Band-phase-randomized surrogate data reveal high-frequency chaos in heart rate variability

32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

Band-Phase-Randomized Surrogate Data Reveal High-Frequency Chaos in Heart Rate Variability

Cheng LI, Guang-Hong DING, Guo-Qiang WU, Chi-Sang POON *(Fellow, IEEE)*

***Abstract*—We propose a new band-phase-randomized surrogate data method to evaluate the chaotic dynamics in the high (HF) and low frequency (LF) bands of heart rate variability (HRV) in healthy subjects. The chaotic strength of normal HRV as assessed by a noise titration assay completely vanished when its power spectrum was phase-randomized over the entire frequency band or the HF band alone, but not the LF band alone. This finding confirms recent evidence that chaotic dynamics in normal HRV is ascribable mainly to the HF component, or respiratory sinus arrhythmia.**

I. INTRODUCTION

IN 1981, Akselrod and coworkers [1, 2] showed that heart rate variability (HRV), when Fourier-transformed into the power spectrum, displayed characteristic high-frequency (HF), low-frequency (LF) and very-low-frequency (VLF) peaks that could be identified with neurohumoral influences. Since then, spectral analysis (or equivalent time-domain analysis) of HRV [3] or other cardiovascular variabilities has been widely adopted as a noninvasive probe of cardiac-autonomic function [4]. Malliani and coworkers [5, 6] proposed that the relative LF and HF powers represent sympathovagal balance reflecting physiologic push-pull activities of sympathetic-parasympathetic branches. This notion has been disputed as to whether these indices are correlated linearly with autonomic regulation [7, 8]. The current debate seems converging toward an emerging consensus that sympathovagal interaction probably represents a nonlinear phenomenon reflecting the dynamic fluctuations of cardiac-autonomic outflows about their means [8, 9].

In a recent study [10], the nonlinear dynamics of HRV was evaluated by using the method of noise titration, a technique that has been shown to be capable of detecting chaotic dynamics under significant measurement noise [11] and dynamic noise [12]. The results showed that the HRV in young healthy subjects displayed significant chaotic dynamics that was correlated to the HF component, and that such HF chaos was markedly attenuated in patients with congestive heart failure but not in age-matched elderly subjects.

In the present work, we applied a novel band-phase-randomized surrogate data method in combination with the noise titration technique to provide strong evidence indicating the underlying chaotic dynamics of the HF component in young healthy subjects. Our results demonstrate that sympathovagal balance is indeed a nonlinear behavior rather than a linear phenomenon.

II. METHODOLOGY

A. Data acquisition

The beat-to-beat (RR) interval series of healthy subjects were extracted from the MIT-BIH Normal Sinus Rhythm Database in Physionet [13] according to annotations for only normal beats. Sample rate was 128 Hz in 24-hr Holter recordings.

B. Spectral analysis

A linear autoregressive model (1) and its power spectral density (2) were applied to analyze the spectral characteristics of 24-hr heartbeat recordings.

$$y_n^{lin} = a_0 + a_1 y_{n-1} + \cdots + a_k y_{n-k} + \varepsilon \tag{1}$$

$$X(\omega) = \frac{\varepsilon}{\left| 1 + \sum_{m=1}^{k} a_m e^{jm\omega} \right|^2} \tag{2}$$

The HRV spectral components were evaluated by integration of the corresponding power spectral density at very low frequency (VLF, < 0.04 Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) bands.

C. Band-phase-randomized surrogate data

The surrogate data method [14] is commonly used in combination with an appropriate statistic, such as approximate entropy (ApEn) [15], correlation dimension or other nonlinear indices. The null hypothesis of the method is that the test data is the output of some linear dynamical system responding to Gaussian white noise input, followed by some static nonlinear transformation that results in

Manuscript received April 20, 2009. CL was supported by the China Scholarship Council. This work was supported in part by Shanghai Leading Academic Discipline Project, No B112 (GHD) and National Natural Science Foundation of China grant No 30370353 (GQW), and U.S. National Institutes of Health grants HL075014 and HL079503 (CSP).

Cheng LI is with Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139 USA and the Department of Mechanics and Engineering Science of Fudan University, Shanghai 200032, P. R. China.

Guang-Hong DING and Guo-Qiang WU are with the Department of Mechanics and Engineering Science of Fudan University, Shanghai 200032, P. R. China.

Chi-Sang POON is with Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA (corresponding author phone: (617)-258-5405; e-mail: cpoon@mit.edu).

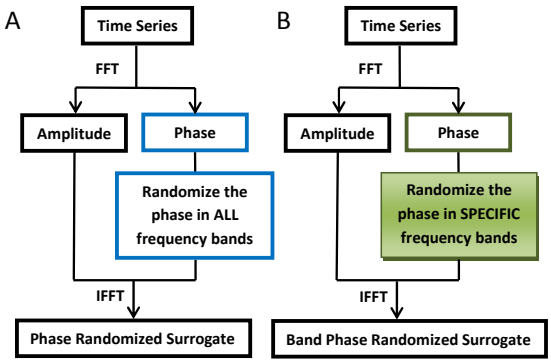

Fig. 1. Flow charts of the conventional phase-randomized surrogate method (A) and band-phase-randomized surrogate method (B). Both phase randomization methods can be amplitude adjusted [14] to account for non-Gaussian probability distribution in the time series.

non-Gaussian variability. Thus, rejection of the null hypothesis indicates that the test data did not come from linear dynamics. To generate phase-randomized surrogate data, the time series is first transformed to the frequency domain by Fast Fourier Transform (FFT); then the phase relationship in the FFT spectrum is randomized. Finally, an inverse FFT is performed with the original amplitude and randomized phase spectra (Fig. 1A). All linear dependencies, such as autocorrelation and power spectral density, are preserved while nonlinear dependencies are eliminated by the process of phase randomization. Any non-Gaussian distribution in the original time series is accounted for by aligning the histogram of the resultant surrogate data to that of the original time series [14].

In order to discern possible nonlinear contributions of specific spectral components, we propose here the band-phase-randomized surrogate method, which has a similar algorithm as the original phase-randomized surrogate method except that phase randomization is made in specific frequency bands while leaving the phase structure in other bands unchanged (Fig.1B). Hence, all linear dependencies are still preserved while the nonlinear dependencies may or may not disappear depending on which phase bands are randomized.

D. Noise titration

In this method [11], nonlinear determinism in a time series is first identified by comparing the fit of linear (1) and nonlinear (3) polynomial autoregressive models of the Volterra type to the time series data [16, 17]:

$$y_n^{nonl} = a_0 + a_1 y_{n-1} + \cdots a_\kappa y_{n-\kappa} + a_{\kappa+1} y_{n-1}^2 + a_{\kappa+2} y_{n-1} y_{n-2} + \cdots + a_M y_{n-\kappa}^d + \varepsilon(\kappa, d) \quad (3)$$

Volterra autoregressive models with varying memory (κ) and dynamical order (d) are iteratively generated to optimally predict the data. The kernels a_m are recursively estimated from (1) or (3) by using the Korenberg algorithm [18]. The total number of terms of the polynomial is $M = (\kappa+d)!/(\kappa!d!)$. In this work we used $\kappa \leq 6$; $d \leq 3$ for nonlinear fitting and $\kappa \leq 84$; $d = 1$ for linear fitting. The best linear and nonlinear models are chosen according to the Akaike criterion:

$$C(r) = \log \varepsilon(r) + \frac{r}{N} \quad (4)$$

where $r \leq M$ is the number of polynomial terms in the model, N is the length of the data series and $\varepsilon(r)$ is residual error. The null hypothesis–a stochastic time series with linear dynamics–is rejected if the best nonlinear model provides a significantly better fit to the data than the best linear model using parametric (F-test) statistics. The detection rate (DR) is calculated as percentage of nonlinearity detection in consecutive 15 data segments.

Once nonlinearity is detected, the method of noise titration is applied to the data to further analyze possible chaotic dynamics. The noise titration technique has been shown to offer a highly sensitive litmus test (sufficient proof) for chaotic dynamics and a relative measure of the chaos level in short noise-contaminated data segments [11, 12]. Specifically, white (or linearly correlated) noise of increasing standard deviations is added incrementally to the data until nonlinearity is no longer detected by using the above Volterra autoregressive modeling method. The noise limit (NL), which has been shown to correlate (to within a constant corresponding to the noise floor) with the Lyapunov exponent of the equivalent noise-free chaotic dynamics, is calculated as the percent of signal power added as noise. Under this numerical titration scheme, chaos is indicated as NL>0 where the chaos strength is estimated by the NL value. Conversely, if NL=0, then it may be inferred that the series either is not chaotic or the chaotic component is already neutralized by the background noise (noise floor) in the data.

III. RESULTS

Figure 2 illustrates the circadian variations of HRV spectral components and noise titration indices in healthy subjects. In Fig. 2A, nocturnal increases of RR interval of an

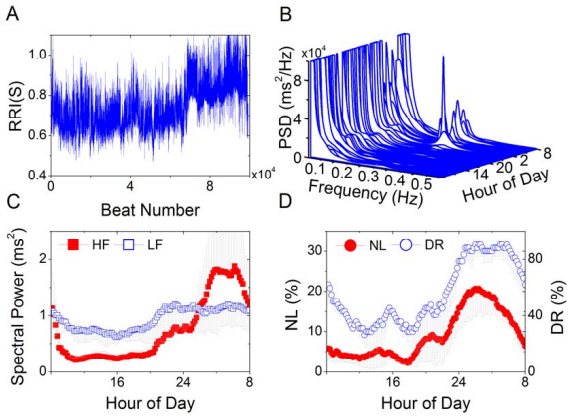

Fig. 2. Linear and nonlinear circadian heart rate variability and mean RR interval in healthy subjects (n=3, age 30±5.3 yrs mean±SD). A. 24-hr beat-to-beat interval tachogram in a representative subject. B. Corresponding power spectral density vs. frequency plot. C. Average spectral powers of HF (red) and LF (blue) bands. Data points were evaluated at 12-min intervals and averaged over a moving 3-hr time window for each subject before group averaging. D. Nonlinear detection rate (blue) and noise limit (red) evaluated for a moving 3-hr time window with 12-min increments. For noise limit, segments with zero noise limit were not included in the moving-average calculation.

individual mirrored well-known increases of vagal-cardiac restraint [19] and decreases of sympathetic stimulation during sleep [20]. Paralleling the circadian RR interval were HF peaks which occurred only at night, with occasional tiny peaks in siesta during daytime (Fig. 2B), acute increases of HF power nocturnally and slightly concomitant increases of LF power (Fig. 2C). Figure 2D illustrates the corresponding circadian variations of detection rate (DR) and noise limit (NL) in the group. Comparison of Figs. 2C and 2D shows that these noise titration indices correlated strongly with the HF component.

To verify the chaotic dynamics of the HF component, we further compared noise titration of the test data in combination with the band-phase-randomized surrogate data method. The total frequency band (0-0.5Hz) was first divided into two sub-bands: a HF band and a "LF band" which included the LF band and the rest of the power spectrum except the HF band [0-0.15 and 0.4-0.5 Hz]. Randomizations of the phases of HF- and LF-band are denoted HF- and LF-randomization respectively. Accordingly, abolition of NL and DR after HF- but not LF-randomization would indicate that heart rate chaos occurred primarily in the HF band, and vice versa. Results were similar when the phase-randomized surrogates were amplitude-adjusted to account for non-Gaussian distributions.

Figure 3 shows the noise titration and ApEn results [15] for the test data and its band-phase- randomized surrogates from a healthy subject. The noise limit of the test data was 34.5±1.5% (mean±SEM) in 20 titrations (Fig. 3A) and was 0 for the conventional surrogate data with phase randomization over the total band width of 0-0.5 Hz (Fig. 3B), indicating the

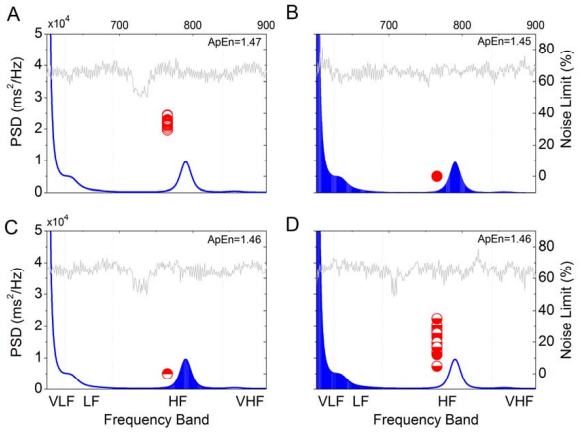

Fig. 3. Noise limit and approximate entropy (ApEn) of test data and its phase-randomized surrogates. The test data was a nocturnal segment with 1024 beats from a representative subject; all surrogates were amplitude adjusted [14]. Right ordinate is noise limit (red circles) and left ordinate is corresponding power spectral density (PSD, blue lines); lower abscissa is frequency band and upper abscissa is beat number of time series (half-tone tracings). A. Noise limit of test data was 34.5±1.5% (mean±SEM) in 20 titrations. B. Noise limits vanished for conventional surrogate data with phase randomization in the entire frequency band (shading under the PSD plot). C. Noise limit also vanished after phase randomization in the HF band (0.15-0.4 Hz) alone. D. In contrast, if phase randomization was restricted to the LF band and the remaining frequency spectrum other than the HF band, noise limit was reduced (22.9±4.2%) but not abolished. ApEn results (right upper corner) are marginally different between the various conditions.

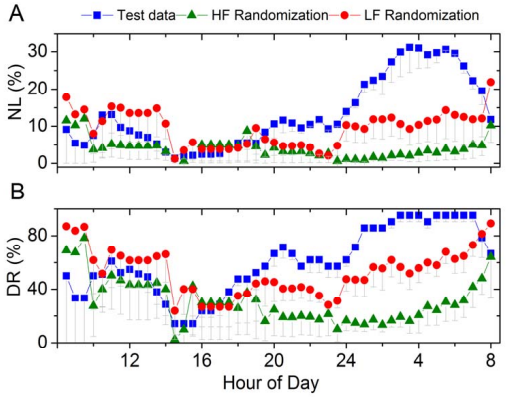

Fig. 4. Circadian variations of noise limit (A) and detection rate (B) of test data and its surrogates in healthy subjects (n=3, 36±8.8 yrs; mean±SD). The 24 hr RR series was divided into 48 segments. In each segment, a series with 1024 beats was analyzed. NL and DR were evaluated in each segment and averaged over a moving 3-hr time window for each subject before group averaging.

inherent nonlinearity in the test data. However, when the test data was band-phase-randomized, the noise limit was reduced to 0 only for HF- (Fig. 3C) but not LF-randomization (Fig. 3D). This observation confirmed that the bulk of the chaotic dynamics was ascribable to the HF component. Chaotic dynamics in the LF band could not be verified because a decrease in NL after LF-randomization could also result from an increase in the noise floor for the primary HF chaos, which remained intact after LF-randomization. In contrast, the ApEn results of test data and its surrogates are similar, indicating the unreliability of the surrogate data method *per se* in distinguishing the nonlinearities of the HF and LF components.

To illustrate the close correlation of the HF component and the noise titration indices as suggested in Fig 2, we analyzed the circadian variations of the noise limit and detection rate of the RR series and its band-phase- randomized surrogates in 3 healthy young subjects (Fig. 4). Circadian variations of the noise titration results for the test data were similar to Fig. 2D. However, strong diurnal/nocturnal variations of NL and DR were seen only in the LF-randomized surrogates, but not the HF-randomized surrogates. Moreover, there were significant differences between HF- and LF-randomizations at night indicating HF-dominant chaotic dynamics, but not during daytime, where HF chaos is weakest.

IV. DICUSSION

Spectral analysis has long been recognized as a linear test of HRV [3]. However, previous studies using the surrogate data method have indicated that the normal HRV has nonlinear components [21]. The surrogate data method is used to answer whether the test data comes from a linear process with possible static nonlinear transformation (null hypothesis) [14]. Rejection of the null hypothesis is only a necessary condition to infer nonlinearity. In contrast, the noise titration technique provides a sufficient test of chaotic dynamics even under significant measurement noise [16, 17]. However, none of the above methods, as well as other

nonlinear indicators, can be applied to test the contribution of specific spectral components to the nonlinearity of HRV. The hybrid method of band-phase-randomized surrogates and noise titration presently proposed is the only method to offer a sufficient test of chaotic spectral component in HRV.

Among the three main peaks in the HRV spectrum, the HF component has received the greatest attention, because it is directly related to respiratory sinus arrhythmia (RSA) in the time domain. The frequency value of RSA is the ratio of respiratory frequency and heart rate, and remains relatively stable during spontaneous breathing. RSA is also considered as an index of cardiopulmonary balance [22-24]. The present revelation of chaotic RSA by using our hybrid method of band-phase-randomization and noise titration strongly supports the previous finding of circadian covariation of HF power with nonlinear detection rate and noise limit [10]. Such HF chaos is imparted possibly in part by chaotic respiratory activity [25] via its gating of vagal-cardiac neural activity [26], and in part by cardio-respiratory coupling at the level of either central nervous system or pre- and post-synaptic interaction on the sinoatrial node [9, 27].

The observed difference between diurnal and nocturnal behaviors in HF chaos may be attributed to circadian changes in neurohumoral activities beyond close-loop regulation of the cardiovascular system. Besides reflex feedback, the activities in both cardiovascular and respiratory centers are also affected by descending signals from high-level centers, such as the defense area in the midbrain, or cerebral cortex. Defense reaction is originally defined as the response when an animal faces an enemy; now it has been extended to behaviors with sympathetic hyperactivity, such as mental arithmetic and the stress of daily urban life [28]. Effects of defense reaction include tachycardia and increase of blood pressure. Such exogenous and endogenous disturbances from either physical or mental activities or from metabolic processes are inevitable especially during daytime. These stochastic disturbances may obscure the intrinsic nonlinear determinism of HRV by increasing the physiologic noise floor that mars the chaotic dynamics of RSA.

REFERENCES

[1] S. Akselrod, D. Gordon, J. B. Madwed, N. C. Snidman, D. C. Shannon, and R. J. Cohen, "Hemodynamic regulation: investigation by spectral analysis," *Am J Physiol Heart Circ Physiol,* vol. 249, pp. H867-875, 1985.

[2] S. Akselrod, D. Gordon, F. Ubel, D. Shannon, A. Berger, and R. Cohen, "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control," *Science,* vol. 213, pp. 220-222, 1981.

[3] "Task Force of the European Society of Cardiology the North American Society of Pacing and Electrophysiology Heart Rate Variability : Standards of Measurement, Physiological Interpretation, and Clinical Use," *Circulation,* vol. 93, pp. 1043-1065, 1996.

[4] G. G. Berntson, J. T. Bigger, Jr., D. L. Eckberg, P. Grossman, P. G. Kaufmann, M. Malik, H. N. Nagaraja, S. W. Porges, J. P. Saul, P. H. Stone, and M. W. van der Molen, "Heart rate variability: origins, methods, and interpretive caveats," *Psychophysiology,* vol. 34, pp. 623-48, 1997.

[5] A. Malliani, "The Pattern of Sympathovagal Balance Explored in the Frequency Domain," *News Physiol Sci,* vol. 14, pp. 111-117, 1999.

[6] A. Malliani, M. Pagani, F. Lombardi, and S. Cerutti, "Cardiovascular neural regulation explored in the frequency domain," *Circulation,* vol. 84, pp. 482-492, 1991.

[7] D. L. Eckberg, "Sympathovagal Balance : A Critical Appraisal," *Circulation,* vol. 96, pp. 3224-3232, 1997.

[8] G. Parati, G. Mancia, M. D. Rienzo, P. Castiglioni, J. A. Taylor, and P. Studinger, "Point:Counterpoint: Cardiovascular variability is/is not an index of autonomic control of circulation," *J Appl Physiol,* vol. 101, pp. 676-682, 2006.

[9] E. Pyetan and S. Akselrod, "Do the high-frequency indexes of HRV provide a faithful assessment of cardiac vagal tone? A critical theoretical evaluation," *Biomedical Engineering, IEEE Transactions on,* vol. 50, pp. 777-783, 2003.

[10] G. Q. Wu, N. M. Arzeno, L. L. Shen, D. K. Tang, D. A. Zheng, N. Q. Zhao, D. L. Eckberg, and C. S. Poon, "Chaotic signatures of heart rate variability and its power spectrum in health, aging and heart failure," *PLoS One,* vol. 4, p. e4323, 2009.

[11] C.-S. Poon and M. Barahona, "Titration of chaos with added noise," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 98, pp. 7107-7112, 2001.

[12] C.-S. Poon, C. Li, and G.-Q. Wu, "A unified theory of chaos linking nonlinear dynamics and statistical physics," *arXiv:1004.1427 (http://arxiv.org/abs/1004.1427),* 2010.

[13] A. L. Goldberger, L. A. N. Amaral, L. Glass, J. M. Hausdorff, P. C. Ivanov, R. G. Mark, J. E. Mietus, G. B. Moody, C.-K. Peng, and H. E. Stanley, "PhysioBank, PhysioToolkit, and PhysioNet : Components of a New Research Resource for Complex Physiologic Signals," *Circulation,* vol. 101, pp. e215-220, 2000.

[14] J. Theiler, S. Eubank, A. Longtin, B. Galdrikian, and J. Doyne Farmer, "Testing for nonlinearity in time series: the method of surrogate data," *Physica D: Nonlinear Phenomena,* vol. 58, pp. 77-94, 1992.

[15] S. M. Pincus, "Approximate entropy as a measure of system complexity," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 88, pp. 2297-2301, 1991.

[16] M. Barahona and C.-S. Poon, "Detection of nonlinear dynamics in short, noisy time series," *Nature,* vol. 381, pp. 215-217, 1996.

[17] C.-S. Poon and C. K. Merrill, "Decrease of cardiac chaos in congestive heart failure," *Nature,* vol. 389, pp. 492-495, 1997.

[18] M. Korenberg, "Identifying nonlinear difference equation and functional expansion representations: The fast orthogonal algorithm," *Annals of Biomedical Engineering,* vol. 16, pp. 123-142, 1988.

[19] G. Mancia, "Autonomic Modulation of the Cardiovascular System during Sleep," *N Engl J Med,* vol. 328, pp. 347-349, 1993.

[20] M. Hornyak, M. Cejnar, M. Elam, M. Matousek, and B. G. Wallin, "Sympathetic muscle nerve activity during sleep in man," *Brain,* vol. 114 (Pt 3), pp. 1281-95, 1991.

[21] C. Braun, P. Kowallik, A. Freking, D. Hadeler, K. D. Kniffki, and M. Meesmann, "Demonstration of nonlinear components in heart rate variability of healthy persons," *Am J Physiol,* vol. 275, pp. H1577-84, 1998.

[22] R. Barbieri, J. K. Triedman, and J. P. Saul, "Heart rate control and mechanical cardiopulmonary coupling to assess central volume: a systems analysis," *Am J Physiol Regul Integr Comp Physiol,* vol. 283, pp. R1210-1220, 2002.

[23] D. C. Galletly and P. D. Larsen, "Relationship between cardioventilatory coupling and respiratory sinus arrhythmia," *Br. J. Anaesth.,* vol. 80, pp. 164-168, 1998.

[24] F. Yasuma and J.-i. Hayano, "Respiratory Sinus Arrhythmia*," *Chest,* vol. 125, pp. 683-690, 2004.

[25] M. Wysocki, M.-N. Fiamma, C. Straus, C.-S. Poon, and T. Similowski, "Chaotic dynamics of resting ventilatory flow in humans assessed through noise titration," *Respiratory Physiology & Neurobiology,* vol. 153, pp. 54-65, 2006.

[26] D. L. Eckberg, "The human respiratory gate," *The Journal of Physiology,* vol. 548, pp. 339-352, 2003.

[27] M. N. Levy, "Brief Reviews: Sympathetic-Parasympathetic Interactions in the Heart," *Circ Res,* vol. 29, pp. 437-445, 1971.

[28] L. C. Schenberg, E. Corral Vasquez, and M. Barcellos da Costa, "Cardiac baroreflex dynamics during the defence reaction in freely moving rats," *Brain Research,* vol. 621, pp. 50-58, 1993.