Characterization of complex heart rate dynamics and their pharmacological disorders by non-linear prediction and special data transformations

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Abstract

Objective: The aim of the presented method was the characterization of different complex heart rate dynamics in conscious rabbits as well as during general anaesthesia and vagal blockade. This was done by non-linear prediction of original measured and special surrogate data in the phase space. Method: The development of the prediction error in dependence on the prediction time interval was investigated in the phase space. Two kinds of surrogate data were produced and tested with regard to non-linearities and orientation in the phase space. Typical characteristics of prediction error development were shown for simulated uncorrelated stochastic, correlated stochastic, regular deterministic, and deterministic chaotic signals. These characteristics were used to evaluate the measured heart rate data in connection with tests of surrogate data. Results: It could be shown that heart rate fluctuation cannot be described by one of these ideal models alone. Common consideration of all investigated prediction characteristics indicated chaos in the heart rate of conscious rabbits as well as during anaesthesia and vagal blockade, where non-linear correlated stochastic properties could not be excluded. The different amount of non-linearities and orientation was described quantitatively. Conclusions: Detailed analysis of prediction error development in the phase space, connected with tests for non-linearities and orientation, enabled a specific quantitative characterization of complex heart rate dynamics and their pharmacological disorders.

Keywords: Heart rate variability; Non-linear phenomena; Autonomic nervous system; Rabbit, anesthetized

1. Introduction

In healthy subjects the time courses of the heart rate show irregular behaviour which changes to become more regular according to functional limitations because of anaesthesia and particular blockades of the autonomous nervous system [1–5]. It could be shown that the seemingly stochastic behaviour of the heart rate fluctuations is caused by dynamic non-linear processes [6,7].

Positive Lyapunov exponents and non-integer correlation dimensions, which are estimated from measured time series such as heart rate fluctuations (HRF), can be based on different deterministic (chaotic) or stochastic processes [8–10]. The characteristics of the underlying process which are to be distinguished as far as possible are linearity and non-linearity, and more specifically regular determinism, deterministic chaos or different stochastic properties. A quantitative description of corresponding signal properties is needed, in particular for the classification of different pharmacological states.

Theiler et al. [11] proposed a test for non-linearity by comparing particular characteristics such as the correlation dimension, the forecasting error or the leading Lyapunov exponent of the original time series with those of phase-randomized versions of the original time series.

Kennel and Isabella [12] proposed a distinction between chaos and coloured noise on the basis of a forecasting...
Sugihara and May [13] found that the development of the forecasting error is different in chaotic and uncorrelated stochastic time series, but that it cannot necessarily distinguish between chaos and coloured noise.

Tsonis and Elsner [14] calculated a prediction error parameter which depends linearly on the prediction time, but only in chaotic time series. However, in correlated stochastic (fractal) time series they found a double logarithmic dependency between the prediction error parameter and the prediction time. This dependency is related to the Hurst coefficient, which is a scaling measure of fractal signals.

Kaplan [15, 16] proposed a search for the particular orientation of the trajectory and coarsed-grained embedding as tools for indicating determinism in phase space sets.

In spite of these impressive approaches a clear differentiation between chaotic and non-linear correlated stochastic processes seems to be problematic in measured time series such as the HRF. Furthermore, it can be expected that the underlying physiological processes do not match exclusively with only one of these mathematical aspects.

The aim of the present study was to analyse different non-linear characteristics of normal and pharmacologically disturbed HRF. Corresponding to the approaches referred to above, the representation of the time series in a multi-dimensional phase space forms an appropriate basis to investigate complex non-linear dynamics. We investigated prediction error development in the multi-dimensional phase space sets for different simulated signals with typical characteristics in comparison to measured heart rate data. Surrogate data sets were used to test for non-linearities and orientation in the phase space.

2. Methods

2.1. Experimental design and measurement

Six adult rabbits (White New Zealand, body weight 2.6–3.8 kg) were anaesthetized by i.m. injection of 22 mg/kg ketamine and 4 mg/kg xylazine. A selective vagal blockade was performed by s.c. injection of 3 mg/kg atropine. The corresponding states investigated were: S1-conscious, S2-general anaesthesia, and S3-vagal blockade (atropine during general anaesthesia). Body temperature (rectal thermocouple) and arterial pressure were recorded continuously. Arterial blood samples were withdrawn for a blood gas and acid-base state check. The ECG was obtained with a standard AC amplifier, and care was taken to record an analog signal with a prominent and positive R-wave that decreased the likelihood of errors in the following steps. After suitable amplification, the ECG was fed through an analog-to-digital (A/D) converter (DT2821, Data Translation, Inc., Marlboro, MA, USA) with a sample rate of 4096 Hz to the mass memory of the personal computer. Then the individual R-waves, with the steepest R-wave rise as the fiducial point, are sequentially recognized, and thus the series of R-R intervals is stored as a function of the beat sequence. This series constitutes the tachogram. The reciprocal of this series represents the instantaneous heart rate. Artifact-corrupted data were rejected. Only time series which were stationary during at least 8192 heart beats were investigated. In order to show the different time structures of HRF in S1-S3 in more detail, parts of 100 heart beats are presented in Fig. 1. The mean heart rate did not differ significantly between the states (S1 200 ± 25, S2 175 ± 48, S3 206 ± 47 beats/min).

The experimental investigations conform with the Guide for the Care and Use of Laboratory Animals published by...

![Fig. 1. Heart rate fluctuations, parts of 100 from 8192 heart beats. S1-conscious; S2-general anaesthesia; S3-vagal blockade during anaesthesia (examples).](https://academic.oup.com/cardiovascres/article-abstract/31/3/434/342316/3134342316)
2.2. Simulated data

The measured heart rate data may consist of a mixture of different deterministic and stochastic parts. It cannot be presumed that only one kind of theoretically well-defined signal property will exist. In order to evaluate the proposed method of non-linear prediction and to find relations between the HRF and theoretical characteristics, different signals with typical well-defined characteristics were simulated. Data length \((N = 8192)\) and amplitude normalization were chosen identical to the heart rate data.

**Regular deterministic data.** Regular deterministic time series were simulated by sinus waves.

**Deterministic chaotic data.** As a deterministic chaotic time series \(z(t)\) the \(x\)-values of the Henon attractor (leading Lyapunov exponent = 0.419) were used:

\[
x_{t+1} = 1 - 1.4x_t^2 - y_t, \quad y_{t+1} = 0.3x_t
\]

**Uncorrelated stochastic (random) data.** Uncorrelated stochastic time series were simulated according to Knuth [17].

**Correlated stochastic data.** The \(1/f\) power law spectra which are found in heart rate data [5,7] indicate statistically self-similar behaviour which is a special case of correlated stochastic signals. We simulated a corresponding time series \([z(t)]\) by superposition of harmonic waves with corresponding scaled amplitudes \([P(\omega)]\) and random phases \((\varphi)\):

\[
z(t) = \sum_{i=1}^{m} \sqrt{P(w_i)} \Delta w_i \cos(w_it + \varphi_i)
\]

with \(P(\omega_i) = 1/\omega_i^\alpha\), \(\alpha = 0.5\) scaling parameter; \(\omega_i = 2\pi i/N\Delta t\), \(N = \) data length, \(\Delta t = \) sampling rate; \(0 < \varphi < 2\pi\), \(\varphi = \) uniformly distributed, \(m = N/2\). This special kind of correlated stochastic signal is called “fractal.”

2.3. Phase space reconstruction

The phase space sets were constructed from the time series \(z(t)\) according to Takens' theorem [18]. The coordinates of the points \(P(t)\) in the phase space are the time-delayed values of the time series:

\[
P(t) = \{z(t), z(t+\tau), z(t+2\tau), \ldots, z(t+(D_e-1)\tau)\},
\]

\(t = 1, 2, 3 \ldots (N-D_e)\)

\(N\) is the number of data points \(P\) in the phase space. The embedding dimension \((D_e)\) is the number of coordinates of the phase space which is equal to the number of time-delayed values of the time series. A one-to-one map of a smooth time series needs \(D_e \geq 2D + 1\) \((D = \) dimension of the process) [19]. We used a time delay \(\tau\) equal to the time of the decay of the autocorrelation function to \(1/e\) according to Albano et al. [20]. The embedding dimension \((D_e)\) was increased until the estimated parameters became approximately constant.

2.4. Estimation of the mean prediction error \((E_m)\)

We investigated the prediction errors in dependency on the prediction time in the multi-dimensional phase space. Beginning from a starting point \(P(t_0)\), the nearest Euclidean neighbour is searched for in the phase space. Its distance is \(L(t_0)\). The distance \(L(t_0 + \Delta t)\) between the developed points (after passing the prediction time interval \(\Delta t\)) is taken into account in order to estimate the prediction.
error \( E_i \). This procedure is repeated for every point \( P(t_i) \). The single prediction errors \( E_i \) are estimated by:

\[
E_i = \log_2 \frac{L(t_i + \Delta t)}{L(t_i)}
\]

(4)

The mean prediction error \( E_m \) can be estimated as the mean value of all prediction errors \( E_i \) by:

\[
E_m = \frac{1}{N - \Delta t} \sum_{i=1}^{N-\Delta t} E_i
\]

(5)

The mean prediction error \( E_m \), normalized to the prediction time interval \( \Delta t \), is an approximation of the leading Lyapunov exponent, if \( N \), \( D_e \), and \( \Delta t \) are optimal [21].

We investigated \( E_m \) for data sets of 8192 points in dependence on the prediction time interval \( \Delta t \) (Figs. 2-5, filled squares). In uncorrelated stochastic data the prediction errors are uniformly distributed over the simulated region of data values (Fig. 3). Consequently, no dependency of \( E_m \) on \( \Delta t \) was found. The linear relation between \( E_m \) and \( \Delta t \) over a particular prediction time region is caused by the exponential divergence of infinitesimal neighbouring pathways. This is typical of the short-time prediction of deterministic chaotic signals (Fig. 4). In the regular deterministic signal, there is obviously a vanishing prediction error (Fig. 5).

In the simulated correlated stochastic signal, the dependency between \( E_m \) and \( \Delta t \) is logarithmic (Fig. 6). According to Sugihara and May [13] the linear dependency between the logarithmic prediction error \( E_m \), Eq. (4) and the logarithm of \( \Delta t \) could be caused by the scaling properties of this fractal signal. We found an increasing prediction error \( E_m \) depending on a decreasing scaling parameter \( \alpha \) (Eq. 2). In this section we could show different typical relations between \( E_m \) and \( \Delta t \) in the simulated signals with different ideal characteristics. Non-linearities and orientation in the phase space were investigated by means of special transformations of these data.

2.5. Test for non-linearities (phase randomization)

Theiler et al. [11] proposed a comparison of the analysis of the original (measured) data with that of phase-randomized surrogate data sets which have the same linear properties but removed non-linear relations. If appropriate measures were statistically different, there would be evidence of non-linearity in the original data. In the present investigation the differences between the prediction errors \( E_m \) of the original and the corresponding surrogate data sets were tested. If it is supposed that the surrogate data sets are linear and stochastic, the rejected null hypothesis indicates non-linear deterministic (regular deterministic or deterministic chaotic) or non-linear stochastic data [9]. If the estimated prediction error \( E_m \) corresponds to a positive leading Lyapunov exponent, the possibility of regular determinism can be excluded. Consequently, non-linear dynamics such as chaotic or non-linear correlated stochastic processes are present.

The small filled squares in Figs. 3–6 show the \( E_m \) values of the phase-randomized time series in comparison with the original time series. A significant difference indicating particular non-linearities could be found only in the chaotic signal. This is due to the linear properties of the simulated regular deterministic signals and the simulated correlated stochastic (fractal, superposition of scaled sinus waves) signals. The results of the tests for non-linearities of all simulated data are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>( \Delta t )</th>
<th>Uncorr. stochast</th>
<th>Corr. stochast</th>
<th>Reg. deterministic</th>
<th>Determin. chaos</th>
</tr>
</thead>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>&lt; 0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>0.01</td>
<td>0.94 *</td>
<td>0.58 *</td>
<td>&gt; 0.99 *</td>
<td>0.96 *</td>
</tr>
<tr>
<td>Orientation</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.96 *</td>
<td>0.07 *</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \) Paired Wilcoxon rank test [26] (\( n = 6 \) simulations).
2.6. Test for orientation (randomly shuffling the phase space data)

In the original data, the orientation of the points (P) in the phase space is organized by the running time parameter (t). To construct another kind of surrogate data set this parameter t is randomly shuffled. The resulting surrogate data sets consist of the identical points in the phase space but in randomized sequence. Therefore the statistical distribution of the data is not altered. The null hypothesis is now that there is no orientation in the original data. Orientation in the phase space data was found in all data sets with the exception of the uncorrelated stochastic data.

The typical prediction characteristics of the phase-randomized and the randomly shuffled data in comparison with the original data are shown in Figs. 2–5. The results of the tests for orientation of all simulated data are summarized in Table 1.

3. Results

We analysed the heart rate fluctuations of the states S1–S3 according to the analysis of the simulated time series. Particularly in the analysis of measured data the choice of appropriate embedding parameters is important in order to avoid misleading results. We found that \( D < D_c < (2D + 1) \) is advantageous if the data length available is limited. Lower embedding dimensions are not able to consider the essential process characteristics and higher embedding dimensions can lead to statistical problems because of lack of data. With regard to the estimated heart rate dimensions (S1, \( D = 7.15 \pm 0.8 \); S2, \( D = 2.4 \pm 0.7 \), S3, \( D = 1.4 \pm 0.5 \) [7,26]), the data length of \( N = 8192 \) heart beats was necessary to obtain reproducible investigation results (\( N > 10^{(1/2)} \), [22]).

In Figs. 7–9 the dependencies of \( E_m \) on \( \Delta t \) for original, phase-randomized, and randomly shuffled data are shown by typical examples of S1–S3. The significant differences between the original and the surrogate data (Table 2) gave evidence of non-linearities and orientation with regard to the 6 investigated rabbits in all states.

We found a continuous increase of \( E_m \) versus \( \Delta t \) during the short time prediction (\( \Delta t: 1 \rightarrow 2 \)) in all states. The mean slopes \( E_m \) versus \( \Delta t \) were largest in S1 (2.6 \pm 0.4/heart beat), reduced in S2 (1.5 \pm 0.3/heart beat) and once more reduced in S3 (0.82 \pm 0.3/heart beat). Also with regard to the long-time prediction (\( \Delta t: 15 \rightarrow 16 \)) a transition to a lower increase in \( E_m \) was found in all states. There, the mean values found of the slopes \( E_m \) versus \( \Delta t \) were 0.26 \pm 0.06/heart beat in S1, 0.1 \pm 0.02/heart beat in S2, and 0.01 \pm 0.001/heart beat in S3 (Figs. 7–9).

During S1 the highest values for non-linearities and orientation (Table 2) as well as the \( E_m \) versus \( \Delta t \) characteristics (Fig. 7) of heart rate characteristics were mostly similar to that of the chaotic signal. A linear dependency of \( E_m \) versus \( \Delta t \) can be approximated for 3–4 heart beats. This corresponds to the prediction characteristics of ideal chaotic signals [23].

During S2 the characteristics of \( E_m \) versus \( \Delta t \) show a similar relation to that in the conscious state. But the predictibility was significantly increased with regard to the short-time and the long-time prediction (Fig. 8 vs. Fig. 7). The number of non-linearities was significantly decreased. The measure of orientation was not changed during the short-time prediction (Table 2). Corresponding to S1, we...
would emphasize the possibility of a deterministic chaotic underlying process that generates the heart rate fluctuations in S2.

During S3 the number of non-linear characteristics was once more decreased (Table 2) but was nevertheless significant. The decreased amount of orientation in the short-time prediction and the constant $E_m$ in the long-time prediction (as in the uncorrelated random signal) indicates a particular stochastic part in the heart rate fluctuations. It could be concluded that the non-linearities and orientation found in S3 may be caused more probably by a regular deterministic, noise-corrupted process than by a low-dimensional chaotic process.

4. Discussion

The starting point of the present study was that non-integer correlation dimensions and positive leading Lyapunov exponents of heart rate fluctuations were found which were significantly decreased during different pharmacological disturbances. In order to characterize the underlying processes in more detail we investigated the orientation and predictability of their trajectories in the multidimensional phase space. The typical behaviour of this dependency of uncorrelated stochastic (random), correlated stochastic (using the example of a fractal time series), regular deterministic (sinus wave), and deterministic chaotic (Henon attractor) signals was shown using simulated signals. The mean prediction errors are quantitative parameters of the time behaviour of infinitesimal neighbouring points in the phase space.

The investigation of surrogate data which indicated non-linearities and orientation in the multidimensional phase space enabled a furthermore specific description. The quantitative heart rate characteristics found and their changes due to anaesthesia and vagal pharmacological disturbance. Essential non-linearities and orientation in the phase space enabled a furthermore specific description. The typical behaviour of this dependency of uncorrelated stochastic (random), correlated stochastic (using the example of a fractal time series), regular deterministic (sinus wave), and deterministic chaotic (Henon attractor) signals was shown using simulated signals. The mean prediction errors are quantitative parameters of the time behaviour of infinitesimal neighbouring points in the phase space.

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The investigation of surrogate data which indicated non-linearities and orientation in the multidimensional phase space enabled a furthermore specific description. The quantitative heart rate characteristics found and their relations to typical simulated signals allowed some essential conclusions about the underlying processes and their pharmacological disturbance. Essential non-linear characteristics and their changes due to anaesthesia and vagal blockade could be described quantitatively. Common consideration of orientation in the phase space, non-linearities and prediction characteristics gives essential indications of participating chaotic processes. The approach presented here for analysis of orientation in the phase space is partly related to the test for determinism proposed by Kaplan and Glass [15,16]. The assumption of chaos could furthermore be supported by Glass and Malta [25]. They demonstrated a deterministic process which corresponds to the heart rate fluctuations using multi-looped negative feedback.

Determination of the underlying dynamic process of a measured time series without any other information is methodically limited. For instance, a deterministic dynamic system can be approximated by a stochastic Markov chain. Furthermore, Barlett [25] showed a special autoregressive model that produces a stochastic data set as time increases but which, when reversed in time becomes deterministically chaotic. In such cases, it would seem to be a meaningless task to distinguish chaos from correlated noise. Corresponding differences between the underlying physiological processes cannot be distinguished by the resulting measured time series. Furthermore, it should be taken into consideration that the physiological process which generates the heart rate fluctuations cannot be completely separated from any other undefined influences. It is also obvious that the physiological system does not match just one mathematical model exclusively.

Nevertheless, the quantitative measures investigated of the multi-dimensional prediction characteristics in connection with estimation of the amount of non-linearities and orientation gave some impressive information about the complex organization of heart rate fluctuations. It could be shown that there are well-organized non-linear processes, Pharmacologically induced changes in these processes could be characterized by means of appropriate non-linear parameters.

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References


