H814-9 *Accepted for publication in the American Journal of Physiology*

# Entropies of short binary sequences in heart period dynamics

**D. Cysarz[1], H. Bettermann[1], and P. Van Leeuwen[2]**

[1]*Department of Clinical Research, Gemeinschaftskrankenhaus, D-58313 Herdecke, Germany*

[2]*EFMT, Research and Development Center for Microtherapy, D-44799 Bochum, Germany*

Abbreviated title:
Entropies in heart period dynamics

Address for correspondence:
Dirk Cysarz
Department of Clinical Research
Gemeinschaftskrankenhaus Herdecke
Gerhard-Kienle-Weg 4
D-58313 Herdecke, Germany
Tel. +49 2330 62-3637
Fax +49 2330 62-4007
Email d.cysarz@t-online.de

## Abstract

Dynamical aspects of RR intervals have often been analyzed by means of linear and non-linear measures. The goal of this study was to analyze binary sequences, in which only the dynamical information is retained, by means of two different aspects of regularity. RR interval sequences derived from 24-hour ECG recordings of 118 healthy subjects were converted to symbolic binary sequences which coded the beat-to-beat increase or decrease in RR interval. Shannon entropy was used to quantify the occurrence of short binary patterns (length N=5) in binary sequences derived from 10-minute intervals. The regularity of the short binary patterns was analyzed on the basis of approximate entropy (ApEn). ApEn had a linear dependence on mean RR interval length, increasing irregularity occurring at longer RR interval length. Shannon entropy of the same sequences showed that the increase in irregularity is accompanied by a decrease of occurrence of some patterns. Taken together, this indicates that irregular binary patterns are more probable when the mean RR interval increases. The use of surrogate data confirmed a nonlinear component in the binary sequence.

Analysis of two consecutive 24-hour ECG recordings for each subject demonstrated good intraindividual reproducibility of the results. In conclusion, quantification of binary sequences derived from ECG recordings reveals properties that cannot be found using the full information of RR interval sequences.

**Index terms:**
heart period dynamics, symbolic dynamics, approximate entropy, Shannon entropy, nonlinear dynamics, surrogate data

# Introduction

In recent years linear measures of heart rate variability (HRV) have been applied in a wide range of contexts, leading to a well established diagnostic tool with more or less accepted standards (16;17;30). Today HRV is not only applied in cardiac diseases but in diseases that generally affect the autonomic nervous system (ANS). However, the influence of the sympathetic and parasympathetic branch of ANS on linear measures of HRV as well as the independent prognostic value of these measures with respect to high risk patients with cardiac diseases is still a matter of investigation (6;9;12). On the other hand, assessing HRV with nonlinear measures may supply information different from that of linear measures with the promise of better risk stratification (13;32-34). But in most cases it is difficult to interpret these complementing findings in one unifying picture. In this study we examine dynamical properties of heart periods with two different nonlinear approaches that can be regarded as two complementing aspects of dynamical properties. The results also shed a new light on the interpretation of power spectral measures of HRV.

Different approaches lead to nonlinear measures of HRV. In nonlinear dynamics theory, the so-called state space is reconstructed from sequences of heart beat periods that are generally defined as the time duration between successive R waves in the electrocardiogram (ECG), the RR tachogram. In a second step the state space and the dynamical behaviour of the reconstructed dynamics can be quantified (e.g. with measures of dimension or lyapunov exponents). For an overview see e.g. (10). Practically, the sequences of heart periods are short, noisy and often nonstationary. Thus the application of nonlinear measures to ECG recordings may lead to spurious indications of chaos (3;7). However, one may guardedly say that this approach has yielded evidence of nonlinearities. Indeed, powerful quantities for describing heart period dynamics and for stratification of high risk patients are still lacking (17).

Another approach to nonlinear measures of HRV is the quantification of complexity from the point of view of information theory. To this end, the sequence of heart periods can be analyzed with the help of entropy measures like Shannon entropy or renormalized entropy (11;25). They are often used in conjunction with the concept of symbolic dynamics or coding theory, i.e. reducing the amount of information by transforming the original time series into a symbolic sequence with a small set of symbols (8). These measures proved to be useful in detection of patients at high risk for sudden cardiac death (34). Another entropy measure for quantification of regularity in a time series is the approximate entropy (18;24). Approximate entropy has the ability to detect subtle differences in heart period dynamics that cannot be observed with commonly used linear measures (14;15). Recently, the evaluation of approximate entropy for RR tachograms derived from 24-hour ECG recordings led to the

suggestion of phase transitions, in the notion of synergetics, between day time and night time heart period dynamics (2). It has also been shown that changes in fetal heart period complexity during pregnancy can be documented using ApEn (31). Though approximate entropy has been introduced for symbolic dynamics (20), the application of approximate entropy to symbolic dynamics derived from physiological data has not been performed yet.
The goal of this study was to examine binary sequences derived from Holter recordings of healthy subjects in order to determine their pure dynamical properties. To this end, a 'dynamic' or differential symbolization is used (1). Such a transformation into binary sequences is of particular interest because this method extracts solely dynamical properties of the RR series, disregarding all information influenced by the absolute values of the RR intervals, e.g. mean RR interval, RR standard deviation and other measures of RR interval variability. Approximate entropy is used as a nonlinear measure of irregularity of short binary sequences to quantify their dynamical properties. Shannon entropy quantifies regularity on a larger scale of the symbolic dynamics under consideration and thus helps to make the results more precise. It is still unknown whether binary coding preserves nonlinear properties of the original RR tachogram. To test the hypothesis that the binary representation of RR dynamics still contains some important nonlinear properties, we make use of surrogate data. To demonstrate the intraindividual reproducibility of the binary approximate entropy, two consecutive 24-hour ECG recordings for each subject are analyzed.

# Methods

### Subjects

The subjects for this study were drawn from a previous study in which 121 healthy subjects were included (5). Three subjects were excluded from this analysis due to missing data. Two consecutively recorded 24-hour ECGs (A and B) were available for the remaining 118 subjects (age: 20 to 40 years, mean ± sd: 27 ± 6 years, 78 females). The 24-hour ECGs were recorded with Oxford FD3 solid state recorders (Oxford Instruments, Abingdon, UK) with simultaneous R wave detection and a maximum sampling rate of 1024 Hz during the QRS complex. This permitted a maximum resolution of 1 ms for the detection of the R waves. An Oxford Excel ECG analyser allowed the visual inspection of the automatically detected R waves. Generally, the number of ectopic or unrecognized beats was small (<1%) and thus such beats were not replaced or inserted. For further analysis the R times were written to a binary data file that was exported to a Personal Computer for further analysis.

### Construction of symbolic sequences

For each 10-minute interval in the 24-hour ECG (max. 144 intervals/recording) the times between subsequent R waves (RR intervals or heart periods) formed the corresponding RR tachogram. Transformation of each 10-minute RR tachogram into a binary sequence was done as follows (see figure 1):

- Differences $RR_{n+1} - RR_n > 0$, i.e. a decrease in heart rate, are set to 1's.
- Differences $RR_{n+1} - RR_n \leq 0$, i.e. an increase in heart rate, are set to 0's.

The binary sequences are quantified by estimation of two different entropies: approximate entropy and Shannon entropy. Each entropy reveals different aspects of the binary sequence under consideration. Approximate entropy is a nonlinear measure of irregularity in time series (24); Shannon entropy quantifies the amount of information in time series (28).

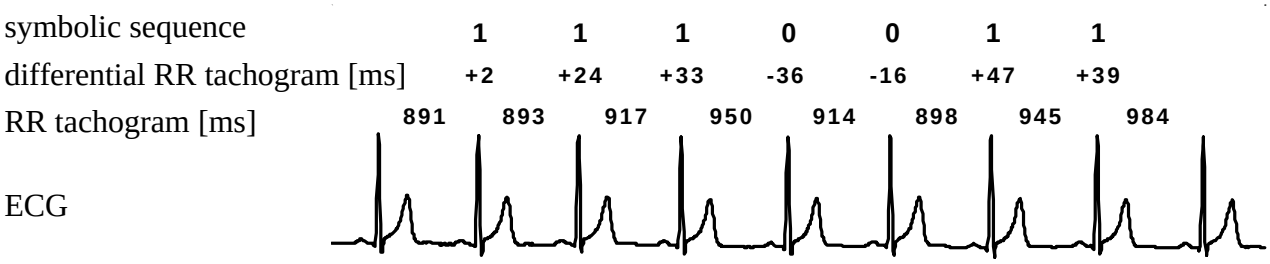


**Fig. 1** Example of the construction of symbolic sequences from ECG recordings keeping the dynamical aspects.

**Approximate entropy**

The goal of approximate entropy is to quantify irregularity or fluctuations in a time series on the basis of Kolmogorov-Sinai entropy (21;23). It quantifies dynamical aspects of the time series under consideration in a statistical manner. In the following, a short description of the formal implementation of approximate entropy is given, for further details, see e.g. (18;22).
Given a time series (e.g. RR tachogram) with $N$ data points $u(1), u(2), \ldots, u(N)$, sequences of vectors $\vec{x}(1), \ldots, \vec{x}(N-m+1)$ are formed by defining $\vec{x}(i) = (u(i), u(i+1), \ldots, u(i+m-1))$. The parameter $m$, the number of components in each vector, has to be fixed. In nonlinear dynamics theory this would be interpreted as a '$m$-dimensional state space reconstruction'. Next, define the distance $d(\vec{x}(i), \vec{x}(j))$ between two vectors $\vec{x}(i)$ and $\vec{x}(j)$ by the maximum difference of all their scalar components:

$$d(\vec{x}(i), \vec{x}(j)) = \max_{k=1,2,\ldots,m} (u(i+k-1) - u(j+k-1)) .$$

Now let the 'correlation sum' of vector $\vec{x}(i)$ be

$$C_i^m(r) = \frac{\text{no. of} \quad j \le N-m+1 \quad \text{such that} \quad d(\vec{x}(i), \vec{x}(j)) \le r}{N-m+1} .$$

The parameter $r$ (not to be confused with correlation coefficient $r$ used below) acts like a filter value: within resolution $r$, the numerator counts the number of vectors that are approximately the same as a given reference vector $\vec{x}(i)$. The quantity $C_i^m(r)$ is called 'correlation sum', because it quantifies the summed (or global) correlation of vector $\vec{x}(i)$ with all other vectors.
Next, define the mean logarithmic correlation sum of all vectors:

$$\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \log C_i^m(r)$$

and the approximate entropy (ApEn):

$$\mathrm{ApEn}(m, r, N)(u) = \Phi^m(r) - \Phi^{m+1}(r), \quad m \ge 1$$

$$\mathrm{ApEn}(0, r, N)(u) = -\Phi^1(r).$$

ApEn($m$,$r$,$N$)($u$) measures the logarithmic frequency with which vectors with $m$ components that are close (within resolution $r$) remain close when increasing the number of vector components by one. This is the key to a measure of irregularity: small values of ApEn indicate regularity and large values imply substantial fluctuations or irregularity in a time series $u$.
This concept can also be applied to short binary sequences or other symbolic dynamics. To understand the notion of irregularity in binary sequences, consider the sequences 00000, 11111, 01010 and 10110. The first two sequences are easily identified as very regular

sequences. In the third sequence 0's and 1's alternate and thus it is suitable to call this sequence regular, too. Only the last sequence does not contain any symmetries or periodically recurring subsequences, in other words this sequence is more irregular. This concept of irregularity for binary sequences can be quantified using the approximate entropy.
Formally, if ApEn is applied to binary sequences consisting of 1's and 0's the distance $d(\vec{x}(i),\vec{x}(j))$ will be either 0 or 1. Thus it only makes sense to set the resolution $r<1$. To keep things as easy as possible, we restrict ourselves to $m=1$. Next, the optimal length of binary sequences to be quantified with ApEn has to be found. As pointed out in (20) the evaluation of ApEn with $m=1$ is based on the calculation of the frequencies of the subsequences {0, 1, 00, 01, 10, 11} in the binary sequence under consideration. In a random binary pattern, the longer the binary sequence the higher is the probability that the subsequences occur with almost the same frequency. This would always lead to approximately the same values of ApEn. Thus short binary patterns would be better suited to produce ApEN values that can be distinguished from one another. In this work we analyze very short binary sequences ($N=5$) permitting a good differentiation of the values of ApEn for the distinct binary patterns. We refer to these very short sequences as 'binary patterns' distinguishing them from the 10-minute 'binary sequences' of heart period dynamics.
To distinguish this use of approximate entropy from the normal use, we call this quantity 'binary approximate entropy (BinApEn)'. Practically, BinApen is evaluated for each binary pattern of length 5 in the whole binary sequence generated from the 10-minute RR tachogram. The average of all BinApEn values is used to quantify heart period irregularity of the binary patterns.

**Shannon entropy**

In contrast to binary approximate entropy, Shannon entropy considers the whole binary sequence generated from the 10-minute RR tachogram. Shannon entropy gives a number which characterizes the probability that different binary patterns of length *N* occur. For a very regular binary sequence only few distinct patterns occur. Thus Shannon entropy would be small because the probability for this patterns is high and only little information is contained in the whole sequence. For a random binary sequence all possible patterns of length *N* occur with the same probability and the content of information is maximal. This case is indicated by maximal values of Shannon entropy.
To formalize this concept, first the probabilities of each pattern of length *N* is estimated from the whole binary sequence (28):

$$\hat{p}(s_1,s_2,\ldots,s_N)=\frac{n_{s_1\cdots s_N}}{n_{tot}}$$

where $n_{s_1\cdots s_N}$ is the number of occurrences of the pattern $s_1,s_2,\ldots,s_N$ and $n_{tot}$ is the total number of patterns. Now, define the entropy estimation

$$S(N)=-\frac{1}{N}\sum_{s_1,\ldots,s_N}\hat{p}(s_1,\ldots,s_N)\log_2\hat{p}(s_1,\ldots,s_N).$$

For a better comparison when using different pattern lengths *N*, *S(N)* is divided by *N*. Thus the maximal estimation of Shannon entropy is always 1. The properties of this measure are as follows. If only one binary pattern occurs in the whole sequence, $S(N)=0$. If all $2^N$ patterns are equally distributed in the sequence, i.e. the probability is $\hat{p}=1/2^N$ for all patterns, then $S(N)=1$. This means that all *N* bits are needed to describe the whole binary sequence properly.
According to the pattern length of the BinApEn algorithm, a length (i.e. embedding dimension) of $N=5$ symbols for the subsequences is used. Keeping in mind that each 10-

minute interval contains approximately 800 heart beats, this guarantees a proper estimation of the probabilities of all $2^5 = 32$ binary subsequences. Deviations from identical distribution of all binary patterns are observed more easily than for shorter or longer pattern lengths. In the following this entropy estimation will be referred to as 'BinShan'.

### Surrogate data

The properties of binary sequences generated from heart period dynamics are still unknown. It is not known whether nonlinear properties can be found in such binary sequences or if it can be fully described with the help of linear methods. In other words, does the sequence of acceleration and deceleration of heart periods already contain nonlinearities or is the nonlinear information only revealed if the absolute RR intervals are taken into account? In order to answer this question we use an iterative scheme introduced by Schreiber et. al. (27) to produce surrogate data. At the moment, this method seems to be the best choice of all randomization techniques, preserving almost all linear properties of the original time series with relatively low computational costs. In contrast to other techniques, the iterative scheme not only retains the mean and the standard deviation (i.e. the distribution), but also maintains the power spectrum (i.e. the autocorrelations) of the original time series (relative error <0.1%). All other properties are randomized. Thus the surrogate data cannot be distinguished from original data with any linear measure of HRV.
In this study surrogate data were constructed for each 10-minute interval of all 24h-ECGs, and in a second step the binary sequences were generated as described above. If the binary sequences derived from original data contain nonlinear properties, the estimation of BinApEn and BinShan should reveal differences between the original and surrogate data.

### Statistics

Dependencies between two variables were quantified by Pearson's correlation coefficient *r*. The dependence between mean BinApEn vs. mean RR and Shannon entropy vs. mean RR was quantified by the linear regression $y = a \cdot x + b$. To test the hypothesis that nonlinear components are still observable in the binary sequences, the distribution of differences between original and surrogate data of slopes and correlation coefficients was used. The probability of rejecting the null-hypothesis that no difference is observable was calculated with Student's t-test and p<.05 was considered statistically significant.

## Results

### Approximate entropy

The results for BinApEn of all 236 24-hour ECGs were examined visually by plotting mean BinApEn against mean RR interval (<RR>) of each 10-minute interval. Figure 2a shows an example (subject PO101A). A linear dependency between mean BinApEn and <RR> is observable: the longer the RR interval, the higher mean BinApEn and hence, the more irregular the binary patterns. The correlation between mean BinApEn and <RR> yielded $r = 0.84$. Generally, we found this dependence in all 24h-ECGs. In figure 3a and 4a the distributions of slopes and correlation coefficients of all ECGs are shown. The distribution of correlation coefficients has a mean of $r = 0.78$ showing strong correlation between mean BinApEn and <RR> in all ECGs. Thus a proper evaluation of linear regression was guaranteed. The distribution of the slopes yielded a mean slope of $a = 4.21 \cdot 10^{-1}\,[1/\mathrm{s}]$.

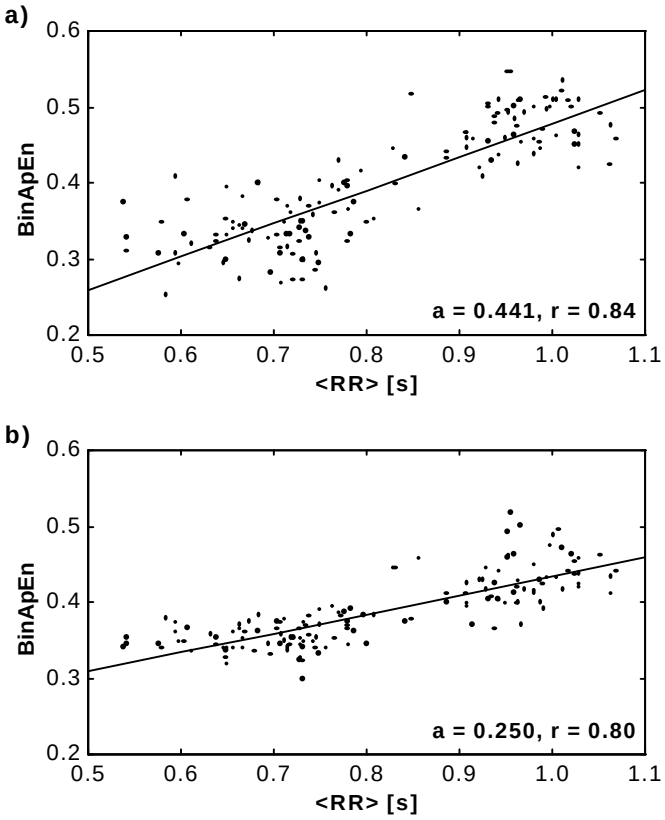


**Fig. 2** Mean BinApEn of 10-minute sequences vs. <RR> of original data (a) and surrogate data (b). Solid line shows linear regression with slope *a*. *r* indicates Pearson's correlation coefficient.

Next, we evaluated BinApEn for the surrogate data in a similar fashion. At first glance the slope of the linear dependence in figure 2b is less steep, *a* and *r* are smaller than that of the original data. However, the distribution of correlation coefficients as depicted in figure 4b shows that the mean coefficient ($r = 0.73$) of the surrogate data is only slightly lower than that of the original data. The distribution of paired differences of correlation coefficients between original and surrogate data has a mean of 0.05 ($p<0.0001$). Thus surrogate data showed a linear dependence to a slightly lesser extent but it is still feasible to evaluate linear regression slopes. On the other hand, the distribution of slopes of all surrogate data as shown in figure 3b revealed a clear reduction of the mean slope ($a = 2.87 \cdot 10^{-1}\,[1/\mathrm{s}]$). The distribution of paired differences of slopes between original and surrogate data has its mean at $1.35 \cdot 10^{-1}\,[1/\mathrm{s}]$ showing a clear deviation from zero mean ($p<0.0001$).

We point out that the evaluation of the linear regression depends on the correlation between mean BinApEn and <RR>. Consequently, the decrease of the slope of the linear regression for the surrogate data is partly due to a decrease in the correlation between mean BinApEn and <RR>.

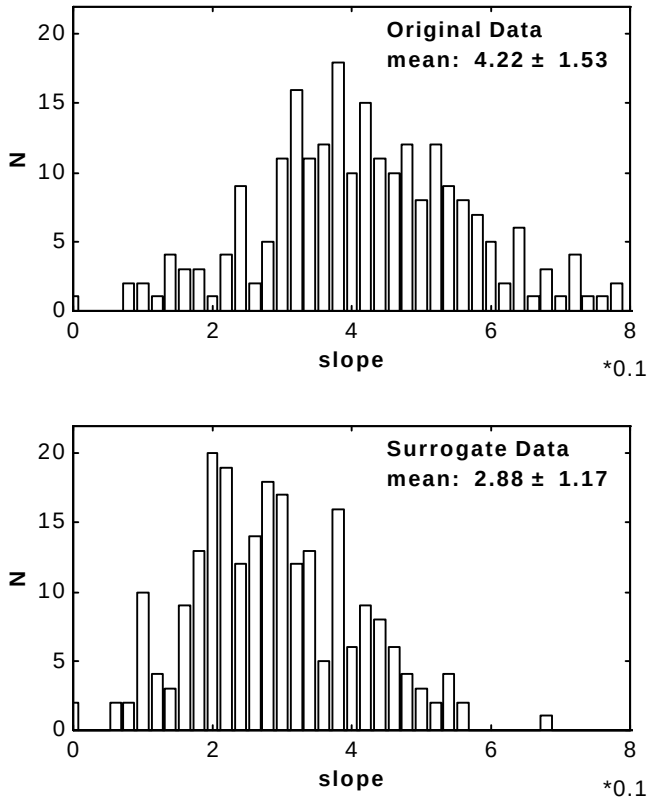


**Fig. 3** Distribution of slopes of linear regression evaluated from mean BinApEn vs. <RR> of all subjects for original data (a) and surrogate data (b).

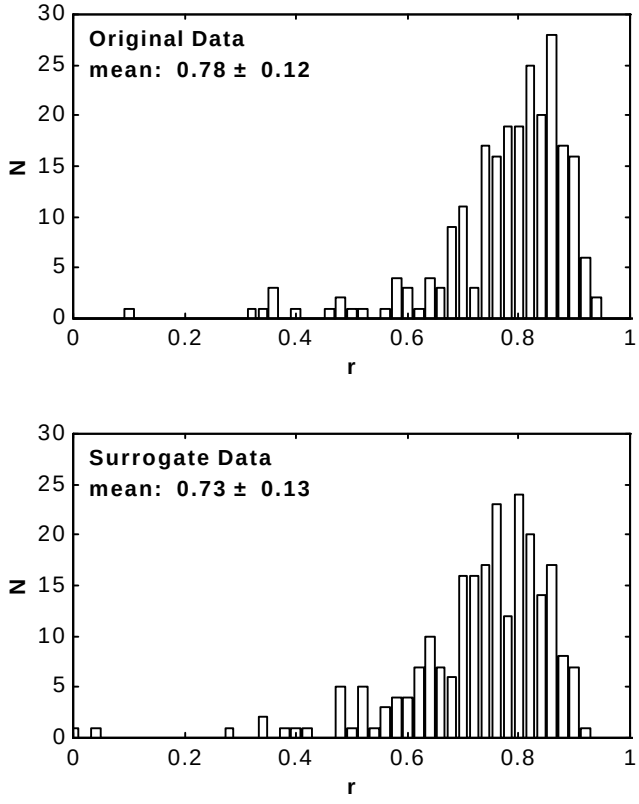


**Fig. 4** Distribution of Pearson's correlation coefficients of mean BinApEn vs. <RR> of all subjects evaluated for original data (a) and surrogate data (b).

**Shannon entropy**

An example of BinShan of 10-minute intervals plotted against <RR> is depicted in figure 5a (subject PO101A). Overall, in all ECGs, as <RR> increased BinShan decreased. This implies that shorter <RR> could be associated with more equally distributed binary patterns. The mean value of *r* (figure 7a, $r = -0.56$) guaranteed a proper evaluation of linear regression. The distribution of slopes yielded a mean of $a = -2.32 \cdot 10^{-1}\,[1/\mathrm{s}]$ (figure 6a).

For the surrogate data, values of BinShan are generally increased as shown in figure 5b. Thus a less marked difference between short and long <RR> was observable and hence, *r* is reduced (figure 7b, mean $r = -0.42$). The distribution of slopes was shifted to higher values (mean $a = -1.04 \cdot 10^{-1}\,[1/\mathrm{s}]$, figure 6b). The distribution of paired differences of slopes showed a clear deviation from zero mean (mean $a = -1.28 \cdot 10^{-1}\,[1/\mathrm{s}]$, p<0.0001).

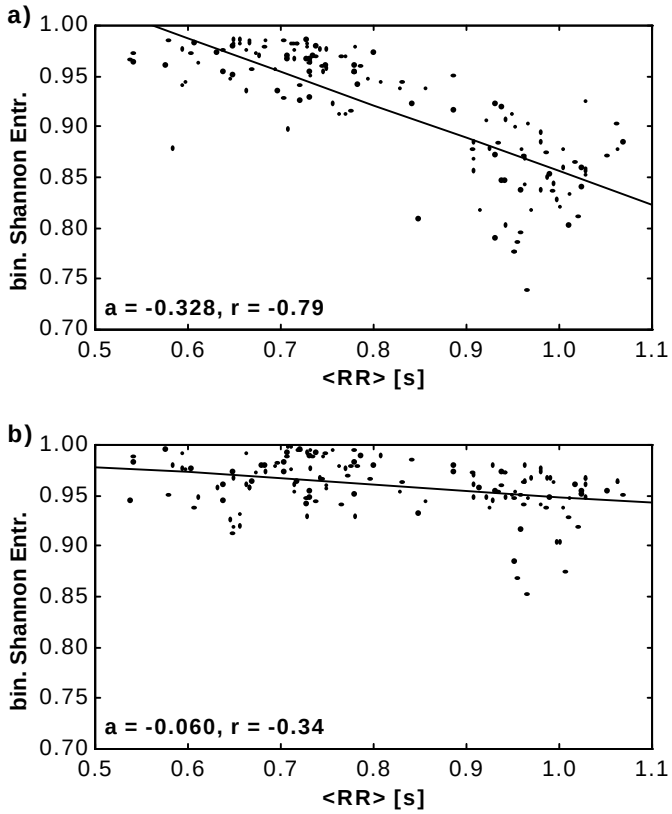


**Fig. 5** Shannon entropy of 10-minute sequences vs. <RR> of original data (a) and surrogate data (b). Solid line shows linear regression with slope *a*. *r* indicates Pearson's correlation coefficient.

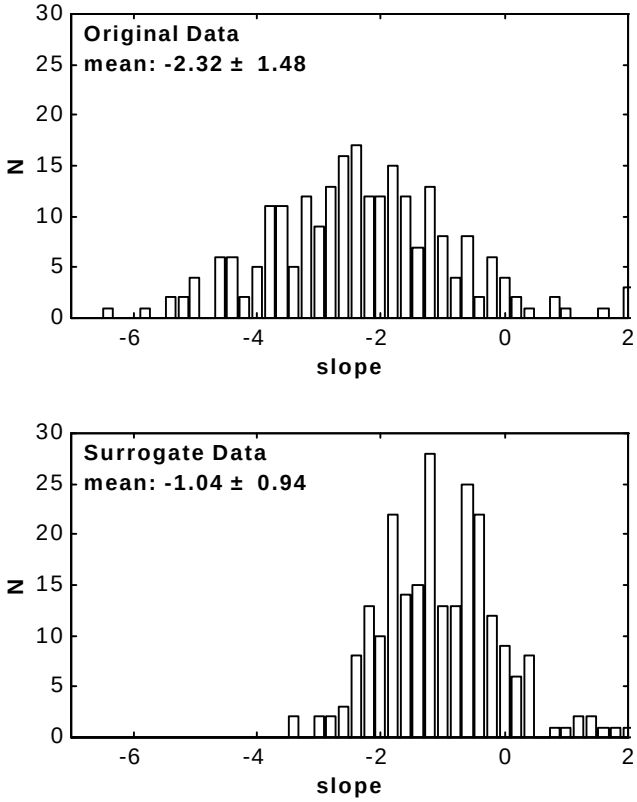


**Fig. 6** Distribution of slopes of linear regression evaluated from binary Shannon entropy vs. <RR> of all subjects for original data (a) and surrogate data(b).

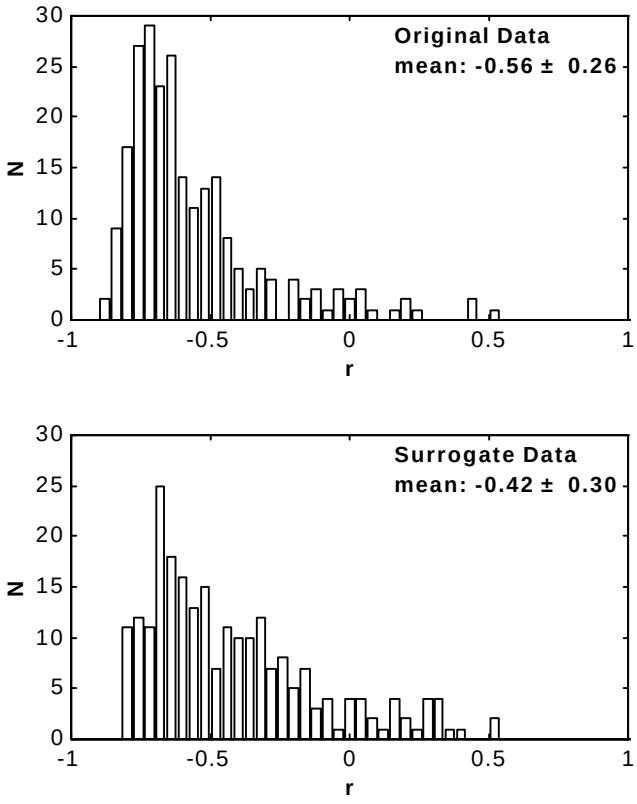


**Fig. 7** Distribution of Pearson's correlation coefficients of binary Shannon entropy vs. <RR> of all subjects evaluated for original data (a) and surrogate data (b).

**Reproducibility of BinApEn and BinShan**

Two consecutive 24h-ECGs were available for each subject. The slopes of linear regression of each subject are used to estimate the reproducibility. The slopes of each subject of ECG A are plotted against those of ECG B (figure 8). Both entropies yielded strong correlation between the slopes of both days (BinApEn: $r = 0.78$, BinShan: $r = 0.85$). This implies a good intraindividual reproducibility of BinApEn and BinShan. As the slopes showed a broad distribution this result may also imply that each subject has its specific slope of linear regression.

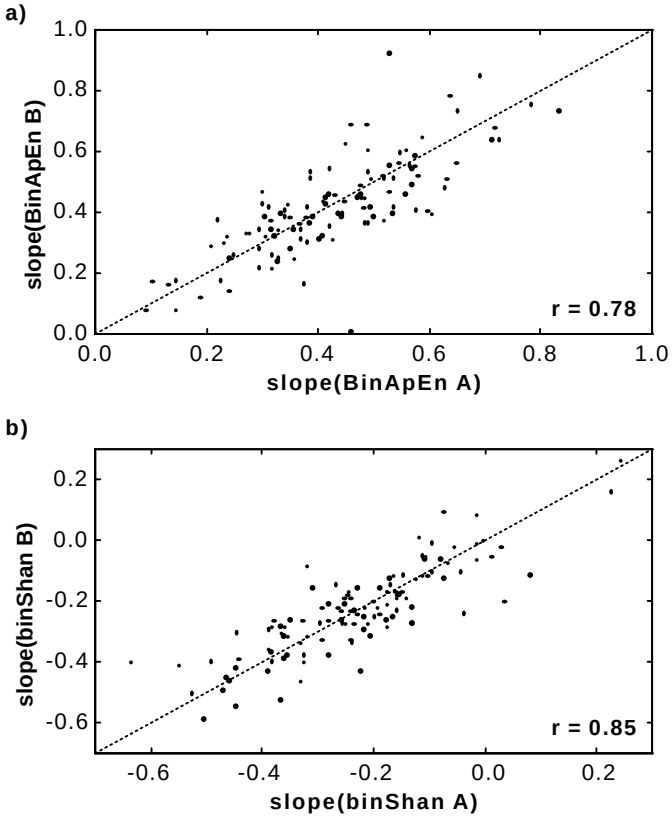


**Fig. 8** a) Slopes of linear regression of BinApEn (ECG A) vs. slopes of linear regression of BinApEn (ECG B). b) Slopes of linear regression of binary shannon entropy (ECG A) vs. slopes of linear regression of binary shannon entropy (ECG B). Streaked line indicates optimal reproducibility.

# Discussion

We used binary sequences derived from RR tachograms of 24-hour ECG recordings that retain only basic dynamical aspects of the RR tachogram, i.e. the acceleration (symbol 0) and deceleration (symbol 1) of heart beat, to estimate approximate and Shannon entropy. This kind of dynamic symbolization allowed the examination of stationary as well as many nonstationary segments because the symbolization of differences between RR intervals eliminates nonstationarities resulting from a minor bias underlying the RR tachogram. We did not calculate entropy estimations using a static symbolization (e.g. using the mean RR interval: all RR intervals above this level are set to 1's and the others are set to 0's). In the literature this kind of transformation is used to detect so-called 'forbidden words', i.e. patterns

in successive RR intervals, that might be of interest in certain cardiac diseases (11;32-34). In the context of entropy estimations established in this study, the latter transformation is not useful because it often yields long chains of 1's or 0's in nonstationary sequences resulting in minimal entropy estimations for BinApEn and BinShan that might be interpreted spuriously.

Evaluation of mean BinApEn of each 10-minute interval exhibits two properties: it strongly correlated with mean RR interval and it was well reproducible for each subject. Mean BinApEn demonstrated that short binary patterns were most regular at short RR intervals and displayed more irregularity with increasing RR intervals. BinShan was maximal for shorter RR intervals indicating that all binary patterns occur with almost the same probability, and was minimal for longer RR intervals exhibiting predominance of certain binary patterns which may result from phase locking with the respiratory rhythm (see below).

We point out that BinApEn and BinShan deal with two different notions of regularity. BinApEn quantifies the regularity of short binary patterns whereas BinShan quantifies the regularity of the occurrence of the binary patterns. Thus the two notions complement each other.

Considering only Shannon entropy would lead to the conclusion that the general behaviour of heart period dynamics seems to be more regular at longer RR intervals in the sense that the certain binary patterns predominantly occur whereas other patterns tend to disappear. On the other hand the results of BinApEn indicate that for long RR intervals the binary patterns in heart period dynamics were those with highest irregularity. Combining these findings, we can conclude that although fewer distinct patterns occurred at longer RR intervals, these patterns were precisely those reflecting greater irregularity. In other words: at longer RR intervals irregular patterns of heart period dynamics appeared more regularly.

Although we did not differentiate between day time and night time (or sleep stages) we note that long RR intervals are likely to appear at night while short ones appear during the day. This is illustrated in figure 2 where two distinct regions are separated at a mean RR interval of approximately 0.85 s. This leads to the conclusion that at night fewer distinct dynamical patterns of the RR intervals occur more regularly, but the dynamics of these patterns is more irregular than during the day.

This finding fills the gap between findings of two former studies conducted in our laboratory. Using the full information of RR interval lengths for the evaluation of ApEn, we could demonstrate that heart period dynamics is more irregular at night than during the day, and that the change from day to night or vice versa is probably accompanied by a phase transition in the notion of synergetics (i.e. no linear dependence on mean RR interval length) (2). In a recent study we emphasized that at night cardiac dynamics reveals a predominance of binary patterns which can be assigned to distinct frequency ratios or even phase locking with some other modulating rhythm, e.g. respiratory rhythm (e.g. 4:1, 7:2, 5:1) (1). For example, if 5:1 phase locking is present the binary pattern 11001 must occur predominantly and cyclically recurrent. This predominance was interpreted as an increase of heart period regularity and an augmentation of musical rhythmicity in cardiac dynamics. In the present analysis, this pattern was identified as one of the most irregular patterns, i.e. with the highest value of BinApEn (20) leading to high values of mean BinApEn. Thus the predominance of binary patterns that result from frequency or phase locking ratios may still lead to strong irregularities within the binary patterns. We point out that synchronization in physiological systems is most often an intermittent phenomenon, detectable during short periods of time with changing locking ratios (26;29). A further distinction of irregularities between synchronized and non-synchronized sequences has still to be established.

The use of surrogate data resulted in a reduction of the slopes of the linear regression between mean BinApEn and mean RR intervals. For short RR intervals mean BinApEn slightly increased and for long RR intervals mean BinApEn slightly decreased. The values of mean BinApEn of binary sequences generated from completely random sequences (independent

identical distribution) tend to the value of $\approx 0.37$. (Note that by construction, purely random sequences are not maximally irregular in the sense of BinApEn, see e.g. (19).) This indicates that the randomization procedure destroyed some inherent nonlinear properties because the values of mean BinApEn tended towards the stated value although almost all linear properties were kept constant. The results for BinShan of the surrogate data can be interpreted in a similar fashion. In conclusion, the dynamical properties under consideration cannot solely be described with linear methods but also show evidence of nonlinearities. Moreover, even binary sequences contain nonlinear properties that cannot be described with measures of HRV derived from linear time series analysis.

By focussing on the beat-to-beat acceleration and deceleration of heart periods, only fast-modulating rhythms in heart period dynamics are captured, i.e. changes in heart periods due to respiratory sinus arrhythmia (RSA) and other parasympathetic activity. The effects of slower rhythms that influence the heart periods, e.g. the blood pressure or slower variations can be neglected because they only give rise to a bias underlying the fastest modulation. These modulations only affect the symbolization scheme if the bias exceeds the modulations of the RSA. Hence, our results are primarily attributed to the vagal activity on the cardiac system. It is well known that the vagal influence shows a circadian pattern with an increasing strength at night (4). This is in accordance with the aforementioned binary pattern types that occur predominantly at longer RR intervals and may indicate frequency or phase locking between heart beat and respiration, but reveal at least certain frequency ratios between these two interacting systems. Keeping our results in mind, the interpretation of a HRV power spectrum can be extended. On the one hand, a pronounced modulation of heart periods by RSA causes high power in the respiratory frequency band. This implies that the heart periods are modulated more regularly. On the other hand, the same modulation may result in more irregular patterns of heart period dynamics attributing to an increase of complexity.

Moreover, the entropies of binary heart period dynamics turned out to be highly reproducible for each subject. This fact supports the findings that each healthy individual maintains the dynamical properties of the heart periods at least over two days (1). Further investigations may show how these properties depend on age and are affected by cardiovascular and autonomic diseases.

In conclusion, the findings of this study have demonstrated that the binary symbolization of RR interval dynamics, which at first glance seems to be an enormous waste of information, gives an important key to a better understanding of normal heart period regularity. Furthermore, differential binary symbolization still enables the identification of nonlinear dynamical properties.

**Acknowledgements**

H.B. and D.C. acknowledge financial support from the Weleda AG, Schwäbisch Gmünd, Germany.

# References

1. Bettermann, H., D. Amponsah, D. Cysarz, and P. Van Leeuwen. Musical rhythms in heart period dynamics - a cross-cultural and interdisciplinary approach to cardiac rhythms. *Am. J. Physiol.* 277: H1762-H1770, 1999.

2. Bettermann, H. and P. Van Leeuwen. Evidence of phase transitions in heart period dynamics. *Biol. Cybern.* 78: 63-70, 1998.

3. Costa, M., I.R. Pimentel, T. Santiago, P. Sarreira, J. Melo, and E. Ducla-Soares. No evidence of chaos in the heart rate variability of normal and cardiac transplant human subjects. *J. Cardiovasc. Electrophysiol.* 10: 1350-1357, 1999.

4. Coumel, P., P. Maisonblanche, and D. Catuli. Heart rate and heart rate variability. In: *Heart rate variability*, edited by M. Malik and A.J. Camm. Armonk: Futura Publishing, 1995, p. 207-221.

5. Cysarz, D., T. Schürholz, H. Bettermann, and H.C. Kümmell. Evaluation of modulations in heart rate variability caused by a composition of herbal extracts. *Arzneimittelforschung* accepted for publication.

6. Eckberg, D.L. Sympathovagal balance: A critical appraisal. *Circulation* 96: 3224-3232, 1997.

7. Glass, L. Chaos and heart rate variability. *J. Cardiovasc. Electrophysiol.* 10: 1358-1360, 1999.

8. Hao, L. Symbolic dynamics and characterization of complexity. *Physica D* 51: 161-176, 1991.

9. Houle, M.S. and G.E. Billman. Low-frequency component of the heart rate variability spectrum: a poor marker of sympathetic activity. *Am. J. Physiol.* 276: H215-H223, 1999.

10. Kantz, H. and T. Schreiber. *Nonlinear time series analysis*. Cambridge: Cambridge University Press, 1997.

11. Kurths, J., A. Voss, P. Saparin, A. Witt, H.J. Kleiner, and N. Wessel. Quantitative analysis of heart rate variability. *Chaos* 5: 88-94, 1995.

12. Lanza, G.A., V. Guido, M.M. Galeazzi, M. Mustilli, R. Natali, C. Ierardi, C. Milici, F. Burzotta, V. Pasceri, F. Tomassini, A. Lupi, and A. Maseri. Prognostic role of heart rate variability in patients with a recent acute myocardial infarction. *Am. J. Cardiol.* 82: 1323-1328, 1998.

13. Makikallio, T.H., S. Hoiber, L. Kober, C. TorpPedersen, C.K. Peng, A.L. Goldberger, and H.V. Huikuri. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am. J. Cardiol.* 83: 836-839, 1999.

14. Makikallio, T.H., T. Ristimae, K.E.J. Airaksinen, C.K. Peng, A.L. Goldberger, and H.V. Huikuri. Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. *Am. J. Cardiol.* 81: 27-31, 1998.

15. Makikallio, T.H., T. Seppanen, M. Niemela, K.E.J. Airaksinen, M.P. Tulppo, and H.V. Huikuri. Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous myocardial infarction. *J. Am. Coll. Cardiol.* 28: 1005-1011, 1996.

16. Malik, M. Heart rate variability standards - Response. *Circulation* 95: 281, 1997.

17. Malik, M., J.T. Bigger, A.J. Camm, R.E. Kleiger, A. Malliani, A.J. Moss, and P.J. Schwartz. Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and Clinical Use. *Circulation* 93: 1043-1065, 1996.

18. Pincus, S. Approximate entropy (ApEn) as a complexity measure. *Chaos* 5: 110-117, 1995.

19. Pincus, S. and R.E. Kalman. Not all (possibly) "random" sequences are created equal. *Proc. Natl. Acad. Sci. U.S.A.* 94: 3513-3518, 1997.

20. Pincus, S. and B.H. Singer. Randomness and degrees of irregularity. *Proc. Natl. Acad. Sci. U.S.A.* 93: 2083-2088, 1996.

21. Pincus, S.M. Approximate entropy as a measure of system complexity. *Proc. Natl. Acad. Sci. U.S.A.* 88: 2297-2301, 1991.

22. Pincus, S.M. Quantification of evolution from order to randomness in practical time series analysis. *Methods Enzymol.* 240: 68-89, 1994.

23. Pincus, S.M., I.M. Gladstone, and R.A. Ehrenkranz. A regularity statistic for medical data analysis. *J. Clin. Monit.* 7: 335-345, 1991.

24. Pincus, S.M. and A.L. Goldberger. Physiological time-series analysis: What does regularity quantify? *Am. J. Physiol.* 266: H1643-H1656, 1994.

25. Schäfer, C., T. Plesser, and H.H. Abel. Methodology for analysis of binary sequences in heart rate. *Wien. Med. Wochenschr.* 145: 521-522, 1995.

26. Schäfer, C., M.G. Rosenblum, J. Kurths, and H.H. Abel. Heartbeat synchronized with ventilation. *Nature* 392: 239-240, 1998.

27. Schreiber, T. and A. Schmitz. Improved surrogate data for nonlinearity tests. *Phys. Rev. Lett.* 77: 635-638, 1996.

28. Schurmann, T. and P. Grassberger. Entropy estimation of symbol sequences. *Chaos* 6: 414-427, 1996.

29. Seidel, H. and H. Herzel. Analyzing entrainment of heartbeat and respiration with surrogates. *IEEE Eng. Med. Biol. Mag.* 17: 54-57, 1998.

30. Taylor, J.A. and L.A. Lipsitz. Heart rate variability standards. *Circulation* 95: 280-281, 1997.

31. Van Leeuwen, P., S. Lange, H. Bettermann, D. Gronemeyer, and W. Hatzmann. Fetal heart rate variability and complexity in the course of pregnancy. *Early Hum. Dev.* 54: 259-269, 1999.

32. Voss, A., K. Hnatkova, N. Wessel, J. Kurths, A. Sander, A. Schirdewan, A.J. Camm, and M. Malik. Multiparametric analysis of heart rate variability used for risk stratification among survivors of acute myocardial infarction. *Pacing Clin. Electrophysiol.* 21: 186-192, 1998.

33. Voss, A., J. Kurths, H.J. Kleiner, A. Witt, and N. Wessel. Improved analysis of heart rate variability by methods of nonlinear dynamics. *J. Electrocardiol.* 28: 81-88, 1995.

34. Voss, A., J. Kurths, H.J. Kleiner, A. Witt, N. Wessel, P. Saparin, K.J. Osterziel, R. Schurath, and 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: 419-433, 1996.