $fSEn_{ref}$. The $fSEn_{ref}$ is calculated by averaging the fSEn of the randomly permuted realizations of the RR-signal under survey. Complexity is thus a function of scale and can be quantified by the variable ($nfSEn_{sur}$ -nfSEn).

On the same note, the quantity (1-nfSEn) can be defined as a measure of regularity. This variable has the property of being 1 for a fully regular signal and 0 when all regularity is disappeared.

The presence of complexity therefore is measurable by the reduction of regularity by randomizing the phase of the signals. Theiler [18] proposed the method of phase surrogate to study the presence of complexity in the phase of the signal. In this method, the Fourier transform of the signal is calculated and the phase of the signal is replaced by random values between $-\pi$ and π. The surrogate of the signal is calculated by back transforming the phase-randomized signal to the time domain using the inverse Fourier transforms. The measure of concern is calculated for the original signal and is compared to the average of the number of surrogate realizations of the signal using appropriate statistical testing approaches (e.g. Student's *t*-test).

To find the scale where complexity is most effectively contributing to fSEn, it is necessary to calculate the fSEn for steadily increasing scales. The curve created by plotting the calculated fSEns with respect to scales displays a transition which is referred to as multi scale transition (MST) [14]. The MST can provide means to find scales where the neurological control mechanism introduce added complexity to the RR-signal.

The signal is neither completely regular nor completely random at most scales. The transition indicates that three conditions of regular, complex, and random coexist with different degrees of contributions, as already suggested for human balance [16]. Furthermore, the physiological mechanism behind the complexity can have different timing characteristics. As time shift in a signal in the time domain manifests itself as a phase shift in the Fourier domain, the recorded biological signal may contain information in its phase that can be suggestive of the timing and control of the signal introduced by various components of the central nervous system. If the physiological mechanism controls the complexity over a large period of time then the transition will be very mild and relatively unvarying, indicating that there is a robust temporal relation in the signal over multiple time ranges that is not affected much by changes in scale. Equally, if the complexity is controlled only for a small period, the transition to fSEn of the randomized scenario will be fairly rapid suggesting that small increase in the scale of the signal disrupts the temporal structure of the signal all together quickly and thus the control mechanism is only effective for a short span of time in the signal. Therefore the shape of the transition is important indicative of the complexity in a signal as it reflects the timing aspect of the underlying physiological mechanism.

To obtain a transition with minimal noise one has to use the most sensitive of the measures of entropy. The fuzzy sample entropy (fSEn), replaces the Heaviside function used in calculation of the SEn by an exponential function. Also in this method m and $m+1$ sequences are transformed to zero mean sequences by subtraction of the mean prior to the entropy calculation [12,13]. The fSEn is a more efficient measure of entropy than SEn and is reported to be applicable to noisy and short data [12]. The fSEn was therefore used in this study to calculate the entropy of the signal.

An essential part of the analysis of HRV is based on the spectral characteristics of this variability [19]. Usually, a transformation into frequency space is performed using the Fourier transform to assess the power at various frequencies (power spectrum). The β of the $f^{-\beta}$ decay is calculated using the power spectrum of the HRV and is independent of any non-random structure or information encoded in the phase, as it is solely dependent on the power spectrum of the signal. To the best of our knowledge, currently the phase of HRV is generally not considered to be informative and therefore neglected all together. We have shown previously for center of pressure data [16] and for electromyograms [20] that there is a substantial amount of information regarding the variability of the signal that is encoded in the phase. Neuromuscular adjustments create a non-random structure in related biological signals, the effects of which manifest itself in part with a non-random structure in the phase. In contrast to β, the SEn is sensitive to the non-random structure in the phase as seen in the analysis of balance and electromyograms [15,20–22]. Therefore it is safe to speculate that the effect of strong HRV regulations by ANS adds structure to the HRV signal, which in turn induces regularity in the phase. This added regularity theoretically lowers fSEn and thus indicate the presence of complexity in the signal. Therefore, it can be hypothesized that additional information can be acquired about the scale dependent presence of complexity in the HRV signal by measuring the variable ($nfSEn_{sur}$ -nfSEn).

To calculate the fSEn generally accepted value for m is accepted to be in the range of 1–2 [1,23,24]. However, the selection of r has to be considered carefully as it is not yet standardized and remains controversial. Pincus et al. [25] proposed to quote r as a fraction of the standard deviation (SD). For a signal that is normalized by division to the SD, r can be described by its absolute value. There was a general tendency to use low r-values as it leads to increased sensitivity of the fSEn to changes in regularity of the signal. The reproducibility of a measured fSEn depends on counting statistics. It is desirable to obtain high sensitivity and high reliability. Lark et al. [1] proposed the selection for neonatal HRV based on statistical considerations of variability and found r values of the order of 0.2 to be appropriate and thus confirmed the range of r-values used in other studies [26,27]. However, the tendency towards low r-values comes at the price of losing specificity whereby m point sequences that should be similar are misclassified as dissimilar. Thus, when a signal is highly regular but has superimposed noise or other measurement inaccuracies, the measured fSEn fails to reflect the actual regularity but becomes more sensitive to changes of the noise level. One additional criterion for the selection of r is for a sufficiently high