Complexity in the living: a modelistic approach
Proceedings of an International Meeting
Rome, February 1997

Complexity and Aging as Correlated with Heartbeat Dynamics

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Abstract

The analysis of heartbeat dynamics is described to illustrate, from a practical viewpoint, some relevant features of biological complexity. Some basic techniques for analyzing time series will be shown, having in mind an operational definition of the amount of complexity in physiological systems. The chosen case-study is the effect of aging on the heartbeat regulation since it can be easily interpreted as an example of decrease in dynamical complexity.

1 Introduction

Physiology has a great tradition in the application of quantitative models to biological systems and in the development of integrative and systemic views to the investigated phenomena. This is a logical consequence of the intertwined nature of physiological regulations aiming to get biological organisms working as a whole [1-4]. All physiological regulations have time as their main dimension and, in general, the peculiar objects of physiological investigation are single biological systems observed in time [3,5]. As a consequence time series are the most widespread mathematical objects in physiology and the question arises about choosing the most useful ones to highlight the general principles of biological organization in time. The relevance of a physiological time series is linked to the assignment of a well defined biological meaning to the time-dependent variables and to the difficulty in getting the data at the proper time-resolution.

Heartbeat expressed as RR tracings or tacograms, i.e. as a set of distances between adjacent R peaks in the ECG corresponding to the time intervals between subsequent beats (RR intervals) is an almost ideal signal in terms of both the above sketched requirements [6-9]. Heart is at the crossroads of many physiological regulations and hence the heartbeat is a privileged observatory of the general physiological status of the individuals. Moreover, RR tracings are directly linked to the functionality of the organ since the principal function of the heart is beating (while, for instance, the main function of the brain is not to give rise to EEG), and the variability of subsequent heart beats (RR intervals) was demonstrated to correlate with a number of physiological as well as pathological conditions, like post-ischemia mortality, neuro-autonomic diseases and senescence [10-13]. From a mathematical point of view, the tacogram is a naturally discrete series offering an obvious choice for the embedding delay (set to one) and thence for the observation scale. Moreover, as we will see in the following, heartbeat shows a very well blended mixture of determinism and stochasticity and can be easily studied by virtually any analytical method developed for time series [14-17]. From a technical point of view, it is worth noting that RR measurements are totally non-invasive as well as very simple to achieve, which endows them with an enormous clinical importance. For such reasons, tacogram analysis was one of the very first biological areas in which the ideas of complexity, deterministic chaos and the alike produced some practical application [8,9].

In the present work the importance of estimating the amount of complexity of tacograms in studying the effect of aging on heartbeat dynamics [13] will be underlined, and to this end heartbeat will be investigated by four techniques, namely Fast Fourier Transform (FFT), Singular Value Decomposition (SVD), Recurrence Quantification Analysis (RQA) and Markov Models (MM).

2 Material and Methods

2.1 Data Collection

The tacograms pertain to 90 healthy subjects from 20 to 91 years old. The tracings refer to a 5' registration in supine position (resting state) and to another 5' registration after postural tilt (tilted state). Thence we had two tracings for each subject, each made of about 512 points representing the time elapsed between subsequent beats [13].

2.2 Data Analysis

Fast Fourier Transform (FFT)

The Fast Fourier Transform is the most widespread method to analyze physiological time series. The time series under study is transformed into a frequency spectrum by the following schematic algorithm [18]:

1. Sample the studied signal S into a sequence of n discrete values (this step is absent in the case of RR tracings which are intrinsically discrete);

2. Take a sinusoid (Y_i) of unitary amplitude, frequency (f_i) and duration equal to the studied signal subdivided in the same number n of points;

3. Compute the products between the pairs of points corresponding to S and Y_i and sum the products of each pair;

4. Repeat from point 2) with different values of f_i.

The more the signal is cyclic at frequency i, the higher the result of the summation (power absorbed by the particular frequency). The spectrum of the power absorbed at the different frequencies is called the Fourier spectrum of the signal [18]. FFT, while giving a very clear picture of the periodic structures present in a given signal, has two important limitations: the first one is the need of a stationary signal, the second one is the possibility to take into consideration only periodic structures.

As we will demonstrate in what follows, both these requirements are very severe limitations in the heartbeat analysis.

2.2.1 Singular Value Decomposition (SVD)

This technique represents the application to the time series analysis of a classical multivariate statistical technique: the principal components analysis (PCA). PCA was developed early this century [19] and has found a very widespread application in fields ranging from hydrodynamics to sociological research [20-22]. PCA allows an N-dimensional data field, made up by m units (observations) and N variables measured on the units, to be described using P dimensions called factors (or components), which represent the degrees of freedom of the system.

From a geometrical point of view, these dimensions indicate the linearly uncorrelated directions in the data field along which the elongation (variability) of the data cloud is maximal. From a mathematical point of view they correspond to the eigenvectors of the correlation matrix among the original N variables, while the corresponding eigenvalues are the amount of variability explained by the particular component [23]. The correlation coefficients between original variables and factors (factor loadings) facilitate the interpretation of the factors. Since PCA is applied to multivariate matrices having N columns and m rows, the time series must be transformed into a multivariate matrix by means of an embedding procedure [24]. Such technique, aims to develop a geometrical multivariate space isomorphic to the unknown state space of the dynamics under study which can be easily investigated by numerical techniques [24,25]. The space is generated by the construction of a multivariate matrix having as columns the original series shifted by a fixed lag. The embedding dimension equals the number of columns of the matrix. For example, given the series $10, 11, 21, 32, 41, \ldots$ the corresponding three-dimensional embedding space (matrix) at a lag = 1 is:

$$
\begin{array}{ccc}
10 & 11 & 21 \\
11 & 21 & 32 \\
21 & 32 & 41 \\
32 & 41 & . \\
41 & . & . \\
. & . & .
\end{array}
$$

Given the discrete character of tacograms, the lag of the embedding is automatically set to one, while the embedding dimension was set to 15. The principal components of the embedding matrix correspond to the distinct temporal structures (regulations) present in the data and allow a straightforward appreciation of the relative complexity of the given time series. The extraction order of the components, in fact, is dictated by the amount of the explained variability: a completely random series displays a spectrum of components all endowed with an almost identical proportion of explained variability (lack of meaningful temporal correlations), while in the case of only few deterministic modes driving the dynamics, the variability is concentrated on the first few components rising above the noise floor. Thus, the number of components clearly exceeding the noise floor roughly corresponds to the complexity of the given signal, and indicates the number of independent dynamical modes displayed by the system [24,26]. The components do not need to be periodic and any kind of temporal structure can be detected by SVD, thus overcoming the problems sketched for FFT.

2.2.2 Recurrence Quantification Analysis (RQA)

RQA technique was first introduced in physics by Eckmann, Kamphorst and Ruelle in 1987 [27]. Seven years later Webber and Zbilut [28] enhanced the technique by defining five non-linear variables that were found to be diagnostically useful in the quantitative assessment of time series structures in many fields, ranging from molecular dynamics to physiology [28-30]. RQA was demonstrated to be particularly suited to quantify transient behavior far from attractors [29]: this is especially important when dealing with complex systems that can hardly be considered at equilibrium and that do not display attractor-like behavior. RQA is based on the computation of a distance matrix between the rows (epochs) of an embedding matrix extracted from the given time series. Starting from this distance matrix, five non-linear descriptors of the dynamics are evaluated (refer to the existing literature for a more thorough description of the methodology [28-30]). As pertains to this work, it is sufficient to describe the two basic descriptors provided by RQA: % Recurrence (REC) and % Determinism (DET) [28]. REC is the fraction of recurrent pairs of points in the distance matrix. A pair of points is considered as recurrent if the distance between the elements is lower than a predetermined cutoff. DET is the fraction of recurrent points that appear in sequence, thus originating diagonal lines in the distance matrix. Determinism corresponds to the existence of patches of recurrent behavior in the series under study. While both FFT and SVD give a global view to the time series, RQA has a local character which allows to pick up any sudden change of the dynamics.

2.2.3 Markov Models (MM)

The Markov models are among the most simple and widespread methods to study systems dynamics [16,31]. The time series are described by means of a sequence of few discrete states among which the system oscillates visiting one state at each time step. The entire dynamics is described by means of a transition matrix (TM) having as rows (i) the states at time $t-1$ and as columns (j) the states at time t. The elements of the TM can be easily transformed into the probabilities for a system in the state i at time $t-1$ of visiting the state j at time t. In order to build a TM from a time series the following two requirements must be fulfilled: i) the existence of a meaningful "discrete clock" to single out the time steps; ii) the existence of a few discrete states out of the continuous set of values constituting the time series. The former constraint is immediately satisfied by the intrinsic discrete character of heartbeat, the latter was found to be consistent with the dynamics along the first mode (first principal component) of heartbeat by means of a cluster analysis carried out on the first component (PC1) scores of the tacograms. The cluster analysis demonstrated how the distribution of PC1 scores could be translated into $5-6$ discrete states (clusters) explaining around 95% of the total variability [16].

3 Results and Discussion

The first feature of RR tracings heavily modified by aging is the amount of variability: Fig. 1a,b show typical young and aged individuals tracings, respectively. In the examined data base, the standard deviation of tacograms of older population (average 65 years) was about half the standard deviation of younger individuals (average 31 years) [13]. This is a very raw indication of the loss of complexity of heartbeat with age. The functional meaning of this phenomenon can only be revealed by a careful investigation of its time structure. The standard deviation, in fact, only deals with the statistical characterization of the system, devoid of any temporal consideration: a time series can be highly variable and nevertheless displaying a very regular temporal structure, i.e. high predictability and low complexity. Thus, the standard deviation is a good indicator of complexity only for essentially random phenomena, while RR tracings display a rich temporal structure.

To realize the richness of the phase information (time structuring) present in the heartbeat it is very instructive to compare the recurrence plots of a tacogram and of its shuffled counterpart. A recurrence plot visualizes the distance matrix relative to the embedding matrix of a given time series, and the darkened pixels correspond to the recurrent points along the series [28,30]. Fig. 2a,b show the dramatic changes in the appearance of the plot, as well as in the correspondent quantitative dynamical descriptors, upon shuffling of the time series. Notice that under the same conditions the purely statistical parameters (mean and standard deviation) remain unchanged.

The plot of the first two embedding variables of the tacogram (Poincaré plot [8], Fig. 3a) highlights the principal feature of the heartbeat dynamics, i.e. the tendency of each beat to be similar to the previous one. This feature is at the basis of the concentration of points along the line of identity between subsequent beats [8,16] and derives from a non-oscillatory regulation, which is by far the most important control

Or.V.	PC1	PC2	PC3	PC4	PC5
1	0.68	-0.37	0.27	-0.37	0.30
2	0.72	-0.42	0.32	-0.28	0.05
3	0.75	-0.43	0.27	-0.06	-0.28
4	0.78	-0.42	0.16	0.15	-0.04
5	0.79	-0.37	-0.02	0.28	0.07
6	0.78	-0.27	-0.26	0.32	-0.20
7	0.79	-0.14	-0.41	0.22	-0.02
8	0.79	0.00	-0.46	0.00	0.31
9	0.78	0.13	-0.42	-0.21	-0.00
10	0.78	0.27	-0.27	-0.32	-0.21
11	0.79	0.37	-0.03	-0.29	0.06
12	0.77	0.42	0.16	-0.16	-0.03
13	0.75	0.43	0.27	0.05	-0.28
14	0.72	0.42	0.32	0.28	0.04
15	0.68	0.37	0.27	0.37	0.30
% expl. var.	57	10	9	5	4

Table 1: SVD of a typical tacogram: factor loadings profile
The table reports the correlation coefficients (factor loadings) of the original variables (Or.V. #) with the principal components. In the case of a time series the original variables are the copies of the original series shifted progressively with a fixed delay of 1. The percentage of explained variability is an indication of the relative entity of the dynamics along the corresponding mode. The first, non-oscillatory, component is by far the most important mode in heartbeat regulation.

factor of heartbeat and which is systematically lost by the classical Fourier analysis of tacograms, due to the forced periodic character of the technique [14,16].

The classical Fourier profile of RR tracing is depicted in Fig.3b: while the LF and HF peaks are truly oscillatory components found to be linked to baroreceptive reflexes and to breathing, respectively, the VLF component essentially collects the non-oscillatory (beat-to-beat regulation) part of the dynamics [6,7,14].

In the SVD-based analysis, however, due to the absence of any constraint of periodicity, we can appreciate the mixing of oscillatory and non-oscillatory controls of heartbeat and the relative importance of these regulations as well as the relative amount of rule-based and purely stochastic variability. Table 1 reports the factor loadings profile of a typical heartbeat. It is worth noting the huge importance of the non oscillatory component (all positive loadings).

The components are generated in order of the decreasing percentage of explained variability, and looking at the correlation (on an ensemble basis) between the variability explained by the principal components and the power absorbed by the different spectral bands the substantial coherence of the two methods can be appreciated (Table 2). The high correlation between PC1 and VLF ($r = 0.82, p < 0.0001$) reflects the non-oscillatory character of VLF. It is important to note that the correlations of Table 2 are computed on the basis of clinical data affected by a huge amount of variability, which makes very relevant a correlation coefficient around 0.80. A general picture of heartbeat regulation made up of several well understood oscillatory controls and a single up to now largely mysterious (although predominant in terms of explained variability) non-oscillatory control can be sketched. Moreover, taking into account that the non-oscillatory regulation is largely maintained in isolated heart, while it is disrupted by Nembuthal deep anesthesia [16], it can be concluded that: i)

Spectral Bands	PC1	PC2	PC3	PC4	PC5
VLF	**0.82**	-0.08	-0.67	-0.75	-0.59
LF	-0.41	**0.58**	**0.65**	0.37	0.09
HF	-0.71	-0.23	0.32	0.**63**	**0.67**

Table 2: Coherence between Fourier and SVD descriptions of tacograms. The correlation coefficients between the relative power of spectral bands in FFT and eigenvectors in SVD are reported. The positive statistically significant correlations are evidentiated. The negative correlations derive from the normalization of the total power. The correlations were computed on the basis of the individual spectra of the 90 patients, which implies a considerable blurring of the correlation due to the differences in shape among subjects. It is worth noting (see also Fig.3b) that each cyclic mode corresponds to two principal components (sin/cosin pair) and to one frequency band; on the contrary, the aperiodic modes necessitate of only one component to be described [26].

this regulation is intrinsic to heart, and ii) the autonomic nervous system impinges on it.

To fully appreciate the aging effects on this picture, it is important to switch from the overall perspective provided by Fourier analysis and SVD, to the local view provided by Markov models and RQA. Markov models, in particular, allow to go in deep into the character of heart regulation as expressed by PC1, i.e. along the non-oscillatory mode of the dynamics. The distribution of the first component scores of RR relative to each patient (tacogram) can be clustered into five-six classes of length, which makes possible to transform the dynamics on PC1 in terms of a dynamics describing the sequence of classes (discrete states). It is important to stress that this clusterization (as well as the dynamical behavior described below) holds for all the individuals examined in this work as well as for laboratory rats [16]. The first order Markov transition matrix between these states is reported in Tab.3. From the table it is evident the quantum-like character of the dynamics on PC1, the system having the highest probability for the $n + 1$ beat to remain in the same state or to escape exclusively to adjacent states [16]. It is interesting to note that: i) if we follow the short-scale dynamics of the system (i.e inside each cluster) we observe exactly the same kind of dynamics: this is the basis of the fractal, scale invariant, characteristic of heartbeat; ii) this type of regulation is completely different from a feedback one: the less visited states have the same behavior of the most visited ones and there is no ideal RR length attracting the dynamics. Such regulation is by far the most relevant one in terms of fraction of explained variability and allows a very fast control on heartbeat, faster than any feedback-like regulation [16,17,32].

The influence of age on heartbeat dynamics in terms of spectral variables was investigated taking into account both resting phase registrations and tilt phase tracings [12,13,33]. The tilt phase corresponds to a tracing recorded after a change of posture of the patient from supine to sitting position had occurred, thus involving the activation of the autonomic system [12,33]. The descriptors used in the analysis were the power absorbed by the different bands both in terms of absolute and relative terms. These descriptors were subjected to a principal component analysis, to get rid of the redundancy linked to the correlations between the power of the different bands. The component scores were then correlated with the age of individuals to highlight the different effects of aging on the spectral profiles. The two most relevant effects of age are the decrease in total power, (i.e. the general amount of variability), and the shifting of the balance between non-oscillatory and oscillatory controls toward an increased importance of the non-oscillatory component [13]. In fact, the decrease

	A	B	C	D	E	F
A	0.966	0.033	0	0	0	0
B	0.015	0.951	0.029	0	0	0
C	0	0.014	0.966	0.020	0	0
D	0	0	0.023	0.949	0.028	0
E	0	0	0	0.030	0.949	0.021
F	0	0	0	0	0.042	0.958

Table 3: Transition matrix between clusters
The states (clusters) are ordered according to the increasing average length of the RR interval. The rows correspond to the i_{th}-state and the columns to the $(i+1)_{th}$ one. Only states that are adjacent in length communicate between each other. This kind of behaviour does not depend upon the relative frequency of the states (e.g. Cluster C has a relative frequency of 0.28, while cluster F has a frequency of 0.04).

of variability linked to age mainly affects the oscillatory regulations while keeping substantially invariant the beat-to-beat regulation. The dynamics becomes simpler with an increase of the percentage of variability driven by the main order parameter (PC1) going from an average of 37% (young group) to 56% (older group) [13]. By using a global index which includes all the age-linked components of tacograms, the chronological age can be predicted with a considerable precision ($r = 0.71, p < 0.001$) (Fig.4).

From the RQA point of view, the descriptor most affected by age is the amount of determinism of the heartbeat. The determinism is significantly increased by age ($r = 0.60, p < 0.001$) and, if measured on a cluster basis, the correlation becomes very cogent ($r = 0.91$). This means that the loss of complexity of the heartbeat subsequent to the elimination of the minor controllers make the heartbeat dynamics more predictable. With increasing age the system progressively eliminates the relatively slow periodic controllers to keep only the most basic beat-to-beat non-oscillatory regulation.

A very recent paper [34] dealing with the application of RQA to the tacograms of diabetic patients demonstrates how the autonomic dysfunction consequent to diabetes can be measured in terms of an increase in the determinism of RR tracings [34]. This result is consistent with the observations reported here and points to the apparently paradoxical character of heartbeat regulation, where the alterations in control mechanisms reinforce the rule-obeying component of the heartbeat dynamics [35].

4 Conclusion

Summarizing our results, we can state that the case of heartbeat is paradigmatic of a deep change in a basic concept in physiology. The loss of adaptive power linked to senescence (or diabetes) is paralleled by an increase in predictability of the system, the less regular system being the more efficient thanks to a higher number of possible modes of functioning [35]. Thus, the classical way to consider homeostasis needs a complete re-thinking: the efficiency of the organism as a whole is measured by the richness of the repertoire of the possible modes of action and not by the ability to keep invariant a given physiological parameter.

From a quite general point of view, systematic of physics-inspired techniques in the analysis of physiological data may reveal extremely proficient, even in the lack of solid general theories about the systems under investigation [21]. Thus, a vaguely defined concept as "biological complexity" finds, in the case of heartbeat dynamics, a relatively simple operational definition stemming from the congruent descriptions provided by different physics-inspired approaches to the time-series analysis.

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Legends to the figures

Fig.1 Heartbeat tracings
Typical heartbeat tracings of young (a) and aged (b) individuals.

Fig.2 Recurrence plots of human heartbeat
The panel (a) and (b) refer to the recurrence plots of the same signal before and after reshuffling, respectively .

Fig.3 Dynamical descriptors of the heartbeat
Panel (a) and (b) show respectively the Poincaré plot of a tacogram and the power spectrum of an heartbeat.

Fig.4 Correlation between cardiac and chronological age in humans [13]

Figures:

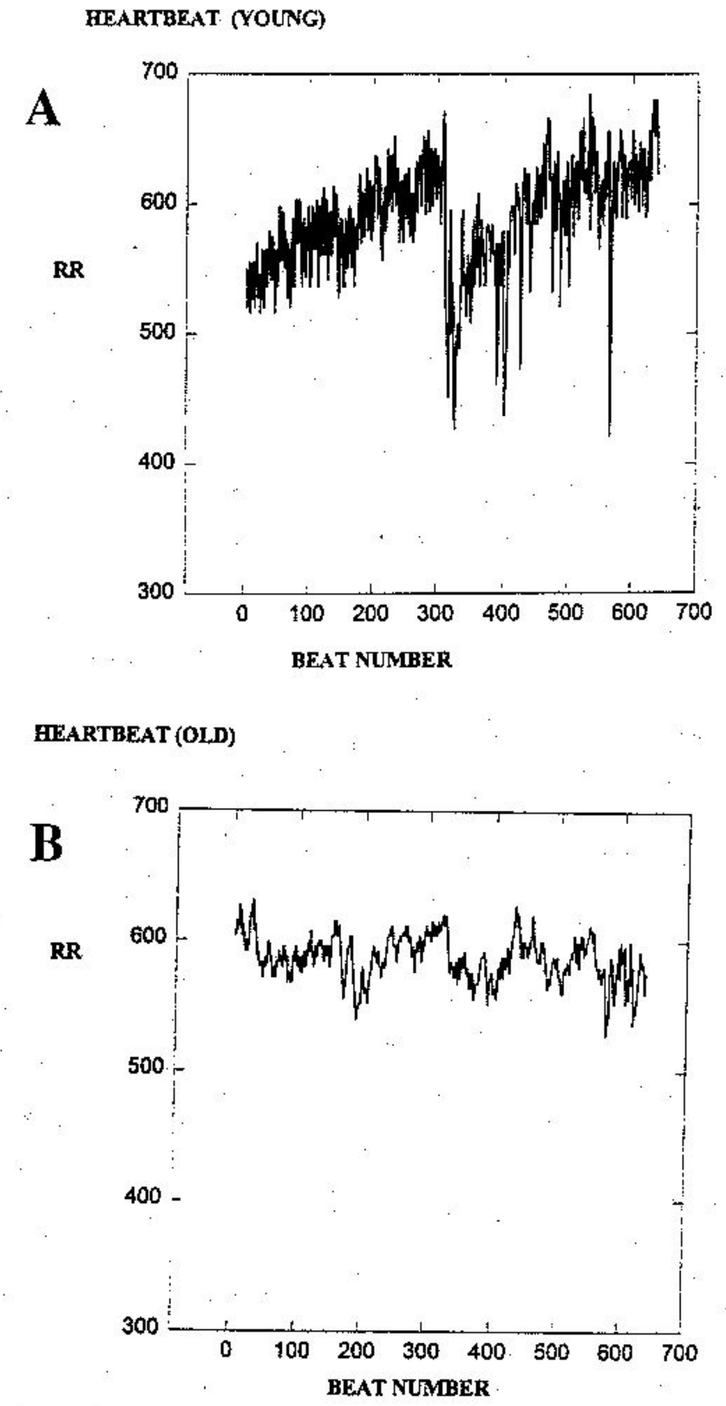


Fig. 1

A

B

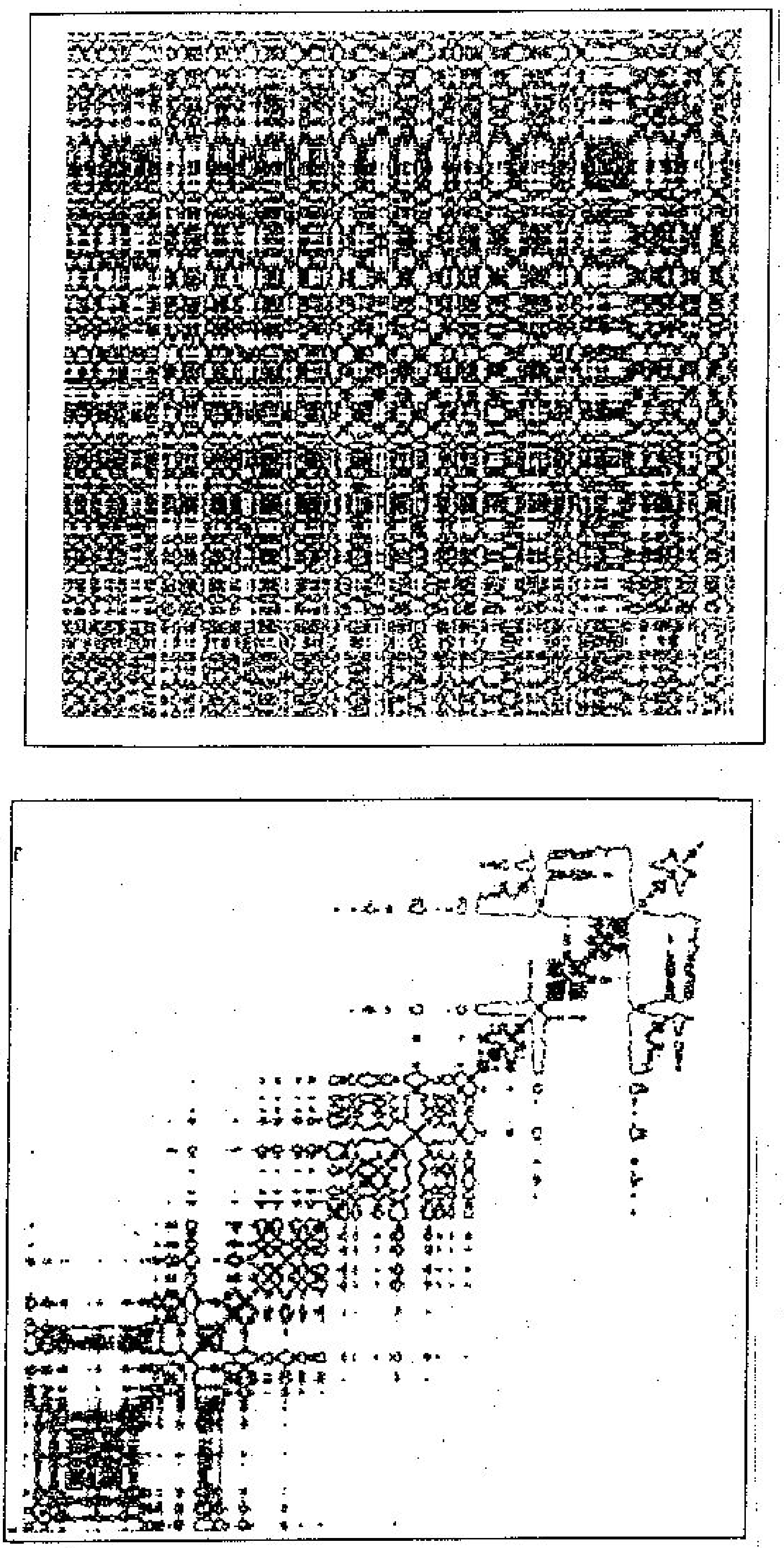


Fig. 2

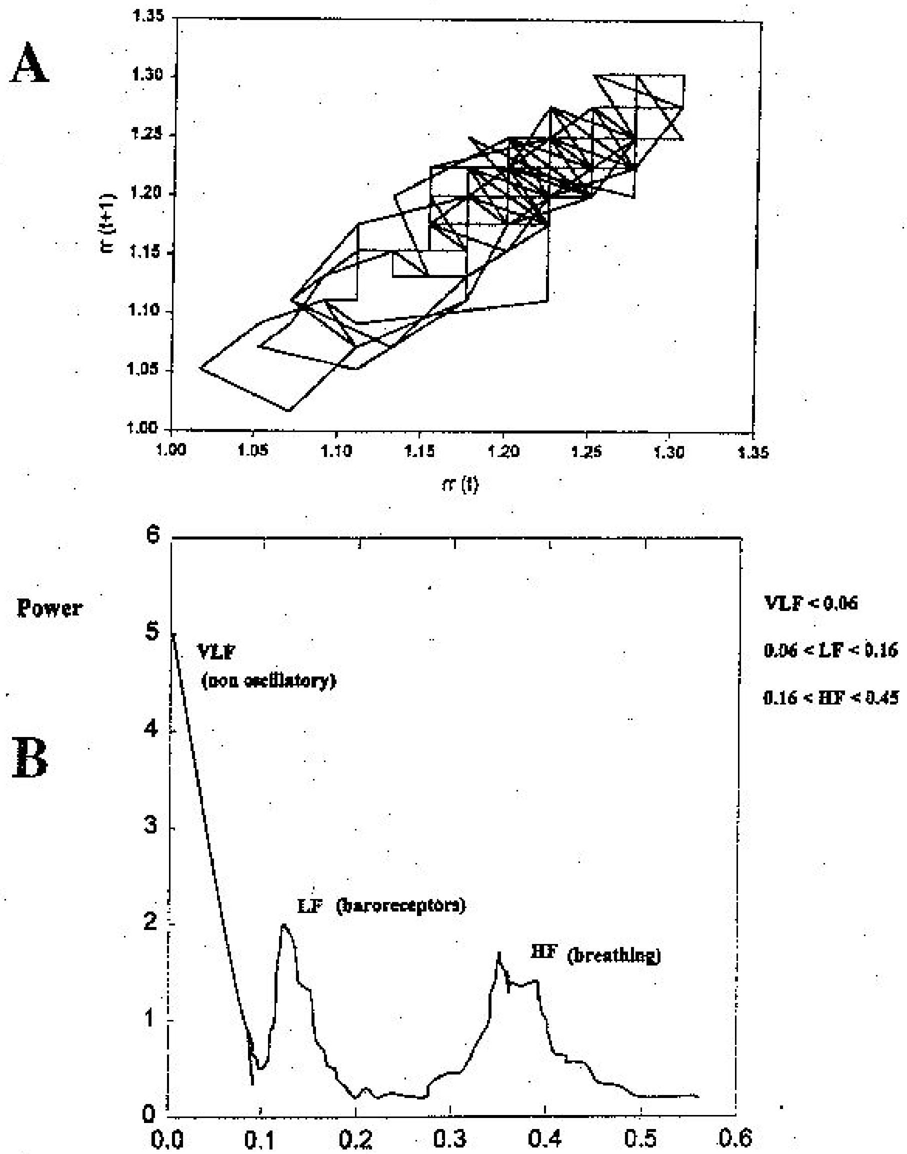
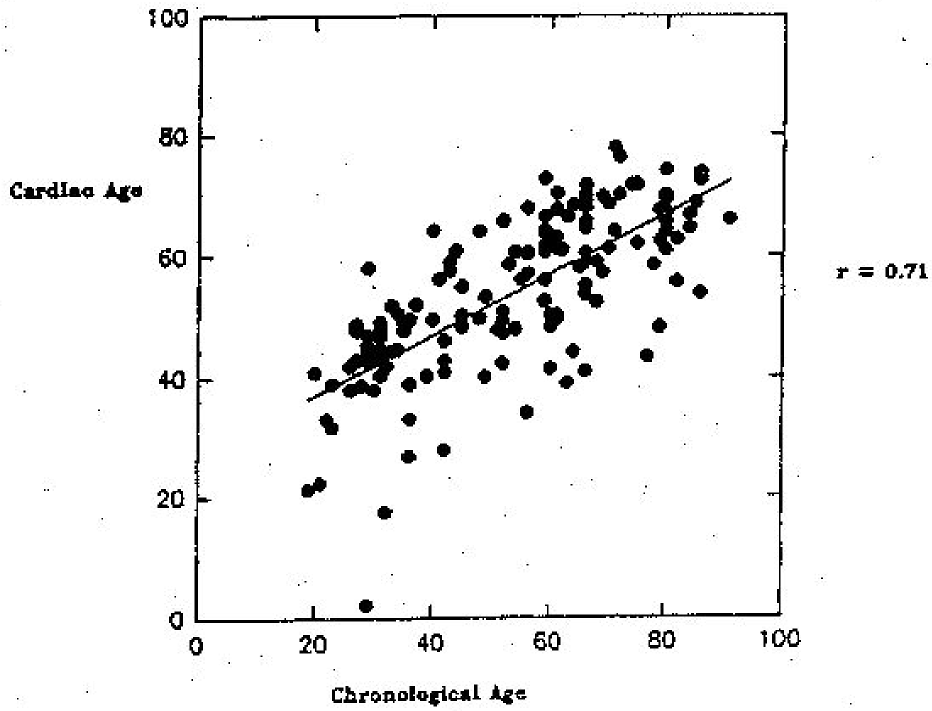

A
rr (t+1)
rr (t)
B
Power
VLF
(non oscillatory)
LF (baroreceptors)
HF (breathing)
VLF < 0.06
0.06 < LF < 0.16
0.16 < HF < 0.45

Fig. 3


100
80
60
40
20
0
Cardiac Age
0
20
40
60
80
100
Chronological Age
r = 0.71
Fig. 4