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PATTERN ENTROPY A TOOL FOR NONLINEAR DYNAMICAL ANALYSIS OF A BIOLOGICAL NONSTATIONARY SYSTEM: THE HUMAN HEART*

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Tools for a nonlinear analysis of the dynamics of the rhythm of the human heart are discussed. Three-dimensional images in the phase space are formed by means of the Takens trajectory reconstruction method of 24-h sequences of time intervals between heart beats (RR intervals). Best projections of these images are sought and a surprising high symmetry is found for some types of pathology. The effects of filtering of arrhythmia on the symmetry is demonstrated. Images of RR intervals are also made in a time window of 100–400 beats and examples of such images preceding cardiac death are given. A new quantitative tool for the analysis of the local time degree of ordering of RR sequences — pattern entropy — is briefly discussed.

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1. Introduction

Analysis of biological systems by means of nonlinear dynamical methods seems to be a challenge of new proportions. This is because the behavior of living systems has the inherent property of nonstationarity. Due to this such methods as fractal analysis — well established in mainline physics and chemistry — when applied to bio-medical systems appear controversial to

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many researchers. Usually these methods simply require too many data points to be able to cope well with nonstationary dynamics.

An area of great interest in medicine is cardiology. In modern routine computer analysis of the action of the heart, several aspects of the electrical potentials (QRS potentials) measured on the surface of the body (electrocardiogram or ECG) are taken into account. One of the most important of these is heart rate variability. This is analyzed by looking at the sequence of time intervals between heart beats (medical term: RR intervals) identified semiautomatically by a computer. Traditionally, either Fast Fourier Transforms are used to identify the frequencies in the signal (frequency analysis) or complicated statistical tools are used to find numbers which may characterize different (pathological or physiological) behavior (time domain analysis). In both types of these extensively researched methods the factor that complicates the analysis is the fact that the heart is activated by two systems: the sympathetic and parasympathetic nervous systems and modified by hormonal action. Occasional extra heart beats make FFT use impossible and the statistics doubtful.

It is well known in cardiology that the extra heart beats have an important effect on the normal heart beat intervals that follow.

We discuss here new nonlinear methods for the analysis of the dynamics of RR intervals in 24 hour electrocardiogram recordings. The approach here is to treat the heart and the systems that drive it as a single nonlinear system. This, however, requires the definition of a tool which is insensitive to the nonstationarity of the signal. To gain this end we do the following.

Three-dimensional images in delay coordinates, formed by way of the theorem by Takens, of medically representative cases of such recordings are analyzed. Similar types of approach have been used in the past [1]. We show that a judicious choice of the projection is of advantage.

A time window is used to scan through the 24 hour recording and bifurcations (abrupt changes in dynamical behavior) in the data are discussed. Images of RR sequences preceding cardiac arrest show a sharp decrease in complexity.

Two new quantitative measures of the complexity of the RR sequence time series — two forms of the pattern entropy of three-dimensional images of the RR intervals — discussed in full elsewhere [2] are briefly defined. These measures differentiate between different cases of pathology and health in medical circumstances such that, often, the frequency and time domain analysis of the RR intervals fail.

2. The data

ECG 24 hour tapes of 24 healthy individuals and of 36 cases of cardiac arrest were analyzed together with 15 patient sex, age and disease status matched control pairs. The data was sampled at 128 Hz and the time distance between consecutive R peaks (the RR intervals) extracted. Each 24 hour long RR intervals time series studied was 80000 to 125000 data points long.

3. Three–dimensional imaging

Three-dimensional images of the return map RR($i+2\tau$) versus RR($i+\tau$) and RR(i), where i is the index of the RR interval and τ is the delay, were formed from the RR interval raw data. We found that the most popular method of defining the length of the delay τ — the position of the minimum of the autocorrelation function — to be very unreliable for the RR interval sequences studied [2]. As a rule of thumb, the delay time should not be too large so that valuable characteristics of the phase space trajectory are not lost in the stretching and folding process which occurs during the time evolution of the system. Note, that the R peaks in the QRS sequence of the ECG signal are a full cycle of heart action away which implies that adjacent points in the RR interval sequence need not be so linearly correlated as in some other (densely sampled) signals. In three dimensions, we found that an integer delay $\tau = 2$ was adequate.

In [2] it was shown that three-dimensional images of 24 hour RR interval sequences in the projections most often used in the literature may be very ambiguous. Different heart ailments like ventricular arrhythmia may be confused, for example, with atrial fibrillation. These medically completely different phenomena when seen in the three dimensional image seem to be only quantitatively different. We studied the three-dimensional images of 24-hour RR interval sequences changing their projection angles. We found that two projections of such images viewed simultaneously give the most unambiguous effect. Fig. 1a and Fig. 1c depicts the RR interval sequence images for the case of ventricular arrhythmia and for the case of atrial fibrillation, respectively — in the most often published by other groups choice of projection. Fig. 1b and Fig. 1d depicts the projection along the axis of these three-dimensional images. It can be seen that there is a definite three-fold symmetry in Fig. 1d (atrial fibrillation) while a much less developed tendency for six-fold symmetry is seen in Fig. 1b (ventricular arrhythmia). It is often discussed whether atrial fibrillation is a random kind of heart action. The well defined three-fold symmetry seen Fig. 1d shows that — although very complex — atrial fibrillation is indeed a very well ordered phenomenon. In fact, the symmetry of this image of atrial fibrillation seems to be extremely robust against filtering. Fig. 2 depicts the effect of a filter which removes all RR intervals which are larger by 20 % from the ones immediately preceding them. It can be seen that no difference in symmetry of the axial projection (Fig. 2b) is obtained.

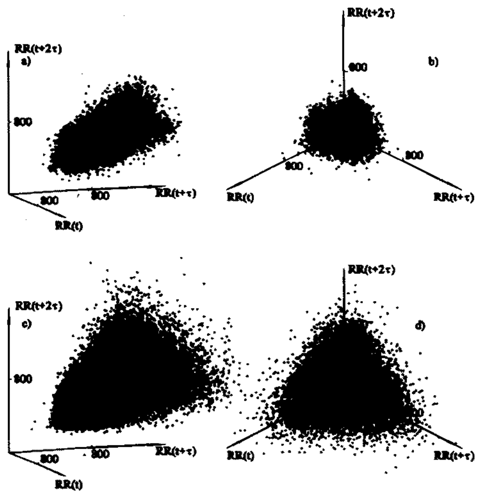

Fig. 1.

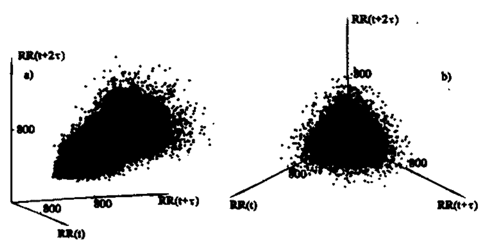

Fig. 2.

The problem with analyzing heart rate variability is that, often, arrhythmia masks the features of the underlying sinus rhythm. An example of well developed arrhythmia of this kind is seen in Fig. 3a and Fig. 3b together with the effect of the 20 % filter (Fig. 3c and Fig. 3d). No symmetry is visible in the three-dimensional images either before or after filtering in this case although the image seen after filtering resembles those obtained for the pure sinus rhythm in individuals considered healthy. On the other hand, there are completely different cases of arrhythmia where a six-fold (Fig. 4a,b — without filtering and Fig. 4c,d — after a 20 % filter was used) or a three-fold symmetry is clearly visible (Fig. 5a,b — without filtering and Fig. 5c,d — after 20% filtering). It can be seen in Fig. 4 that, for such a well ordered arrhythmia, filtering the data has a tendency to change the symmetry from the initial six-fold to a three-fold one.

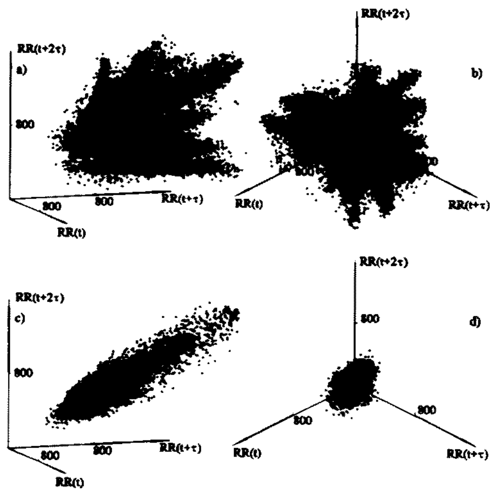

Fig. 3.

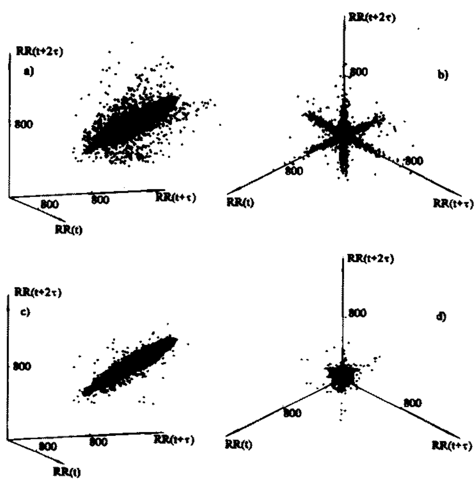

Fig. 4.

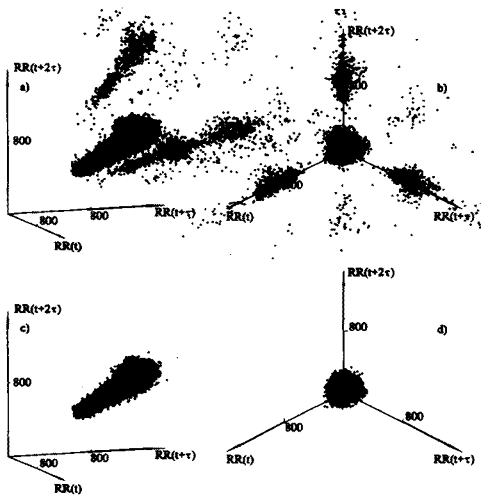

Fig. 5.

We note here that it is most often that a well defined axial symmetry of three-dimensional images of RR sequences is noticed in patients in whom it is known that cardiac arrest occurs rather than in individuals exhibiting arrhythmia but who are otherwise healthy.

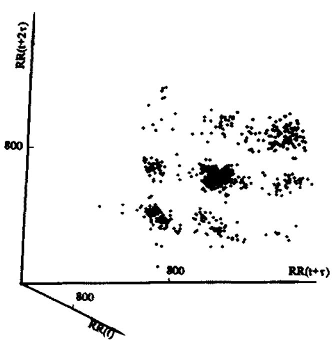

Fig. 6.

We see then that reconstruction of the phase space trajectory of the RR intervals yields a qualitative tool assessing the degree of ordering of the given heart action. The surprising high symmetry we found for many cardiac arrest cases encourages to probe deeper by introducing a time window. Since the heart varies its rate rapidly the window we use is defined in integer time measured in heart beats. This is also well within the spirit of nonlinear dynamics as one heart beat constitutes a complete cycle of the system studied. Among the 6 cases of cardiac arrest cases recorded, in two

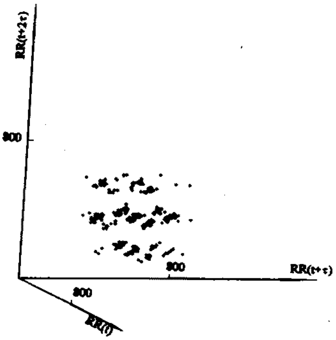

Fig. 7.

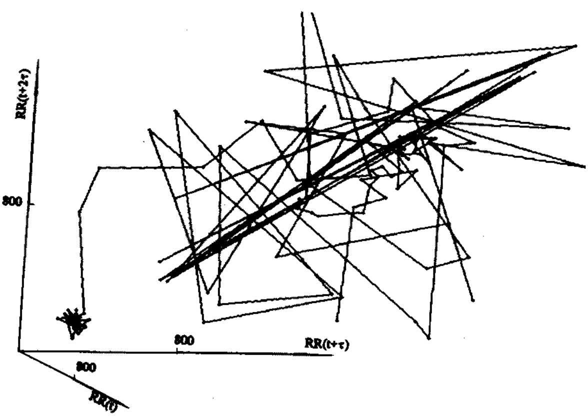

Fig. 8.

cases the image in the time window was found to have a spectacularly insular character. Fig. 6 depicts 800 heart beats which preceded ventricular fibrillation. A similar case which preceded an asystole is seen in Fig. 7 (400 RR intervals). Although not all cardiac arrest cases show such a severe examples of a decrease of heart rate variability it should be stressed that the highly insular character of three-dimensional image was seen only for cases of cardiac arrest. A completely different type of sequence preceding a cardiac arrest event (medically termed "torsade de pointes") is seen in Fig. 8. From these examples it may be seen that images in phase space of short sequences of RR intervals give an additional insight into the nature of the phenomenon of cardiac arrest.

4. Pattern entropy

The high degree of ordering seen in some three-dimensional images of 24 hour RR sequences indicates the need for a quantitative measure allowing a comparison between cases. Previously attempts have been made by other groups [3–5] to use fractal dimension analysis for this purpose. Our experience with calculations of such type in well behaved physical systems and the problems which such calculations pose [7] made us look for an alternative measure. We first calculated the histogram of RR interval lengths within a given time window length (measured in the number of beats). We used 25 ms for histogram box size. Next, we divided the histogram by the total number of beats in window (*i.e.* window length) to obtain the probability $p(\mathrm{RR}(i))$ of the RR interval falling within the i-th histogram box.

We used Shannon information entropy which is defined as:

$$I_p = -\sum_{i=1}^{N} p_i \ln(p)_i$$

but with the joint probability:

$$p_i = p(\mathrm{RR(i)})\mathrm{p}(\mathrm{RR(i} + \tau))\mathrm{p}(\mathrm{RR(i} + 2\tau)).$$

If just the simple probability $p(\mathrm{RR}(i))$ is used for p_i the results are totally misleading: no distinction can be made between a healthy person and a case of pathology [2]. A good prognostic is obtained, however, when the conditional probability given by the formula above is used: $\mathrm{RR}(i)$, $\mathrm{RR}(i+\tau)$, $\mathrm{RR}(i+2\tau)$ are the Takens time delay coordinates (forming the pattern in a 3-dimensional phase space as seen in Fig. 1–7). We used $\tau = 2$. Two forms of such pattern entropy were calculated for each case analyzed. Window pattern entropy was calculated within a time window of 400 beats while cumulative pattern entropy was obtained similarly but with time window summed from first beat index ($i = 1$) to the running RR interval index (*i.e.* "now"). Both types of pattern entropy undulate with the time — window pattern entropy changing more sharply while cumulative pattern entropy changes more smoothly. Their precise values depend on what action the patient is performing at a given time and on the state of his heart. We found that the minimum, the maximum and the average of the pattern entropies for each 24-hour ECG recording are good measures for comparison between different medical cases. Table I gives the values of these quantities for 24 healthy individuals. A comparison between pattern entropies obtained for 36 cardiac arrest cases and for their individually sex, age and disease matched controls is given in Table II. It can be seen that three of these quantities give a statistically relevant correlation ($p \leq 0.05$).

TABLE I

Pattern entropy of RR intervals for 24 healthy individuals

	Cumulative pattern entropy		
	Average	Maximum	Minimum
Normals	432 ± 152	1350 ± 698	227 ± 93
	Window pattern entropy		
	Average	Maximum	Minimum
Normals	1463 ± 424	3747 ± 651	247 ± 97

TABLE II

Pattern entropy of RR intervals for 36 Cardiac Arrest Cases and for their Age/Disease Matched Controls

	Cumulative pattern entropy		
	Average	Maximum	Minimum
Cardiac arrest	814 ± 468	2332 ± 952	419 ± 231
	p= 0.05	**p= 0.003**	$p = 0.07$
Controls	568 ± 199	1389 ± 560	299 ± 101
	Window pattern entropy		
	Average	Maximum	Minimum
Cardiac arrest	2012 ± 832	4429 ± 648	307 ± 141
	$p = 0.1$	**p= 0.03**	$p = 0.3$
Controls	1692 ± 484	3986 ± 432	337 ± 129

5. Conclusions

Nonlinear dynamics is shown to be a meaningful tool for the analysis of data on a nonstationary biological system: the RR interval data extracted from 24 hour electrocardiogram recordings — both in the global (24 hour) scale and in the local time scale (*i.e.* in a time window).

Axial projections of three-dimensional images of 24 hour sequences of the time intervals between heart beats for cardiac arrest patients display six-fold or three-fold symmetry. Such symmetry was not seen in cases of arrhythmia not leading to cardiac arrest.

Three-dimensional images of the RR interval data preceding cardiac arrest viewed through a time window (100–800 beats) show characteristic types of dynamical behavior — and may lead to new insight into the nature of sudden cardiac death.

Pattern entropy — especially its cumulative form — is seen to be statistically well correlated with the data on sex, age and disease matched pairs of patient-control. Pattern entropy thus appears to have promising prognostic value.

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