

Nonlinear Analysis of Heart Rate Variability

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Abstract *This article reports nonlinear analysis of ECG R-R interval time-series obtained from healthy individuals and some cardiac patients. The R-R interval time-series data from 6 healthy individuals and 3 cardiac patients were transformed into multidimensional phase-space vectors by time-delay embedding. The largest Lyapunov exponent and correlation dimension (CD) were calculated. Nonlinearity was tested by comparing the CDs obtained from the original data with those obtained from surrogate data sets. Results are discussed with reference to results obtained in previous studies.*

1. INTRODUCTION

As the reader must have already realized the main theme of this book is almost exclusively *solitons* which was also the subject matter discussed at the ARW itself in Tashkent. Therefore, the present chapter is a significant deviation from the bulk of the topics covered with due respect to the title of the ARW. The present chapter is a report on our experimental study on the nonlinearity and disorder of a physiological system, namely the heart.

Spontaneous variability is indeed a common observation in living systems¹⁴. But whether this variability arises from *random noise* (stochastic effects) or is due to *nonlinear deterministic* effects is difficult to assess. In recent years, nonlinear analysis methods have found a growing number of applications in physiology. Variability in heart rate, blood pressure, cardiac output, blood neutrophil density, electroencephalogram (EEG), blood hormone levels and other physiological processes, has been treated as deriving from nonlinear dynamic systems^{3-5,9-11,16}, and chaotic dynamical properties have been observed in several systems^{4,5}. In what follows, we will first give a summary of the key concepts and the various recent tools developed to deal with nonlinear dynamic systems and then report the results of analysis of our heart rate data.

2. DYNAMIC SYSTEMS AND TIME SERIES

A system that evolves into successive states in time is called a *dynamic system*. The dynamic behavior of the system can be best described by its *state space* or *phase space*. Each state, \mathbf{s} , of the system is represented by a point in an m -dimensional phase space. Thus, the number of variables necessary to completely describe the system gives the dimension of its phase space. Hence,

$$\mathbf{s} \in \mathbf{R}^m \quad (1)$$

where \mathbf{R}^m represents the m -dimensional real *vector* or *phase space*. Most natural systems are continuous systems and therefore \mathbf{s} is a function of time, $\mathbf{s}(t)$. As the system evolves in time its states trace a *trajectory* in the state space.

If the present state of the system uniquely determines its next state, $\mathbf{s}(t)$ $t > 0$, then the system is a *deterministic dynamic system*. If there is no such relationship between the successive states, the system is called a *stochastic* dynamic system. A common feature of these two types of system is that they both behave irregularly. There are methods available to distinguish between the two¹⁸.

Chaotic dynamical properties can be determined from the phase space plot, various dimensions and Lyapunov exponents (LE). Phase spaces of chaotic systems are characterized by *attractors*. *Correlation dimension* (CD) is a measure of the complexity of the system while the largest *Lyapunov exponent* is a measure of its chaotic nature, that is, its sensitive dependence on initial conditions. For example, a linear deterministic system has a Lyapunov exponent of 0 whereas a nonlinear system has at least one positive Lyapunov exponent. In order to calculate CD and LE properly, a large number of accurately measured data are necessary.

2. 1. Phase space of a dynamic system

When only a one-dimensional time series, $x(t)$ consisting of scalar values is available as the output of a dynamic system, its states $\mathbf{s}(t)$ can not be determined directly but $x(t)$ can be assumed to represent the states of the system in 1-dimensional space, \mathbf{R}

$$x(t) = h(\mathbf{s}(t)) \quad h: \mathbf{R}^m \rightarrow \mathbf{R} \quad (2)$$

where h is the *measurement function*. In this sense, the time series $x(t)$ can be regarded as the projection of the real states on one dimension. In most cases, the time series is obtained in digital form, $x[n]$, by sampling the continuous output.

In order to reconstruct the phase space using a time series, it is resolved into coordinate values of a d dimensional embedding space by one of the known embedding methods. The most frequently used embedding method is the *time delay embedding* in which delayed values of the time series are used to obtain the reconstruction vectors:

$$\mathbf{x}[n] = [x[n], x[n - \tau], x[n - 2\tau], \dots, x[n - (d - 1)\tau]] \quad (3)$$

here τ is the delay time and d is the embedding dimension. If the time series has N elements, the number of reconstruction vectors will be $N - (d - 1)\tau$. It should be noted that if d is high enough the reconstructed phase portrait gives the phase portrait of the real system.

2.1.1. Delay time and embedding dimension

The most important problem of phase space reconstruction is the determination of the delay time (τ) and the embedding dimension (d). A highly recommended method for determining the delay time is the one introduced by Fraser and Swinney². In this method *mutual information* defined by:

$$I = \sum_{ij} p_{ij}(\tau) \ln \frac{p_{ij}(\tau)}{p_i p_j} \quad (4)$$

is used as the criterion to set the delay time. Here p_i is the probability that the time series will have a value in the i th interval, and $p_{ij}(\tau)$ gives the *joint* probability that the time series which was in the i th interval before, will be in the j th interval τ time units later. In a plot of this function versus τ , the value of τ at which the function attains its first minimum or begins to fall sharply is taken as the delay time.

The procedure introduced by Kennel, et al.¹³ is an appropriate method to determine the minimum embedding dimension. Briefly, this procedure examines the behavior of neighboring points in the phase space when the embedding dimension is increased by one (i.e. from d to $d+1$). Specifically, the method distinguishes the “false nearest neighbors” from “true neighbors”. False neighbors arise due to using a smaller number of embedding dimensions than the appropriate minimum, d_E . A method that eliminates the disadvantages of using an unnecessarily large embedding dimension was introduced by Theiler¹⁸.

Calculation of a dimension meeting the condition $d \geq d_E$ involves two steps. First, false neighborhood ratios (FNR) are determined from the

time series for a number of embedding dimensions, say, $d = 1, \dots, 10$. Next, a graph of FNRs versus the embedding dimension is plotted. The dimension value for which FNR is zero is taken as d_E .

2.2. Correlation dimension:

Correlation dimension (CD) which is a measure of the complexity of a deterministic system gives the number of independent variables necessary to describe the system's behavior. Linear deterministic systems possess CDs having integer values whereas chaotic systems have fractional values. However, stochastic systems may also have fractional correlation dimensions.

An efficient and time saving algorithm to calculate the correlation dimension has been offered by Grassberger and Proccaccia⁶. Correlation dimension is calculated using the *correlation sum*, $C(\varepsilon, N)$, which is defined as the ratio of the number of points near each other within a distance ε , to the total number of points;

$$C(\varepsilon, N) = \frac{2}{N(N-1)} \sum_{i=1}^N \sum_{j=1}^N \Theta(\varepsilon - \|\mathbf{x}[i] - \mathbf{x}[j]\|) \quad (5)$$

where $\|\cdot\|$ denotes the distance function and Θ is the Heaviside step function. In short, the correlation sum gives the number of $(\mathbf{x}[i], \mathbf{x}[j])$ pairs that are separated by a distance less than ε , and as N goes to infinity and ε goes to zero the following relationship holds:

$$C(\varepsilon, N) \propto \varepsilon^{CD} \quad (6)$$

Accordingly, CD can be expressed as:

$$CD = \lim_{\varepsilon \rightarrow 0} \lim_{N \rightarrow \infty} \frac{\partial \ln C(\varepsilon, N)}{\partial \ln \varepsilon} \quad (7)$$

But the accuracy of this definition is limited due to finite N , and inaccuracy in measurements to set ε to a small enough value.

Calculation of CD involves two steps. First, the correlation sum, $C(\varepsilon, N)$ is calculated for a given value of ε and for different values of the embedding dimension, d . Then a plot of $C(\varepsilon, N)$ versus d is obtained. The slope of the linear region of this curve gives CD.

2.3. Lyapunov Exponents

Lyapunov exponent is simply a measure of how fast two initially nearby points on a trajectory will diverge from each other as the system evolves, thus giving information about the system's dependence on

initial conditions¹. A positive Lyapunov exponent is a strong indicator of chaos^{3,12,19}.

The average largest Lyapunov exponent is calculated as follows. First, a starting point is selected in the reconstructed phase space and all the points which are closer to this point than a predetermined distance, ε , are found. Then the average value of the distances between the trajectory of the initial point and the trajectories of the neighboring points are calculated as the system evolves. The slope of the line obtained by plotting the logarithms of these average values versus time gives the largest Lyapunov exponent. To remove the dependence of calculated values on the starting point, the procedure is repeated for different starting points and the average is taken as the average largest Lyapunov exponent.

2.4. Test of nonlinearity: Surrogate data analysis

In order to check the applicability of the methods described so far, nonlinearity of the time series should be tested. It is customary to do this by *surrogate data analysis*¹⁷ which involves the following steps. First a surrogate time series is formed from the original time series by taking its Discrete Fourier Transform (DFT), randomly varying its phase and then taking the inverse transform. The new series formed in this way will have the same autocorrelation and power spectral density as the original time series. The next step is the test against the null hypothesis that the time series under consideration can be characterized by Gaussian noise with linear properties and that a measure of chaotic dynamics such as CD, LE, etc. computed from the original time series is not significantly different from that computed from the surrogate time series. If the difference is statistically significant the null hypothesis is rejected. Theiler et al.¹⁸, using Takens'¹⁵ CD estimator as their statistic, have introduced a “significance” measure of this difference defined by:

$$S = \frac{|CD_{original} - \overline{CD}_{surrogate}|}{\sigma_{CD_{surrogate}}} \quad (8)$$

where $\overline{CD}_{surrogate}$ and $\sigma_{CD_{surrogate}}$ denote the mean and the variance of the surrogate data set respectively. To improve robustness of the test several surrogate sets are formed and their average CD is computed. Hoyer^[2] and Theiler^[18] report that if $S > 10$ the null hypothesis can be rejected, that is

the time series can not be represented by Gaussian noise but it can be nonlinear deterministic.

3. EXPERIMENTAL

3.1. Subjects and data acquisition

In this study, electrocardiograms (ECG) of 6 healthy individuals (all males) and 3 cardiac patients (two females) were recorded. Detailed information on subjects is given in Table I. Cardiac patients were outpatients of the Cardiology Clinic of Ege University Medical School. Patient P1 had arrhythmia (Arr) plus chronic obstructive lung disease (COLD) and rheumatoid arthritis (RA), patient P2 with angina pectoris (AP) had coronary by-pass surgery seven years ago and patient P3 had congestive heart failure (CHF) plus COLD.

Table I. Subject information (H: Healthy, P: Patient)

Subject	G	Age	H(cm)	W(kg)	Condition
H1	M	55	170	75	Healthy
H2	M	22	178	76	Healthy
H3	M	22	155	54	Healthy
H4	M	23	175	82	Healthy
H5	M	31	185	97	Healthy
H6	M	21	185	97	Healthy
P1	F	69	155	53	Arr + COLD + RA
P2	M	59	169	70	AP

The analog ECG signal was sampled and digitized at 400 Hz. Approximately 4000 R-R intervals were measured from each data set and stored in the hard disk of a PC. ECG recording time varied among subjects, but it was slightly more than one hour on the average.

3.2. Calculations

Mutual information to determine delay time (τ), minimum embedding dimension (d_E) for phase space reconstruction, correlation dimension (CD) and average largest Lyapunov exponent (LE) were calculated with algorithms given in the literature^{7,8}.

3.3 Test of nonlinearity: Surrogate data analysis

Surrogate data analyses were performed using the method described previously. Every original time series was compared with 20 surrogates derived from it.

Finally, phase spaces were reconstructed using the delay times shown in Table II in a 3D embedding space (embedding spaces with more than three dimensions can not be visualized) to have an idea about their phase portraits.

4. RESULTS:

Delay times (τ) and minimum embedding dimensions (d_E), correlation dimensions for (CD), average Largest Lyapunov exponents (LE) and S values of significance of surrogate data analyses determined for each subject are all listed in Table II.

Table II. Various Measures of Subjects

Subject	τ	d_E	LE	CD	S
H1	2	6	0.4718	3.33	0.30
H2	5	6	0.4992	3.58	5.62
H3	5	7	0.6755	4.00	0.93
H4	6	4	0.5304	2.50	23.67
H5	3	6	0.5299	3.20	0.01
H6	6	6	0.5343	3.45	18.63
P1	2	9	0.4301	1.20	42.10
P2	8	6	0.3083	1.50	29.59
P3	2	6	0.3691	1.65	7.86

Time series obtained from patient P1 and its surrogate, both with normalized amplitudes, are shown in Figure 1a. 3D phase portrait of the same patient is shown in Figure 1b.

5. DISCUSSION AND CONCLUSIONS

Heart rate variability (HRV) has been attributed to nonlinear dynamics by some authors^{4,5} while others contend that it is stochastic^{11,16}. Teich et al.¹⁶ in particular rule out chaos definitely.

The finite values of CD and positive values of LE we have found for all of our subjects in this study suggest that heart rate variability (HRV) in all of our subjects has low-dimensional chaos, and HRV in cardiac patients is less complex than that in healthy subjects. Also, LEs of cardiac patients are smaller than those of healthy subjects implying that HRV is less chaotic in cardiac patients than in healthy subjects. These findings are all in conformity with those of some previous studies^{4,5,9}. However surrogate data analysis does not support these findings at least

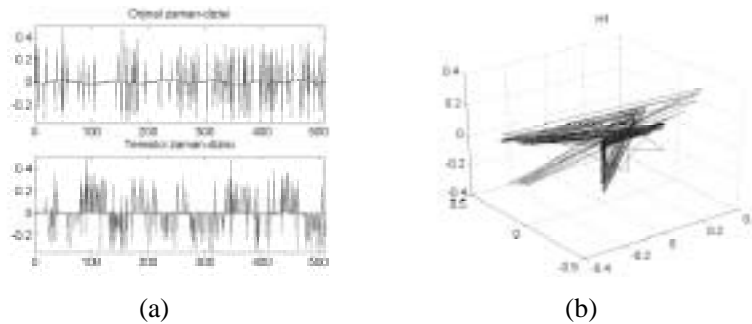


Figure 1. Times series with normalized amplitudes from subject P1 (left top trace) and surrogate series obtained from it (left lower trace). Three dimensional phase portrait reconstructed by the time delay embedding method for the same subject (right trace), $\tau = 2$ and $d = 3$.

for subjects H1, H2, H3, H5 and P3. Only P3 had a cardiac pathology (COLD). Surrogate data analysis has been documented to be a robust test of nonlinearity in that it yields the expected results when it is applied to a time series known to be nonlinear deterministic (Theiler). Therefore, unless CD and LE findings are supported by surrogate data analysis CD and LE values are meaningless.

On the other hand, the data of subjects H4, H6 and P1, P2 can be regarded as nonlinear deterministic on all grounds (i.e. CD, LE and surrogate analysis) (see Table II), but again one can not ascertain this, because as Thieler et al.¹⁷ state, low dimensional chaos and uncorrelated noise are not the only alternatives; "...nonchaotic but still nonlinear determinism, linear correlations and noise, both in the dynamics and in the measuring apparatus" may be involved. Controversial results obtained by several authors are surely not unique to HRV; it has been reported that electroencephalograms recorded from two different leads from the same subject at different times gave similarly contradictory results (i.e. one nonlinear deterministic, the other stochastic).

In the light of the foregoing arguments the most one can say at this juncture is perhaps the following: Heart rate variability be it in a healthy or pathological heart may at times and in some individuals display chaotic nonlinear determinism. This unfortunately is of no diagnostic value, but to arrive at more decisive conclusions further investigations with more refined mathematical tools are needed.

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