

## Scaling and Ordering of Neonatal Heart Rate Variability

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By analyzing cardiac beat-to-beat intervals and interbeat increments, we find that—unlike adults—the difference in the pattern of interbeat increments in healthy and sick newborn infants is more due to a change in the amplitude and much less to a change in the ordering of the interbeat increments. This suggests that very low-frequency elements of neonatal and adult heart rate variability rise from fundamentally different mechanisms.

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The time between heartbeats varies incessantly. Though it is generally recognized that this heart rate variability (HRV) is reduced during acute and chronic illness, the mathematical characteristics of this change are not well understood. Each heartbeat is characterized by a ventricular depolarization (QRS) complex in the voltage recorded by the electrocardiograph, and the time between consecutive heartbeats is called the RR interval. One way to study the mechanism is to analyze time series of RR intervals. Another is to analyze the time series of *interbeat increments* obtained from the time series of RR intervals by subtracting one RR interval from the next. The two strategies yield different kinds of information. The RR interval results from many influences, some of which are nearly *static* such as age and body temperature. The interbeat increments, on the other hand, capture the local *dynamics* of the system. This kind of study allows distinction between possible mechanisms of a reduction in HRV during illness. If the interbeat increments are smaller during illness, the pattern of HRV might be otherwise qualitatively similar—with the same distribution and ordering of the interbeat increments—to that during health, but occur on a smaller scale. We would call this a difference in *scaling*. In this scenario, the interbeat increments during illness and during health, once normalized, would have the same distribution and ordering. Another possible mechanism is that the distributions of interbeat increments are the same during illness (low HRV) and health (normal HRV), but that these differences are *ordered* differently.

Peng *et al.* have recently developed techniques to quantify such fundamental ordering properties of series of nucleotides [1] and interbeat increments of heart rate data [2]. Interestingly, they have demonstrated long-range correlations in interbeat increments of a low-pass filtered heart rate signal in adults, and have found that these correlations are not present in adults with heart disease. They showed that the difference in time series of RR intervals

in sick and healthy adults lies not in the distribution of interbeat increments, but rather in their ordering.

To identify the mechanism and to test the idea that these properties found in adults are also present in newborn infants, we have analyzed the increase in neonatal HRV that accompanies recovery from severe illness in a large clinical data set. We find that the HRV of sick and recovered *newborn infants*, in contrast to that of *adults*, differs much more in the amplitude of the interbeat increments and much less in their ordering. This suggests that very low-frequency elements of neonatal and adult HRV arise from different physiologic mechanisms, and that the difference in HRV of sick and recovered neonates is one primarily of scaling.

The patient population and data acquisition have been described [3]. For this analysis, we constructed 114 time series of 8192 RR intervals from nine newborn infants during episodes of severe cardiorespiratory failure ( $n = 27$ ), and from the same infants 5 to 15 days later after they had recovered ( $n = 87$ ). We call these time series  $RR_n$ , and we call the time series of differences from one beat to the next  $D_n$ .

We constructed a low-pass filtered  $RR_n$ , which we call  $B_L(n)$ , with a cutoff frequency  $\omega_c = 0.005$ . The effect of this digital filter is to remove frequencies above  $0.005 \text{ beat}^{-1}$ . Many of the calculations were carried out on the time series of the interbeat increments [2] obtained *after filtering*, by subtracting the value of one RR interval from the next. This series is called  $I(n)$ . Calculations were performed on two versions of these series—the raw data, which we call  $I_{\text{raw}}(n)$ , or after transformation to a series with zero mean and unit standard deviation called  $I_{\text{norm}}(n)$ .

Frequency histograms of interbeat increments were fitted by the Lévy stable distribution [4]

$$P(i, \psi, \gamma) = \frac{1}{\pi} \int_0^{\infty} \exp(-\gamma q^\psi) \cos(qi) dq,$$

or an exponential decay function

$$P(i) = A_0 \exp\left(\frac{-i}{\tau}\right),$$

using nonlinear least-squares methods. Data are given as mean  $\pm$  standard deviation.

Figure 1 shows the analysis of the series of RR intervals. Figures 1(a) and 1(b) are plots of RR intervals as a function of beat number for approximately 80 000 beats from the same infant. The time series in Fig. 1(a) was acquired at a time of severe cardiorespiratory failure, and that in Fig. 1(b) 10 days later, after recovery. Qualitatively, there is a great deal more HRV after recovery [Fig. 1(b)]. Power spectra of these time series are shown in Fig. 1(c). The record lengths were 65 536 beats; spectra of overlapping windows of 8192 beats were averaged. After recovery there is a large increase in power at all frequencies.

The filtered time series  $B_L(n)$  shown in Figs. 1(d) and 1(e) isolate HRV information over long time scales. Their power spectra are shown in Fig. 1(f). The total power after recovery is about twice that during illness—0.19 and 0.08 msec<sup>2</sup> Hz, respectively.

Figure 2 shows the analysis of the *interbeat increments*,  $I(n)$ . The time series  $I_{\text{raw}}(n)$  in Figs. 2(a) and 2(b) show that the interbeat increments during illness are smaller than those after recovery. After normalization, though, the time series  $I_{\text{norm}}(n)$  appear more the same [Figs. 2(d) and 2(e)]. Frequency histograms of both  $I_{\text{raw}}(n)$  and

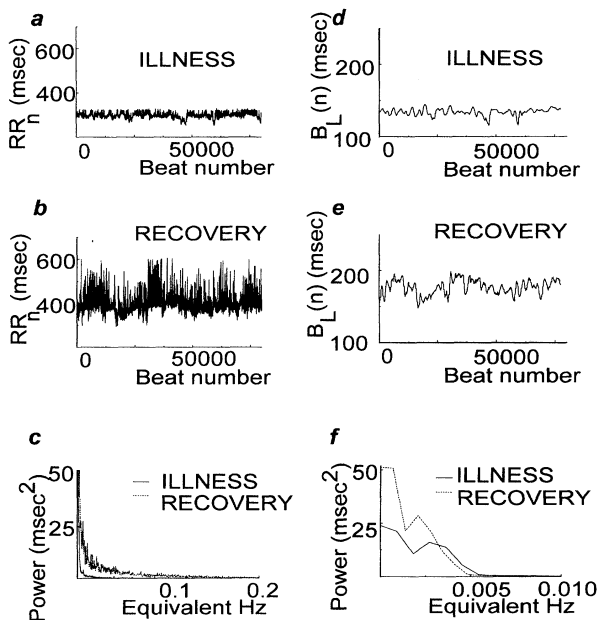


FIG. 1. Time series of RR intervals from the same infant during illness (a) and after recovery (b). (c) shows their power spectra—after recovery there is a fourfold rise in total power and a fivefold rise in power from 0.02 to 0.2 equivalent Hz. (d) and (e) are the low-pass filtered versions of time series in (a) and (b). (f) shows their power spectra.

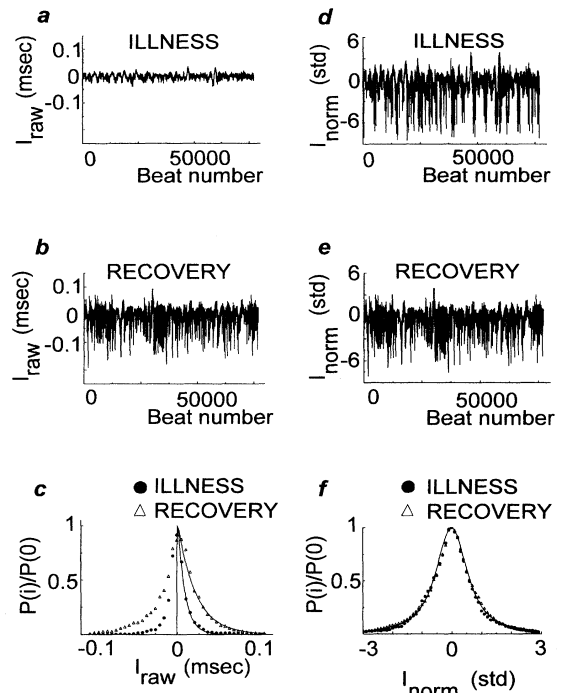


FIG. 2. (a), (b), (d), and (e) are time series of the differences between successive RR intervals of the time series in Fig. 1. In (a) and (b) the raw differences are plotted; in (d) and (e) the differences have first been normalized to (0,1) distributions. (c) is a frequency histogram of all the raw differences; for the histogram in (f), the data were first normalized to (0,1) distributions.

$I_{\text{norm}}(n)$  are shown in Figs. 2(c) and 2(f). The  $x$ -axis bin width is 0.01 msec, and the highest frequency in both histograms has been made 1 to allow comparison. In Fig. 2(c), the histograms of  $I_{\text{raw}}(n)$ , the data distributions are obviously very different. The mean (of the absolute) interbeat increment increases significantly after recovery. To quantify the difference, we fit the values greater than 0 with an exponential decay function. The exponential factor for the data during illness was 0.0084 msec; after recovery it was 2.5-fold higher at 0.021.

Figure 2(f) shows the frequency histogram of the *normalized* interbeat increments,  $I_{\text{norm}}(n)$ . The two histograms are superimposable. The smooth line is a fit by the Lévy stable distribution with  $\gamma = 0.5$  and  $\psi = 1.14$ , and describes either data set equally well. It also shows that the distribution of interbeat increment is non-Gaussian [2]. The finding that the normalized data sets share the same probability distribution is very strong evidence that one data set is a scaled version of the other. Thus, the interbeat increments differ in absolute magnitude—by more than twofold—but share a common distribution once normalized. This finding suggests that a major difference between interbeat increments in low and normal neonatal HRV is that of *scaling*.

Of course, in addition to the differences in scaling, low and normal neonatal interbeat increments could still be ordered very differently. To determine the contribution of ordering of interbeat intervals in neonatal HRV during illness and after recovery, we used several strategies. First, we implemented the mean fluctuation function  $F(n)$  of Peng *et al.* [2], defined as

$$F(n) \equiv \overline{|B_L(n' + n) - B_L(n')|},$$

where the bar denotes an average over all  $n'$ . The slope of the straight line through the mean difference  $F(n)$  as a function of the lag on a log-log plot between lag values of 200 and 4000 is calculated. Peng *et al.* found that these slopes for healthy adults were significantly different from those for adults with heart disease. Figure 3(a) is a log-log plot of  $F(n)$  for the two time series presented in Fig. 1. The slopes, surprisingly, are much the same—0.48 during illness and 0.52 after recovery. Figure 3(b) shows the slopes of  $F(n)$  for all of the data sets. There was a 13% difference—the mean  $\alpha$  were  $0.46 \pm 0.13$  during illness and  $0.52 \pm 0.09$  after recovery. This suggests that there was relatively little difference in the ordering of the interbeat intervals, as judged by the fluctuation function, despite the large differences in clinical status and in HRV. Peng *et al.*, on the other hand, found  $\alpha$  of  $0.19 \pm 0.05$  for healthy adults and  $0.41 \pm 0.18$  for adults with heart disease [2].

To confirm this surprising finding, we used another approach to assess the ordering of  $I(n)$ —we counted runs of the interbeat increments. We defined a run as a sequence of consecutive points falling above or below an arbitrary

defined threshold value [5]. Runs were counted above and below thresholds of msec [for  $I_{\text{raw}}(n)$ ] or standard deviations [for  $I_{\text{norm}}(n)$ ]. Figures 3(c) and 3(d) show plots of the number of runs in the illness and recovery data sets as a function of an arbitrarily defined threshold value. Figure 3(c) shows that there are many fewer runs in the data acquired during illness. For  $I_{\text{norm}}(n)$ , the threshold was set in multiples of the standard deviation. The normalization procedure reduces the difference between the data sets, as shown in Fig. 3(d). When the threshold was 60% of the standard deviation, the difference in the mean number of runs was only 10%. Thus there is little difference in the ordering, as judged by runs analysis, of the interbeat increments of newborn infants during illness and those after recovery.

Peng *et al.* [2] evaluated correlations among interbeat increments by measuring the slope of a log-log power spectrum of  $D(n)$  from  $10^{-4}$  to  $10^{-2}$  beat $^{-1}$ , which they called  $\beta$ . The finding of  $\beta = 1$  implies strong long-term anticorrelation, and was characteristic of normal HRV. Heart disease led to lower values of  $\beta$ . If the ordering is the same in low and normal neonatal HRV, then  $\beta$  should be the same for both sets. In fact, it is not. Like Peng *et al.*, we find  $\beta$  is  $1.01 \pm 0.07$  for  $D(n)$  after recovery and  $0.55 \pm 0.04$  during illness.

This relatively large change in  $\beta$  between sick and normal HRV differs significantly from the 10% to 13% changes in fluctuation function and runs analysis. One possible explanation for this unexpected result is that  $\beta$  is more sensitive to changes in ordering. Hence, we studied  $\beta$ 's sensitivity to changes in ordering both in simulated data and in our clinical data sets.

We performed numerical experiments on two number sets stimulating time series of  $I(n)$ . The first is a set of 65 536 random numbers with a Gaussian distribution around a mean of 0 with standard deviation of 50. We call this  $S_{\text{rand}}$ . The second is a set of 65 536 numbers derived by adding sinusoidal functions of increasing frequency and amplitude with random phases. We call this  $S_{\text{detrn}}$ . The numbers were scaled so that  $S_{\text{detrn}}$  also had a Gaussian distribution with a mean of 0 and standard deviation of 50. Figures 4(a)–4(c) show segments of  $S_{\text{rand}}$  and  $S_{\text{detrn}}$ , their power spectra, and frequency histograms. By design the power spectrum of  $S_{\text{detrn}}$  has a slope of 1 and  $S_{\text{rand}}$  has a slope of 0. The strategy was to perturb the highly correlated  $S_{\text{detrn}}$  by introducing a wide range of degrees of randomness. We accomplished this by adding scaled versions of  $S_{\text{detrn}}$  and  $S_{\text{rand}}$  together. Accordingly, we constructed number sets of the form  $S_{\omega} = \omega(S_{\text{detrn}}) + (1 - \omega)(S_{\text{rand}})$ . As  $\omega$  rises from 0 to 1,  $S_{\omega}$  varies from random to deterministic. The value of  $\omega$  is thus an estimate of the randomness of the time series. We then calculated  $\beta$  as a function of  $\omega$ . Figure 4(d) shows that  $\beta$  falls from 1 to 0.5 after incorporating about 35% randomness.

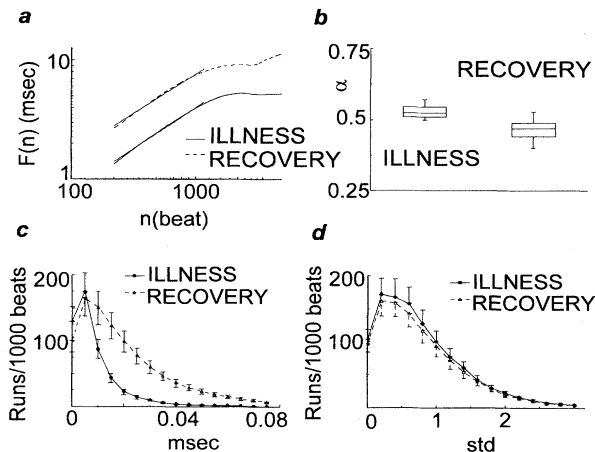


FIG. 3. (a) shows  $F(n)$ , the fluctuation function of the filtered time series of Figs. 1(d) and 1(e). The straight lines were fit to the data points from 200 to 1000 beats. The slopes are 0.48 (illness) and 0.52 (recovery). (b) shows box plots of  $\alpha$ , the slope of  $F(n)$ , for 114 time series. The horizontal line in the middle of each box is the median; the box encloses 50% of the data points; the vertical bars enclose 80%. (c) and (d) show the number of runs of interbeat increments for all the time series. Bars are standard deviation.

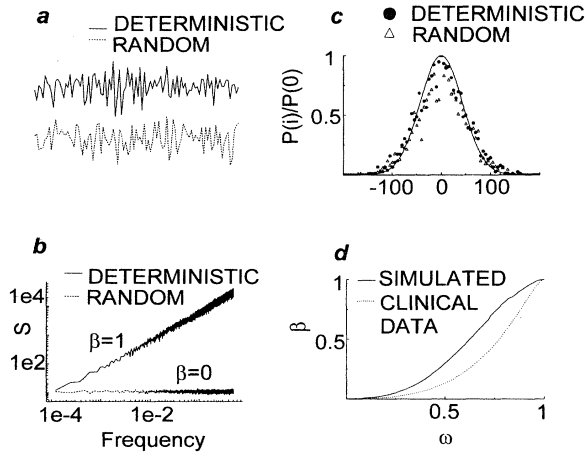


FIG. 4. Numerical simulations and the effect of incorporating randomness on  $\beta$ . (a) shows 100 point segments of  $S_{\text{rand}}$  and  $S_{\text{detn}}$ , and (b) shows their power spectra. (c) is a superimposition of frequency histograms overlaid with a single Gaussian with mean 0 and standard deviation 50. (d) shows the relationship of  $\beta$ , the slope of the log-log power spectrum, to  $\omega$  for simulated and clinical data.

Because  $S_{\text{detn}}$  is not a true representation of heart rate data, we performed the same calculation replacing  $S_{\text{detn}}$  with clinical data sets. The same figure shows that, for clinical data obtained after recovery,  $\beta$  falls from 1 to 0.55 after incorporating 15% randomness. This level of randomness is very much in keeping with the results of the fluctuation function and runs analysis. We interpret this result to mean that a relatively small reordering of clinical HRV data results in a relatively large change in  $\beta$ , a measure of long-term correlation. Thus, the observed fall in  $\beta$  from 1 to 0.55 need not imply a major change in the ordering of the interbeat increments. To test this idea, we reordered a data set from a *healthy* infant by randomly shuffling about 10% of the data. [Shuffling is carried out by forming a new time series consisting of—starting from the  $i$ th point—every  $n$ th point of the original time series  $X$  ( $= x_1, x_2, x_3, \dots$ ), which is then shuffled and inserted back in (the original time series)  $X$  to form  $X_i^n$ . The shuffled time series  $X_i^n$  is used to calculate  $\beta_i$ . An average

$\beta$ ,  $\bar{\beta} = n^{-1} \sum_{i=1}^n \beta_i$ , is calculated from  $n$  different time series. For 10% shuffling,  $n = 10$ .] The power spectrum of the transformed data set now had  $\bar{\beta} = 0.55$ , the same as for clinical data during illness. Our findings thus suggest that normal HRV can be transformed to low HRV by a twofold to threefold rescaling and 10%–15% reordering.

We found no fixed relationship between  $\alpha$  and  $\beta$ . For perfect fractional Brownian motion, on the other hand,  $\beta = 1 - 2\alpha$ . Given the fact that the records are of finite length, and heart rate is not a perfect fractional Brownian motion [2], we have no reason to expect a fixed relationship between  $\alpha$  and  $\beta$ .

Our argument that ordering of interbeat increments plays a small role in neonatal HRV rests on the findings that the fluctuation functions and the runs analyses for healthy and sick data show little difference, and the observed change in  $\beta$  can be explained by a small change in ordering. All three techniques point toward approximately 10%–15% reordering of the series of interbeat increments. The physiological causes for these differences between neonatal and adult HRV are not straightforward to explain. One plausible interpretation is that newborn infants have not fully developed the autonomic or nonautonomic mechanisms for the long range correlations so clearly evident in adults. Thus, the normal HRV of newborns is fundamentally different from the normal HRV of adults.

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