Broken Asymmetry of the Human Heartbeat: Loss of Time Irreversibility in Aging and Disease

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Time irreversibility, a fundamental property of nonequilibrium systems, should be of importance in assessing the status of physiological processes that operate over a wide range of scales. However, measurement of this property in living systems has been limited. We provide a computational method derived from basic physics assumptions to quantify time asymmetry over multiple scales and apply it to the human heartbeat time series in health and disease. We find that the multiscale time asymmetry index is highest for a time series from young subjects and decreases with aging or heart disease. Loss of time irreversibility may provide a new way of assessing the functionality of living systems that operate far from equilibrium.

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Living systems are subject to mass, energy, entropy, and information fluxes across their boundaries. Under healthy conditions, these open dissipative systems function in conditions far from equilibrium. In contrast, for extreme cases presaging death, a state approaching maximum equilibrium is reached.

Such living systems utilize energy to evolve to more hierarchically ordered structural configurations and less entropic states in comparison with the surrounding environment. Their self-organizing capability is related to the unidirectionality of the energy flow across the system's boundaries and the irreversibility of the underlying processes. To the extent that loss of self-organizing capability is associated with aging or disease, loss of time irreversibility may be a marker of pathology.

Analytically, time irreversibility refers to the lack of invariance of the statistical properties of a signal under the operation of time reversal [1]. It is a fundamental property of nonequilibrium systems [2] and, therefore, is expected to be present in biological systems ranging from the cellular to the system levels [3]. Surprisingly, relatively little work has been published on practical implementation of time reversibility to biological time series [4–9].

In this Letter, we provide systematic evidence to support the hypotheses that (i) time irreversibility is greatest for healthy physiologic systems under free-running conditions, which exhibit the most complex dynamics [10,11], and (ii) time irreversibility decreases with aging or pathology, providing a marker of loss of functionality and adaptability. Therefore, quantitative measurements of time irreversibility may be of basic and practical importance [12,13].

Time irreversibility has been reported in tremor time series of patients with Parkinson's disease [5,6] and in electroencephalographic seizure recordings [7,9]. These studies, suggesting an increase of time asymmetry with disease, are based on analyses that focus on single scale measurements. However, physiologic time series generate complex fluctuations over multiple time scales associated with a hierarchy of interacting regulatory mechanisms. Therefore, it is important to introduce an asymmetry measure that takes into account the multiple time scales inherent in physiologic control mechanisms.

To illustrate how such a measure can be implemented for physiologic signals analysis, we use the heart rate time series—the output signal of an integrative physiologic control system—as an example. For this application, we first map the original heart rate time series, denoted as $X = \{x_i\}$, $1 \le i \le N$, to the sequences of heart rate increments and decrements, $Y = \{y_i\}$, $1 \le i \le N-1$, where $y_i = x_{i+1} - x_i$ and N is the number of data points. Physiologically, this new sequence reflects the competition between the neuroautonomic stimuli impinging on the sinus node.

In order to extract information on multiple time scales, we analyze the original signal at different resolutions by constructing a set of coarse-grained time series [14]. Each coarse-grained time series is built by taking the average inside a moving window with τ data points, where τ is the scale factor. Each element of a coarse-grained time series is defined as

$$y_\tau(i) = \sum_{j=0}^{\tau-1} y_{i+j}/\tau. \quad (1)$$

Using a statistical physics approach, we make the simplifying assumptions that each transition (increase or decrease in heart rate) is independent and requires a specific amount of "energy," E. The probability density function of this class of system [15,16] can be assumed to follow

$$\rho \propto \exp(-\beta E - \gamma Q), \quad (2)$$

where Q represents the nonequilibrium heat flux across the boundary of the system, and β and γ are the Lagrange

multipliers derived from the constraints on the average value of the energy E per transition and the average contribution of each transition to the heat flux Q.

Since the time reversal operation on the original heart rate time series inverts an increase of heart rate to a decrease, and vice versa, the difference between the average energy for the *activation* of heart rate, i.e., $\langle \beta E + \gamma Q \rangle_{y_\tau > 0}$, and the *relaxation* of heart rate, i.e., $\langle \beta E + \gamma Q \rangle_{y_\tau < 0}$, can be used as a measurement of time reversal asymmetry.

Taking into consideration that the assumption of Eq. (2) links the energy to the empirical distribution, we define the following measure of temporal irreversibility:

$$a(\tau) = \frac{\int_0^\infty [\rho(y_\tau)\ln\rho(y_\tau) - \rho(-y_\tau)\ln\rho(-y_\tau)]^2 dy_\tau}{\int_{-\infty}^\infty \rho(y_\tau)\ln\rho(y_\tau) dy_\tau}. \quad (3)$$

The time series is reversible if and only if $a(\tau) = 0$.

For biological systems, it is not only important to quantify the degree of irreversibility of a time series but also to know which time series represents the ''forward'' direction and which is time reversed. Equation (3) does not provide this information. Therefore, we consider instead the equation

$$A(\tau) = \frac{\int_0^\infty [\rho(y_\tau)\ln\rho(y_\tau) - \rho(-y_\tau)\ln\rho(-y_\tau)] dy_\tau}{\int_{-\infty}^\infty \rho(y_\tau)\ln\rho(y_\tau) dy_\tau}. \quad (4)$$

If $A(\tau) > 0$, then for scale τ the time series is irreversible. However, if $A(\tau) = 0$, the time series may or may not be irreversible for scale τ.

Real-world signals, such as heart rate time series, are sampled at a finite frequency, in which case y_τ is a discrete variable. For the analysis of these signals, the following equation provides an estimator of $A(\tau)$:

$$\hat{A}(\tau) = \frac{\sum_{y_\tau > 0} \Pr(y_\tau)\ln[\Pr(y_\tau)]}{\sum_{y_\tau} \Pr(y_\tau)\ln[\Pr(y_\tau)]} - \frac{\sum_{y_\tau < 0} \Pr(y_\tau)\ln[\Pr(y_\tau)]}{\sum_{y_\tau} \Pr(y_\tau)\ln[\Pr(y_\tau)]}, \quad (5)$$

where $\Pr(y_\tau)$ denotes the probability of the value y_τ.

For a range of time scales, we can then define an easily computed multiscale asymmetry index (A_I) as the summation of the asymmetry values obtained for each time scale, i.e.,

$$A_I = \sum_{\tau=1}^{L} \hat{A}(\tau). \quad (6)$$

To apply this measurement to real-world data [17], we analyze human cardiac interbeat intervals time series from an open-access database [18] (Fig. 1) for four groups: healthy young, healthy elderly, those with congestive heart failure, and those with atrial fibrillation. In Fig. 1 the solid line connects the values $\sum_{y_\tau > 0} \Pr(y_\tau)\ln[\Pr(y_\tau)]$ for scales 1 to 20 [19]. Each of these values reflects the average amount of energy associated with an increase of the heart rate for a particular scale. Similarly, the dotted line connects the values $\sum_{y_\tau < 0} \Pr(y_\tau)\ln[\Pr(y_\tau)]$ for the same set of scales. Each of these values reflects the average amount of energy associated with a decrease of the heart rate for scale τ.

The time asymmetry index A_I is significantly higher for healthy young subjects than for both healthy elderly subjects and subjects with pathology ($p < 0.005$). Furthermore, the time asymmetry is higher for the elderly group than for the pathologic groups ($p < 0.005$). In contrast, current (single scale-based) time asymmetry measures do not yield consistent differences.

The results are compatible with the general concept that time irreversibility degrades with aging and disease over multiple time scales. Note that both highly irregular heartbeat time series, such as those from subjects with atrial fibrillation, and less variable, more regular time series, such as those from heart failure subjects in sinus rhythm, tend to be more time symmetric than time series observed in healthy subjects.

We next tested the hypothesis that cardiac interbeat interval time series of healthy subjects have greater time asymmetry than artificial time series generated by algorithms designed to model heart rate dynamics. We applied our method to the 26 physiologic and 24 synthetic time series of an international time series competition database [20]. As predicted, the asymmetry index was higher for physiologic time series ($A_I = 8.9 \pm 5.1$, mean $\pm$ standard deviation) than for the synthetic ones ($A_I = -0.25 \pm 1.5$). This finding indicates that the proposed models do not fully account for the nonequilibrium properties of the control mechanisms regulating heart rate under healthy conditions.

The presence of irreversibility in dynamical systems excludes Gaussian linear processes and static nonlinear transformations of such processes as possible models [21,22]. However, it does not rule out the possibility of trivial sources of irreversibility not generated by the dynamical system, e.g., artifacts and certain types of nonstationarities which predominantly affect the signal on a single scale.

Consider the signal that results from superimposing Gaussian white noise on a piecewise linear signal with a characteristic scale S. For the resulting signal, $A(\tau) \to 0$ only for scales $\tau \gg S$, meaning that the linear segments affect the asymmetry values over a range of scales and not only on scale S. Therefore, obtaining $A(\tau) \neq 0$ for a set of scales does not necessarily imply that the structure of the time series at all scales is asymmetric.

To further address this question, we use the empirical mode decomposition (EMD) method introduced by Huang *et al.* [23], with which any signal $X(t)$ can be decomposed into a finite number of ''intrinsic mode functions'' (IMFs),

$$X(t) = \sum_{i=1}^{n} \mathrm{IMF}_i + r_n, \quad (7)$$

where r_n is a residue, which can be either the mean trend or a constant.

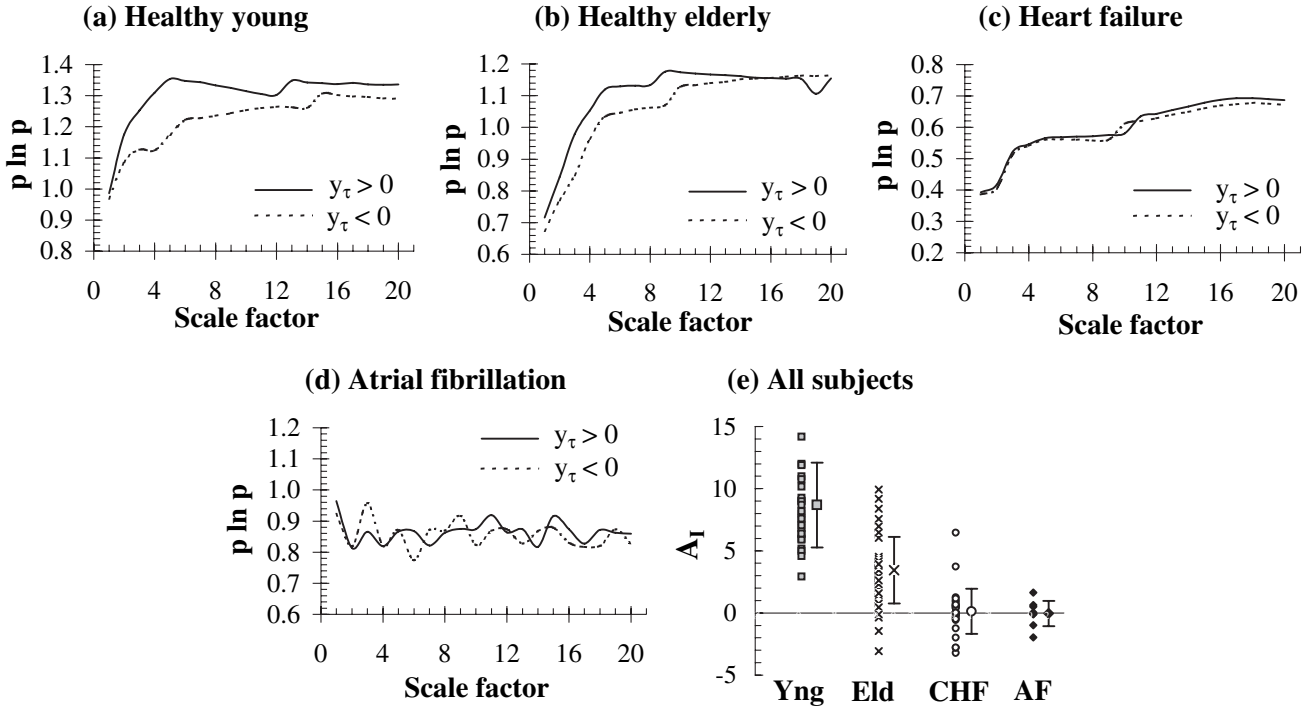

FIG. 1. Multiscale time irreversibility (asymmetry) analysis of the cardiac interbeat interval sequences derived from 24 h Holter monitor recordings of representative subjects: (a) healthy young (Yng); (b) healthy elderly (Eld); (c) congestive heart failure (CHF); and (d) atrial fibrillation (AF). Scale factor is referenced to heartbeat number. For each scale, the values of A_I from the dotted and solid lines reflect, respectively, the average amount of "energy" associated with increases and decreases of the heart rate (see text). (e) Asymmetry index A_I for groups of 26 healthy young subjects ($A_I = 8.68 \pm 3.40$, mean $\pm$ standard deviation), 46 healthy elderly subjects ($A_I = 3.44 \pm 2.67$), 43 CHF subjects ($A_I = 0.13 \pm 1.80$), and 9 subjects with AF ($A_I = -0.04 \pm 1.01$). Differences between groups are significant ($p < 0.005$, t test), with the exception of the two pathologic states (CHF vs AF). Cardiac interbeat interval time series obtained during the sleeping period yield comparable results. Therefore, nonstationarities due to physical activity do not account for these asymmetry properties. Note that, in terms of the mean A_I values, the results indicate that the time series from the group of healthy young subjects are the most temporally irreversible, followed by those from the group of healthy elderly subjects and those from the groups of patients, both of which have A_I values close to zero.

The EMD method is based on the assumption that a signal consists of different, not necessarily stationary IMFs, each oscillating around a mean value at a characteristic time scale. Unlike wavelet and Fourier analysis, the EMD uses a fully adaptive basis that is derived from each data set by means of a sifting process. Therefore, it is applicable to the analysis of nonlinear and nonstationary time series [24].

To the extent that the asymmetry property has a nontrivial source affecting the system's dynamics over multiple scales, a certain degree of asymmetry is expected in several IMFs. To test this hypothesis, we applied the EMD method to the time series of healthy subjects and those generated by the heart rate dynamics models included in the PhysioNet international time series competition database [20]. The mean values and the standard deviations of the asymmetry index for the physiologic ($N = 26$) and the model ($N = 24$) generated time series groups were (i) IMF 1: $A_I = 0.46 \pm 1.20$ (physiologic) and $A_I = -0.26 \pm 0.60$ (model), (ii) IMF 2: $A_I = 1.37 \pm 1.56$ (physiologic) and $A_I = -0.89 \pm 1.22$ (model), and (iii) IMF 3: $A_I = 3.07 \pm 3.01$ (physiologic) and $A_I = -0.43 \pm 3.64$ (model) [25]. Note that the difference between the A_I values for each comparison was statistically significant ($p \leq 0.005$).

These results confirm that (i) time asymmetry is not just a local property of the healthy heartbeat; instead, it extends over a wide range of scales; (ii) proposed models of heart rate dynamics fail to account for this multiscale property; (iii) nonstationarities or artifacts with a characteristic time scale are not the explanation of the multiscale asymmetry property. It is, however, unclear whether this robust property of the healthy cardiac interbeat variability results from a superposition of individual contributions, e.g., sinus arrhythmia (coupling between heartbeat and respiration), baroreflexes, circulating hormones, and other mechanisms operating on different time scales, or whether it is a collective property of the system.

In summary, multiscale time irreversibility analysis provides information not extractable by conventional methods, including entropy measures and spectral techniques. Since time asymmetry is a fundamental property of

healthy, far from equilibrium systems, this approach may be useful for both the development and testing of realistic models of physiologic control and for bedside diagnostics.

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[14] Fourier analysis also extracts information at various scales, since it decomposes a signal into a set of trigonometric functions, each of which oscillates with a different frequency. However, when applied to intrinsically nonlinear, nonstationary signals, individual Fourier components do not capture important features of the system on different time scales. For example, although a signal may be irreversible, all its Fourier components are time reversible. The time direction information is encoded in the phase relationships between the Fourier components. This information, however, is not extractable from the analysis of individual Fourier components.
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[17] Given a time series $\{x_1, x_2, \ldots, x_i, \ldots, x_N\}$, the A_I can be calculated as follows. (i) For each scale τ, construct the coarse-grained time series according to the equation $y_\tau(i) = (x_{\tau+i} - x_i)/\tau$, with $i \leq N - \tau$. (ii) Calculate the histogram for each coarse-grained time series. We used the inverse of the electrocardiographic Holter recording sample frequency as the histogram's bin size, denoted as Δ. Note that the histogram is a function $H(n)$ that associates the number of data points between $n\Delta$ and $(n + 1)\Delta$ to each $n \in N$. (iii) For each coarse-grained time series, calculate the values
$$\hat{A}(\tau) = \frac{\sum_{n>0} H(n) \times \ln[H(n)] - H(-n) \times \ln[H(-n)]}{\sum_{n\neq 0} H(n) \times \ln[H(n)]}.$$
(iv) Given a finite set of scale factors, $\tau = 1, 2, \ldots, L$, calculate the A_I according to the equation $A_I = \sum_{\tau=1}^{L} \hat{A}(\tau)$.
[18] http://www.physionet.org/physiobank/database/.
[19] In the case of time series containing a dominant oscillation with a characteristic time scale (e.g., heart rate time series of subjects with central or obstructive sleep apnea), the values of $\sum_{y_\tau>0} \Pr(y_\tau) \ln[\Pr(y_\tau)]$ and $\sum_{y_\tau<0} \Pr(y_\tau) \times \ln[\Pr(y_\tau)]$ over a set of scales oscillate with a frequency close to the frequency of the dominant component in the original time series.
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[25] In order to calculate the A_I values for a set of IMFs, with comparable confidence intervals, all IMFs should comprise a minimum number of cycles (zero-crossing points). Since the number of cycles in the IMFs depends on their characteristic time scale, higher order IMFs should contain more data points than lower order IMFs. Therefore, for finite length time series, it is not possible to calculate reliable A_I values for all the IMFs. In the case of time series with approximately 3×10^4 data points used here, we calculated the A_I values only for the first three IMFs.