Scaling Behavior of Heartbeat Intervals

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(April 26, 1996)

A major problem in biology is the quantitative analysis of nonstationary time series generated under free-running conditions [1–3]. A central question is whether such noisy fluctuating signals contain hidden dynamical patterns essential for understanding underlying physiological mechanisms. Here we analyse the properties of human cardiac activity by means of a wavelet transform and analytic signal approach designed to address nonstationary behavior. We find a homogeneous scaling function for the distribution of the variations in the beat-to-beat intervals for healthy subjects. However, such a scaling function does not exist for a group with cardiopulmonary instability due to sleep apnea. This scaling form allows us to express the global characteristics of a highly heterogeneous time series of interbeat intervals of each healthy individual with a single parameter. We find also that the observed scaling represents the Fourier phase correlations attributable to the underlying nonlinear dynamics. The present approach has the potential to quantify the output of other biological signals with nonlinear behavior.

Time series of beat-to-beat (RR) heart rate intervals (Fig.1a) obtained from digitised electrocardiograms are known to be nonstationary and exhibit extremely complex behavior

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[4]. A typical feature of these signals is the presence of "patchy" patterns which change over time (Fig.1b). Heterogeneous properties may be even more strongly expressed in certain cases of abnormal heart activity. Traditional approaches — such as the power spectrum and correlation analysis [5,6] — are not suited for such nonstationary (patchy) sequences, and do not carry information stored in the Fourier phases (crucial for determining nonlinear characteristics).

To address these problems, we present an alternative method — "*cumulative variation magnitude analysis*" — to study the subtle structure of physiological time series. This method comprises sequential application of a set of algorithms based on wavelet and Hilbert transform analysis. First, we apply the wavelet transform (Fig.1c), because it does not require stationarity and preserves the Fourier phase information. The wavelet transform [7–9] of a time series $s(t)$ is defined as

$$T_\psi(t_0, a) \equiv \; a^{-1} \int_{-\infty}^{+\infty} s(t) \psi \left(\frac{t - t_0}{a} \right) dt,$$

where the analysing wavelet ψ has a width of the order of the scale a and is centred at t_0. For high frequencies (small a), the ψ functions have good localization (being effectively non-zero only on small sub-intervals), so short-time regimes or high-frequency components can be detected by the wavelet analysis. The wavelet transform is sometimes called a "mathematical microscope" because it allows one to study properties of the signal on any chosen scale a. However, a wavelet with too large a value of scale a (low frequency) will filter out almost the entire frequency content of the time series, thus losing information about the intrinsic dynamics of the system. We focus our "microscope" on scale $a = 8$ beats which smooths locally very high-frequency variations and best probes patterns of specific duration ($\approx \frac{1}{2} - 1$ min) (Fig.2). The wavelet transform is attractive because it can eliminate local polynomial behavior in the nonstationary signal by an appropriate choice of the analysing wavelet ψ [10]. In our study we use derivatives of the Gaussian function: $\psi^{(n)} = d^n / dt^n e^{-\frac{1}{2}t^2}$.

The wavelet transform is thus a cumulative measure of the variations in the heart rate signal over a region proportional to the wavelet scale, so study of the behavior of the wavelet

values can reveal *intrinsic properties of the dynamics* masked by nonstationarity.

The second step of the cumulative variation magnitude analysis is to extract the instantaneous variation amplitudes of the wavelet-filtered signal by means of an analytic signal approach [5,11] which also does not require stationarity. Let $s(t)$ represent an arbitrary signal. The analytic signal, a complex function of time, is defined by $S(t) = s(t) + i\tilde{s}(t) = A(t)e^{i\phi(t)}$, where $\tilde{s}(t)$ is the Hilbert transform [12] of $s(t)$. The instantaneous magnitude $A(t)$ and the instantaneous phase of the signal $\phi(t)$ are defined as $A(t) \equiv \sqrt{s^2(t) + \tilde{s}^2(t)}$ and $\phi(t) \equiv \tan^{-1}(\tilde{s}(t)/s(t))$.

We study the distribution of the amplitudes of the beat-to-beat variations (Fig.1d) for a group of healthy subjects ($N = 18$; 5 male, 13 female; age: $20-50$, mean - 34) and a group of subjects [13] with obstructive sleep apnea [14] ($N = 16$ males; age: $32-56$, mean - 43). We begin by considering night phase (12pm-6am) records of interbeat intervals ($\approx 10^4$ beats) for both groups to minimize nonstationarity due to changes in the level of activity. Inspection of the distribution functions of the amplitudes of the cumulative variations reveals marked differences between individuals (Fig.2a). These discrepancies are not surprising given the underlying physiological differences among healthy subjects. To test the hypothesis that there is a hidden, possibly universal structure to these heterogeneous time series, we rescale the distributions and find for all healthy subjects that the data conform to a single scaled plot ("*data collapse*") (Fig.2b). Such behavior is reminiscent of a wide class of well-studied physical systems with universal scaling properties [15,16]. In contrast, the subjects with *sleep apnea* show individual probability distributions which *fail* to collapse (Fig.2d).

We next analyse the distributions of the beat-to-beat variation amplitudes. For the healthy group, we find that these are well fit by the Gamma form: $P(x) = (b^{\nu+1}/\Gamma(\nu + 1))x^{\nu}e^{-bx}$, where $b = \nu/x_0$, $\Gamma(\nu + 1)$ is the Gamma function, x_0 is the position of the peak $P = P_{max}$, and ν is the fitting parameter (Fig.3a). Although individual distributions have different values of b, the homogeneous property of the functional form of $P(x)$ leads to reduction of the independent variable x and parameter b to a single scaled variable $u \equiv bx$. Instead of the data points falling on a family of curves, one for each value of b, we find the

data points *collapse* onto a single curve given by the scaling function $\tilde{P}(u) \equiv P(x)/b$. Thus, it is sufficient to specify only one parameter b in order to characterize the heterogeneous heartbeat variations of each subject in this group.

We also analysed heart rate dynamics for the healthy subjects during day-time hours (noon — 6pm). Our results indicate that the observed, apparently universal behavior holds not only for the night phase but for the day phase as well (Fig.3b).

To ascertain whether the observed scaling of the distributions for healthy subjects is an intrinsic property of normal heart beat dynamics, we test the cumulative variation magnitude method on artificially-generated signals with known properties. Our analysis of uniformly-distributed random numbers in the interval $[0, 1]$ and of Gaussian-distributed noise with and without long-range power law correlations shows that after the wavelet transform the amplitude distributions follow the Rayleigh probability distribution $(x/\sigma^2)e^{-x^2/\sigma^2}$. This finding agrees with the central limit theorem, which can be expressed as a property of convolutions (in our case wavelet transform): the convolution of a large number of positive functions is approximately a Gaussian function, and the instantaneous amplitudes of a Gaussian process follow the Rayleigh probability distribution [17].

We perform the same test on surrogate data obtained from a healthy subject by Fourier transforming the original time series, preserving the amplitudes of the Fourier transform but randomising the phases, and performing an inverse Fourier transform (Fig.4). Thus both the original and surrogate signals have *identical* power spectra. Application of the cumulative variation magnitude analysis on this surrogate signal results again in a Rayleigh distribution, whereas the original time series has a distribution with an exponential tail. This test clearly indicates the important role of *phase correlations* in the RR time series. The presence of these correlations is most likely related to the underlying nonlinear dynamics. Thus our procedure preserves collective phase properties of the original signal which cannot be detected by power spectrum analysis.

This study uncovers a previously unknown nonlinear feature of healthy heart rate fluctu-

ations. Prior reports of universal properties of the normal heart beat and other physiological signals were related to long-range correlations and power law scaling [18–20]. However, these properties, detected by Fourier and fluctuation analysis techniques, ignore information related to the phase interactions of component modes. The nonlinear interaction of these modes accounts for the patchy, non-homogeneous appearance of the heartbeat time series.

Our finding suggests that for healthy individuals, there may be a common structure to this nonlinear phase interaction. The scaling property cannot be accounted for by activity, since we analysed data from subjects during nocturnal hours. Moreover, it cannot be accounted for by sleep stage transitions, since we found a similar pattern during day-time hours. The basis of this robust temporal structure remains unknown and presents a new challenge to understanding nonlinear mechanisms of heartbeat control.

Additionally, we find that subjects with sleep apnea, a common and important instability of cardiopulmonary control, show a dramatic alteration in the scaling pattern — possibly related to pathologic mode locking associated with periodic breathing dynamics [21]. Thus, the dual use of wavelet and Hilbert transform techniques may be of practical diagnostic and prognostic value, and may also be applicable to a wide range of heterogeneous, "real world" physiological signals.

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FIGURES

FIG. 1. (a) Segment of electrocardiogram showing beat-to-beat (RR_i) intervals. (b) Plot of RR-time series vs. consecutive beat number for a period of 6h ($\approx 2.5 \times 10^4$ beats). Nonstationarity (patchiness) is evident over both long and short time scales. Although these patches clearly differ in the amplitude and frequency of variations, their quantitative characterization remains an open problem. (c) Wavelet transform $T_\psi(RR)$ of the RR-signal in Fig.1b. Nonstationarities related to constants and linear trends have been filtered. The first derivative of the Gaussian $\psi^{(1)}$ is orthogonal to segments of the time series with approximately constant local average. This results in fluctuations of the wavelet transform values around zero with highest spikes at the positions where a sharp transition occurs. Thus, the larger spikes indicate the boundaries *between* regimes with different local average in the signal, and the smaller fluctuations represent variations of the signal within a given regime. Since $\psi^{(1)}$ is not orthogonal to linear (non-constant) trends, the presence of consecutive linear trends in the RR-intervals will give rise to fluctuations of the wavelet transform values around different nonzero levels corresponding to the slopes of the linear trends. $\psi^{(2)}$ and higher order derivatives can eliminate the influence of linear as well as nonlinear trends in the fluctuations of the wavelet transform values. (d) Instantaneous amplitudes $A(t)$ of the wavelet transform signal in Fig.1c; $A(t)$ calculated using the Hilbert transform measures the cumulative variations in the interbeat intervals over an interval proportional to the wavelet scale a.

FIG. 2. (a) Probability distributions $P(x)$ of the amplitudes of heart rate variations $x \equiv A(t)$ for a group of 18 healthy adults. Individual differences are reflected in the different average value and widths (standard deviations) of these distributions. All distributions are normalised to unit area. (b) Same probability distributions as in Fig.2a after rescaling: $P(x)$ by P_{max}, and x by $1/P_{max}$ to preserve the normalization to unit area. The data points collapse onto a single curve. (c) Probability distributions for a group of 16 subjects with obstructive sleep apnea. We note that the second (rightward) peak in the distributions for the sleep apnea subjects corresponds to the transient emergence of characteristic pathologic oscillations in the heart rate associated with periodic breathing [14, 21]. (d) Distributions for the apnea group after the same rescaling as in (b). The absence of data collapse demonstrates deviation from the normal heart behavior. We note that direct analysis of interbeat interval histograms does *not* lead to data collapse or separation between the healthy and apnea group. Moreover, we find that the direct application of the Hilbert transform yielding the probability distribution of the instantaneous amplitudes of the original signal does *not* clearly distinguish healthy from abnormal cardiac dynamics. Hence the cricial feature of the wavelet transform is that it extracts dynamical properties hidden in the cumulative variations. We observe for the healthy group good data collapse with stable scaling form for wavelet scale $a = 2$ up to $a = 32$. However, for very small scales ($a = 1, 2$) the average of the rescaled distributions of the apnea group is indistinguishable from the average of the rescaled distributions of the healthy group. Hence very high frequencies are equally present in the signals from both groups. Our analysis yields the most robust results when a is tuned to probe the collective properties of patterns with duration of $\approx \frac{1}{2} - 1$ min in the time series ($a = 8, 10$). The subtle difference between day and night phases is also best seen for this scale range (Fig.3).

FIG. 3. (a) The solid line is an analytic fit of the rescaled distributions of the beat-to-beat variation amplitudes of the 18 healthy subjects during sleep hours to a stable Gamma distribution with $\nu = 1.4 \pm 0.1$ (note that stable Gamma form has been used previously in the literature to describe other processes — e.g. the spike activity of a single neuron [22]). (b) Data for 6h records of RR intervals for the day phase of the same control group of 18 healthy subjects demonstrate similar scaling behavior with a Gamma distribution and $\nu = 1.8 \pm 0.1$, thereby showing that the observed universality for the healthy heart dynamics is not confined to the nocturnal phase. Semilog plots of the averaged distributions show a systematic deviation — crossover — in the tails of the night-phase distributions, whereas the day-phase distributions follow the exponential form over practically the entire range. Note that the observed crossover for the night phase indicates higher probability of larger variations in the healthy heart dynamics during sleep hours in comparison with the daytime dynamics. We find that the maximum difference between the cumulative distributions of the individual subjects and the Gamma fit in point (a) evaluated with the Kolmogorov-Smirnov test can serve as a good index to separate the healthy from the apnea group. Analysis of the first and second moments of the individual distributions also shows clear separation for both groups.

FIG. 4. (a) Original RR-time series as a function of beat number. (b) Wavelet transform $T_\psi(RR)$ of this series. (c) Surrogate ($RR_{\rm sur}$) signal after phase randomisation. (d) Wavelet transform of the surrogate signal which is more homogeneous (less patchy) in comparison with (b). (e) Probability distributions of the amplitudes of variations after wavelet transform of the original and surrogate signals, as well as the theoretical Rayleigh distribution. The theoretical Rayleigh agrees with the distribution of the wavelet transform of the surrogate signal with randomised phases.