Back

8 page(s) will be printed.

Record: 1

Title: Non-equilibrium dynamics as an indispensable characteristic of a healthy biological system.

Authors: Peng, Chung-Kang
Buldyrev, Sergey V.

Source: Integrative Physiological & Behavioral Science; Jul-Sep94, Vol. 29 Issue 3, p283, 11p, 1 diagram, 9 graphs

Document Type: Article

Subject Terms: FRACTALS
HEART beat
MATHEMATICAL models
NUCLEOTIDE sequence

Abstract: Discusses the application of non-equilibrium fractals in biological systems. Long-range correlation in nucleotide sequences; Long-range correlations in heartbeat intervals.

Full Text Word Count: 4087

ISSN: 1053-881X

Accession Number: 9511031519

Database: Psychology and Behavioral Sciences Collection

NON-EQUILIBRIUM DYNAMICS AS AN INDISPENSABLE CHARACTERISTIC OF A HEALTHY BIOLOGICAL SYSTEM

Abstract--Healthy systems in physiology and medicine are remarkable for their structural variability and dynamical complexity. The concept of fractal growth and form offers novel approaches to understanding morphogenesis and function from the level of the gene to the organism. For example, scale-invariance and long-range power-law correlations are features of non-coding DNA sequences as well as of healthy heartbeat dynamics. For cardiac regulation, perturbation of the control mechanisms by disease or aging may lead to a breakdown of these long-range correlations that normally extend over thousands of heartbeats. Quantification of such long-range scaling alterations are providing new approaches to problems ranging from molecular evolution to monitoring patients at high risk of sudden death.

We briefly review recent work from our laboratory concerning the application of fractals to two apparently unrelated problems: DNA organization and beat-to-beat heart rate variability. We show how the measurement of long-range power-law correlations may provide new understanding of nucleotide organization as well as of the complex fluctuations of the heartbeat under normal and pathologic conditions.

Long-Range Correlations in Nucleotide Sequences

GENOMIC SEQUENCES contain numerous "layers" of information. While the means of encoding some of these instructions is understood (for example, the codes directing amino acid assembly and intron/exon splicing, etc.), relatively little is known about other kinds of information encrypted in the DNA molecule. In higher eukaryotic organisms, only a small portion of the total genome length is actually used for protein coding. The role of introns and the intergenomic sequences that constitute a large portion of these DNA polymers remains unknown.

Recently we (Peng, et al., 1992a) proposed a novel method for studying the global organizational properties of genomic sequences by constructing a 1:1 map of the sequence onto a "DNA walk." Consider

a one-dimensional walker (Mortroll and Shlesinger, 1984) dictated by the sequential order of nucleotides. The walker steps up [u(i) = +1] if a pyrimidine occurs at position a linear distance i along the DNA chain, while the walker steps down [u(i) = -l] if a purine occurs at position i. The question we ask is whether such a walk displays only short-range correlations (as in an n-step Markov chain) (Tavare and Giddings, 1989) or long-range correlations (as in critical phenomena and other scale-free "fractal" phenomena).

This DNA walk provides a novel graphical representation for each DNA sequence and permits the degree of correlation in the nucleotide sequence to be directly visualized (Figure 1). A useful quantity that measures the degree of the correlation is obtained by calculating the "net displacement" y(n) of the walker after n steps, which is the sum of the unit steps u(i) for each step i,

[Multiple line equation(s) cannot be represented in ASCII text] (1)

A useful statistical description of any "landscape" can then be derived by considering a sliding window of size I through the landscape and measuring the change of the "altitude" across this window, i.e.,

delta y_1 = y(n+l)-y(n) (2)

where n indicates the starting position of the window. We define the fluctuation measurement, F(l), as the standard deviation of the quantity delta y_l.

The calculation of F(l) can distinguish three possible types of behavior: (i) If the nucleotide sequence were random, then the landscape has the same statistical properties as that generated by a normal random walk, i.e., F(l) -l 1/2. (ii) If there were a local correlation extending up to a characteristic range (such as in Markov chains), then the behavior F(l) -I 1/2 would be unchanged from the purely random case (for l >>1). (iii) If there is no characteristic length (i.e., if the correlation is "infinite-range"), then the fluctuations will be described by a power law

$F(l) - l^{alpha}$ (3)

with alpha not equal to 1/2 (Stanley, 1971). If alpha > 1/2, then it indicates persistent correlation, i.e., one type of nucleotide (purine or pyrimidine) is likely to be close to another close to another of the same type. In contrast, alpha < 1/2 indicates that the nucleotides are organized such that purines and pyrimidines are more likely to alternate ("anti-correlation") (Havlin, et al., 1988).

The power-law form of equation (3) implies a self-affine (fractal) property in the DNA walk landscape. To visualize this finding, one can magnify a segment of the DNA walk to see if it resembles (in a statistical sense) the overall pattern. Figure l(a) shows the DNA walk representation of a gene and Figure l(b) shows a magnification of the central portion. Figure l(c) is the further magnification of a sub-region of Figure lb. Note the similar fluctuation behavior on all three different length scales.

We calculate alpha from the slope of double logarithmic plots of the mean square fluctuation F(l) versus l (Figure 2). Measurement of this exponent for a broad range of representative genomic and cDNA sequences across the phylogenetic spectrum reveals that long-range correlations (alpha > 1/2) are characteristic of intron-containing genes and non-transcribed genomic regulatory elements (Peng, et al., 1992a; Peng, et al., 1992b; Peng, et al., 1993). The finding of long-range correlations in intron-containing genes appears to be independent of the particular gene or the encoded protein--it is observed in genomic sequences as disparate as myosin heavy chain, beta globin, adenovirus and yeast chromosome III (Peng, et al., 1992a, Munson, Taylor and Michaels, 1992).

In contrast, for cDNA sequences (i.e., the spliced together coding sequences) and genes without introns, we find that alpha *(This character cannot be represented into ASCII Text.) 1/2, indicating no long-range correlation (Figure 2). In fact, the lack of long-range correlations in coding regions is not very surprising that an uncorrelated sequence can carry more information than a correlated sequence (Peng, 1992a). On the other hand, the existence of long-range correlations in the non-coding regions is paradoxical and

suggests a new organizational role for so-called "junk DNA." Ongoing investigations are directed at studying the implications of these correlations for DNA structure and function, as well as for molecular evolution (Buldyrev, et al., 1993a, 1993b). Since power-law behavior represents a scale-invariant (fractal) property of DNA, it cannot be attributed simply to the occurrence of nucleotide periodicities such as those associated with nucleosome packaging. Whether these long-range correlations are related to higher order DNA/chromatin structure or to DNA bending and looping remains speculative.

A complementary approach to interpreting this correlation behavior is to relate it to the dynamic processes that modify nucleotide sequences over time. Buldyrev et al. (1993a, 1993b) recently proposed a generalized Levy walk model to account for the genesis of these correlations, as well as a plausible evolutionary mechanism based on nucleotide insertion and deletion.

From a practical viewpoint, the calculation of F (l) for the DNA walk representation provides a new, quantitative method to distinguish genes with multiple introns from in-tronless genes and cDNAs based solely on their statistical properties. The fundamental difference in correlation properties between coding and non-coding sequences also suggests a new approach to rapidly screening long DNA sequences for the identification of introns and exons (Ossadnik, et al., 1994).

Long-Range Correlations in Heartbeat Intervals

The healthy heartbeat is generally thought to be regulated according to the classical principle of homeostasis whereby physiologic systems operate to reduce variability and achieve an equilibrium-like state (Cannon, 1929). However, our recent findings (Peng, et al., 1993) indicate that under normal conditions, beat-to-beat fluctuations in heart rate display the kind of long-range correlations typically exhibited by dynamical systems far from equilibrium. Since the heartbeat is under neuroautonomic control, our findings also imply that this feedback system is operating in a non-equilibrium state. Our results demonstrate that such power-law correlations extend over thousands of heart beats in healthy subjects. In contrast, heart rate time series from patients with severe congestire heart failure show a breakdown of this long-range correlation behavior,. with the emergence of a characteristic short-range time scale. Similar alterations in correlation behavior may be important in modeling the transition from health to disease in a wide variety of pathologic conditions.

Clinicians traditionally describe the normal activity of the heart as "regular sinus rhythm." But in fact, rather than being metronomically regular, cardiac interbeat intervals normally fluctuate in a complex, unpredictable manner. Much of the analysis of heart rate variability has focused on short-term oscillations associated with respiration (0.15-0.40 Hz) and blood pressure control (0.01-0.15 Hz). Fourier analysis of lengthy heart rate data sets from healthy individuals typically reveals a 1/f-like spectrum for lower frequencies (<0.01 Hz), and some alterations in spectral features have been reported with a variety of pathologies. However, the long-range correlation properties of physiologic and pathologic heart rate time series had not been systematically described.

The mechanism underlying complex heart rate variability is related to competing neuroautonomic inputs. Parasympathetic stimulation decreases the firing rate of pacemaker cells in the heart’s sinus node. Sympathetic stimulation has the opposite effect. The nonlinear interaction between these two branches of the nervous system is the postulated mechanism for the type of erratic heart rate variability recorded in healthy subjects (even during resting or sleeping hours), although non-autonomic factors may also be important.

Our analysis is based on the dignitized electrocardiograms of beat-to-beat heart rate fluctuations over long time intervals (up to 24 h equal 10^5 beats) recorded with an ambulatory (Holter) monitor. The time series obtained by plotting the sequential intervals between beat n and beat n + 1, denoted by B(n), typically reveals a complicated type of variability. To quantitatively study these dynamics over large time scales, we pass the time series through a digital filter that removes fluctuations of frequencies > 0.005 $beat^{-1}$, and plot the result, denoted by $B_L(n)$, in Figure 3. We observe a more complex pattern of fluctuations for a representative healthy adult (Figure 3a) compared to the pattern of interbeat intervals for a subject with severe heart disease associated with congestive heart failure (Figure 3b). These heartbeat time series produce a contour reminiscent of the irregular "landscapes" of DNA walks (Figure 1).

To apply the previous fractal landscape analysis, we can make a simple mapping such that $B_L(n)$ for the heartbeat is equivalent to y(n) for DNA. Thus we can measure the heartbeat fluctuation F (l) the same way as in a DNA walk, where l indicates the size of the observational window (number of beats). Figure 4 is a log-log plot of F(l) vs l for the data in Figures 3. This plot is approximately linear over a broad physiologically relevant time scale (l-200 to 400 beats) implying that $F(l) - l^{alpha}$.

We find that the scaling exponent alpha is markedly different for the healthy and diseased states; for the healthy heartbeat data, A is close to 0, while alpha is close to 0.5 for the diseased case in this example. As we discussed previously, alpha = 0.5 corresponds to a random walk (Brownian motion). Thus the low-frequency heartbeat fluctuations for the diseased state can be interpreted as a stochastic process, in which case the interbeat increments l(n) equivalent to B(n+l)-B(n) corresponding to u(n) in the DNA case) are uncorrelated for l > 200. For the healthy subject, the interbeat increments are anti-correlated (alpha<0.5).

To study further the correlation properties of the time series, we choose to study l(n). Since I(n) is stationary, we can apply standard spectral analysis techniques (Buldyrev, 1993). Figures 5a and 5b show the power spectra $S_I(f)$, the square of the Fourier transform amplitudes for l(n), derived from the same data sets (without filtering) used in Figure 3. The fact that the log-log plot of $S_I(f)$ vs f is linear implies

$$S_l(f) = f^{beta}$$

The exponent beta is related to alpha by beta = 1 -2alpha (Havlin, et al., 1988).

For the data set from the patient with severe heart disease, we observe a fiat spectrum (beta approximate equals to 0) in the low frequency region (Figure 5b) confirming that l(n) values are not correlated over long time scales (low frequencies). Therefore, l(n), the first derivative of B(n), can be interpreted as being analogous to the velocity of a random walker, which is uncorrelated on long time scales, while B(n) values--corresponding to the position of the random walker--are correlated. This correlation, however, is of a trivial nature since it is simply due to the summation of uncorrelated random variables.

In contrast, for the data set from the healthy subject (Figure 5a), we obtain beta*[This character cannot be represented into ASCII Text]1, indicating non-trivial long-range correlations in B(n)--these correlations are not the consequence of summation over random variables or artifacts of non-stationarity. Furthermore, the "anti-correlation" properties of I(n), indicated by the positive beta value, are consistent with a nonlinear feedback system that "kicks" the heart rate away from extremely high or low values. This tendency, however, does not only operate on a beat-to-beat basis (local effect) but over a wide range of time scales, a fractal property of cardiac regulation.

We (Peng, et al, 1993) analyzed data from two different groups of subjects: 10 adults without clinical evidence of heart disease (age range: 32--64 years, mean 44) and 10 adults with severe heart failure (age range: 22--63 years; mean 54). Data from patients with heart failure due to severe left ventricular dysfunction are likely to be particularly informative in analyzing correlations under pathologic conditions since these individuals have well-defined abnormalities in both the sympathetic and parasympathetic control mechanisms that regulate beat-to-beat variability. Furthermore, such patients are at very high risk for sudden death. Both exponents (alpha and beta) were significantly different between the diseased and normal groups (Peng, et al., 1993).

Previous studies have demonstrated marked changes in short-range heart rate dynamics in heart failure compared to healthy function, including the emergence of intermittent relatively low frequency (- 1 cycle/min) heart rate oscillations associated with the well-described syndrome of periodic (Cheyne-Stokes) respiration, an abnormal waxing and waning breathing pattern often associated with low cardiac output. This pathologic, characteristic time scale is indicated by a vertical arrow in Figure 5b.

The long-range power-law correlations in healthy heart rate dynamics may be adaptive for at least two

reasons (West and Goldberger, 1986 and 1987; Goldberger, Righey and West, 1990): (i) the long-range correlations serve as an newly described organizing principle for highly complex, non-linear processes that generate fluctuations on a wide range of time scales, and (ii) the lack of a characteristic scale helps prevent excessive mode-locking that would restrict the functional responsiveness (plasticity) of the organism. Support for these two related conjectures is provided by observations from severely pathologic states, such as heart failure where the breakdown of long-range correlations is often accompanied by the emergence of a dominant frequency mode (e.g., the Cheyne-Stokes frequency). Analogous transitions to highly periodic behavior have been observed in a wide range of other disease states including certain malignancies, sudden cardiac death, epilepsy, fetal distress syndromes and with certain drug toxicities (West and Goldberger, 1987; Goldberger, Righey and West, 1990).

Important unanswered questions currently under study include: What are the physiological mechanisms underlying such long-range correlations in cardiac beat-to-beat intervals? Are these fluctuations entirely stochastic or do they represent the interplay of deterministic and stochastic mechanisms (Rigney, et al., preprint)? How do these findings relate to the suggestion that some features of normal heart rate variability are due to chaotic dynamics (Righey, et al., 1993; Righey, Mietus and Goldberger, 1990; Skinner, Carpeggiani, Landisman and Fulton, 1991 and Goldberger, 1991)?

From a practical viewpoint, these findings may have implications for physiological monitoring and in particular for cardiac rhythm analysis. The complete breakdown of normal long-range correlations in any physiological system could theoretically lead to three possible dynamical states (Figure 6): (i) a random walk (brown noise), (ii) highly periodic behavior, or (iii) completely uncorrelated behavior (white noise). Cases (i) and (ii) both indicated only "trivial" long-range correlations of the types observed in severe heart failure. Case (iii) may correspond to certain cardiac arrhythmias such as atrial fibrillation. More subtle or intermittent degradation of long-range correlation properties may provide an early warning of incipient pathology, including an increased risk of sudden cardiac death. A breakdown of long-range correlations may also be an important marker of aging (Lipsitz and Goldberger, 1992). Finally, we observe that the long-range power-law correlations present in the healthy heartbeat imply that the underlying control mechanisms actually drive the system away from a single steady state. Therefore, the classical theory of hoeostasis, according to which stable physiological processes seek to maintain "constancy" (Cannon, 1929), and its more recently proposed modifications under the rubric of "hemodynamics," need to be revised and extended to account explicitly for this far from equilibrium behavior.

Acknowledgments
We wish to thank C. DeLisi, F. Sciortino, M.M.E. Matsa and S.M. Ossadnik for help at various stages of this work, and AHA, CONACYT, Mathers Charitable Foundations, NIH, NIDA, NIMH, NSF, ONR and the US-Israel Binational Foundations for support. This discussion is an updated version of the chapter by Peng, C.K., Buldyrev, S.V., Hausdorff, J.M., Havlin, S., Mietus, J.E., Simons, M., Stanley, H.E., and Goldberger, A.L. (1994), Fractal landscapes in physiology and medicine: Long-range correlations in DNA sequences and heart rate intervals. In T.F. Nonnenmacher, G.A. Losa and E.R. Weibel (Eds.), Fractals in Biology and Medicine, Basel: Birkhauser, 55--65.

GRAPHS: FIG 1. The DNA walk representation for the rat embryonic skeletal myosin heavy chain gene. (a) The entire sequence. (b) The magnification of the solid box in (a). (c) The magnification of the solid box in (b). The statistical self-affinity of these plots is consistent with the existence of a scale-free or fractal phenomenon termed a fractal landscape. In order to observe statistically similar fluctuations within successive enlargement, the magnification factor along the vertical direction (M*(This character cannot be represented into ASCII Text.)) and horizontal direction (M*(This character cannot be represented into ASCII Text.)tttt) follows a simply relation: log M[Multiple line equation(s) cannot be represented in ASCII text]. Here alpha = 0.63. Note that these DNA walk representations are plotted so that the end point has the same vertical displacement as the starting point.

GRAPH: FIG. 2. Double logarithmic plot of F(l) versus (l) for rat embryonic skeletal myosin heavy chain gene shown in Figure 1 (75% non-coding regions) and its cDNA. Note that the slope (alpha = 0.63) for the intron-containing sequence is > 1/2 indicating the presence of long-range correlations. In contrast, the slope is 0.5 for the coding sequence (cDNA) indicating the absence of long-range correlations.

GRAPHS: FIG. 3. The interbeat interval B_L (n) after low-pass filtering for (a) a healthy subject and (b) a patient with severe cardiac disease (dilated cardiomyopathy). The healthy heartbeat time series shows more complex fluctuations compared to the diseased heart rate fluctuation pattern that is close to random walk ("brown") noise. The low-pass filter removes all Fourier components for $f>/=f_c$. The results shown here correspond to f_c=0.005 beat $^{-1}$, but similar findings are obtained for other choices of f_c</= 0.005. This cut-off frequency f_c is selected to remove components of heart rate variability associated with physiologic respiration or pathologic Cheyne-Stokes breathing as well as oscillations associated with baroreflex activation (Mayer waves). (After Peng, et al., 1993b).

GRAPH: FIG. 4. Double logarithmic plot of F(l) vs n. The circles represent F(l) calculated from data in Figure 3(a) and the triangles from data in Figure 3(b). The two best-fit lines have slopes alpha = 0.07 and alpha = 0.49 (fit from 200 to 4000 beats). The two lines with slopes alpha = 0 and alpha = 0.5 correspond to "l/f noise" and "brown noise," respectively. We observe that F(l) saturates for large l (of the order of 5000 beats), because the heartbeat intervals are subjected to physiological constraints that cannot be arbitrarily large or small.

GRAPHS: FIG. 5. The power spectra $S_I(f)$ for the interbeat interval increment sequences over - 24 hours for the same subjects in Figure 3. (a) Data from a healthy adult. The best-fit line for the low frequency region has a slope beta = 0.93. The heart rate spectrum is plotted as a function of "inverse beat number" (beat $^{-1}$) rather than frequency (time $^{-1}$) to obviate the need to interpolate data points. The spectral data are smoothed by averaging over 50 values. (b) Data from a patient with severe heart failure. The best-fit line has slope 0.14 for the low frequency region, $f < f_c$ = 0.005 beat $^{-1}$ The appearance of a pathologic, characteristic time scale is associated with a spectral peak (arrow) at about 10^{-2} beat $^{-1}$ (corresponding to Cheyne-Stokes respiration). (After Peng, et al., 1993b).

DIAGRAM: FIG. 6. The breakdown of long-range power law correlations may lead to any of three dynamical states: (i) a random walk ("brown noise") as observed in low frequency heart rate fluctuations in certain cases of severe heart failure; (ii) highly periodic oscillations, as also observed in Cheyne-Stokes pathophysiology in heart failure, and (iii) completely uncorrelated behavior ("white noise"), exemplified by the heart rate during atrial fibrillation.

References

Buldyrev, S.V., Goldberger, A.L., Havlin, S., Peng, C.-K., Simons, M., and Stanley, H.E., (1993a). Generalized Levy walk model for DNA nucleotide sequences. Physical Review E, 47: 4514--4523.

Buldyrev, S.V., Goldberger, A.L., Havlin, S., Peng, C.-K., Stanley, H.E. and Simons, M., (1993b). Fractal landscapes and molecular evolution: Modeling the myosin heavy chain gene family. Biophysical Journal, 65: 2673--2679.

Cannon, W.B. (1929). Organization for physiological homeostasis. Physiology Reviews, 9:399--431.

Goldberger, A.L., Rigney, D.R. and West, B.J. (1990). Chaos and fractals in human physiology. Scientific American, 262: 42--49.

Goldberger, A.L. (1991). Is the normal heartbeat chaotic or homeostatic? News in Physiological Sciences, 6: 87--91.

Havlin, S., Selinger, R.B., Schwartz, M., Stanley, H.E. and Bunde, A. (1988). Random multiplicative processes and transport in structures with correlated spatial disorder. Physical Review Letters, 61: 1438--1441.

Lipsitz, L.A. and Goldberger, A.L. (1993). Loss of "complexity" and aging. Potential applications of fractals and chaos theory to senescence. Journal of the American Medical Association, 267: 1806--1809.

Montroll, E.W. and Shlesinger, M.F. (1984). Nonequilibrium phenomena II, From stochastics to hydrodynamics. In J.L. Lebowitz (Ed.), The wonderful world of random walks. Amsterdam: North-Holland, 1--121.

Munson, P.J., Taylor, R.C., and Michaels G.S. (1992). DNA correlations. Nature, 360: 636.

Ossadnik, S.M., Buldyrev, S.V., Goldberger, A.L., Havlin, S., Mantegna, R.N., Peng, C.-K., Simons, M. and Stanley, H.E. (1994). Correlation approach to identify coding regions in DNA sequences. Biophysical Journal, 67: 64--70.

Peng, C.-K., Buldyrev, S.V., Goldberger, A.L., Havlin, S., Simons, M. and Stanley, H.E. (1992a). Long-range correlations in nucleotide sequences. Nature, 356: 168--170.

Peng, C.-K., Buldyrev, S.V., Goldberger, A.L., Havlin, S., Sciortino, F., Simons, M. and Stanley, H.E. (1992b). Fractal analysis of DNA walks. Physica A, 191: 25--29.

Peng, C.-K., Buldyrev, S.V., Goldberger, A.L., Havlin, S., Simons, M. and Stanley, H.E. (1993a). Finite size effects on long-range correlations: Implications for analyzing DNA sequences. Physical Review E, 47: 3730--3733.

Peng, C.-K., Mietus, J., Hausdorff, J.M., Havlin, S., Stanley, H.E. and Goldberger, A.L. (1993b). Long-range anti-correlations and non-Gaussian behavior of the heartbeat. Physical Review Letters, 70: 1343--1346.

Rigney, D.R, Mietus, J.E. and Goldberger, A.L. (1990). Is normal sinus rhythm "chaotic"? Measurement of lyapunov exponents. Circulation, 83 (Suppl III): 236.

Rigney, D.R., Goldberger, A.L., Ocasio, W.C., Ichimaru, Y, Moody, G.B. and Mark, R.G. (1993). Description and analysis of multi-channel physiological data: Forecasting fluctuations in data set B of the 1991 Santa Fe Institute Time Series and Analysis Competition. In A. Weigen and N. Gershenfeld (Eds.), Predicting the future and understanding the past. Reading, MA: Addison-Wesley, 105--129.

Skinner, J.E., Carpeggiani, C., Landisman, C.E. and Fulton, K.W. (1991). Correlation dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia. Circulation Research, 68: 966--976.

Stanley, H.E. (1971). Introduction to phase transitions and critical phenomena. Oxford and New York: Oxford University Press.

Tavare, S., Giddings, B.W. (1989). Some statistical aspects of the primary structure of necleotide sequences. In M.S. Waterman (Ed.), Mathematical methods for DNA sequences. Boca Raton: CRC Press, 117--132.

West, B.J., Bhargava, W. and Goldberger, A.L. (1986). Beyond similitude: Renormalization in the bronchial tree. Journal of Applied Physiology, 60:1089--1097.

West, B.J. and Goldberger, A.L. (1987). Physiology and fractal dimension. American Scientists, 75: 354.

~~~~~~~~

BY CHUNG-KANG PENG, SERGEY V. BULDYREV, JEFFREY M. HAUSDORFF, SHLOMO HAVLIN, JOSEPH E. MIETUS, MICHAEL SIMONS, H. EUGENE STANLEY, AND ARY L. GOLDBERGER

Harvard Medical School, Beth Israel Hospital, Boston, M
~~~~~~~~

Center for Polymer Studies, Boston University, Boston, M

Bar-Ilan University, Ramat-Gan, Israel 4 MIT, Cambridge, MA Address for correspondence: A. L. Goldberger, Harvard Medical School, GZ-435 Beth Israel Hospital, 330 Brookline Ave., Boston, MA 02215.

Back