Linear and Nonlinear Approaches to the Analysis of R-R Interval Variability

Autumn Schumacher, PhD, RN

Analysis techniques derived from linear and nonlinear dynamics systems theory qualify and quantify physiological signal variability. Both clinicians and researchers use physiological signals in their scopes of practice. The clinician monitors patients with signal-analysis technology, and the researcher analyzes physiological data with signal-analysis techniques. Understanding the theoretical basis for analyzing physiological signals within one's scope of practice ensures proper interpretation of the relationship between physiological function and signal variability. This article explains the concepts of linear and nonlinear signal analysis and illustrates these concepts with descriptions of power spectrum analysis and recurrence quantification analysis. This article also briefly describes the relevance of these 2 techniques to R-to-R wave interval (i.e., heart rate variability) signal analysis and demonstrates their application to R-to-R wave interval data obtained from an isolated rat heart model.

Key words: *linearity, nonlinearity, power spectrum analysis, recurrence quantification analysis, heart rate variability, isolated rat heart model*

Physiological signals are endpoint manifestations of cellular events that depict how physiological systems vary over time. Analysis techniques derived from linear and nonlinear dynamics systems theory qualify and quantify signal variability. In cardiac physiology, for example, analysis of the electrocardiographic signal has provided information concerning control of electrical function (Cabo and Rosenbaum 2002). When analyzing physiological signals, understanding the theoretical principles associated with these techniques ensures proper interpretation of the relationship between physiological function and signal variability. The purpose of this article is to 1) explain the theoretical concepts of linear and nonlinear signal analysis; 2) illustrate these concepts with descriptions of the power spectrum analysis and recurrence quantification analysis as exemplars of linear and nonlinear techniques, respectively; 3) briefly describe the relevance of these 2 techniques to R-to-R wave interval (heart rate variability) signal analysis; and 4) compare the application of these 2 techniques to the R-to-R wave interval signal from an isolated rat heart model. This article is not meant as a comprehensive review but rather as a general primer for clinicians and researchers.

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Framework Definitions

A *system* is a collection of variables interacting with each other to accomplish some purpose (McGillem

Autumn Schumacher, PhD, RN, is a postdoctoral fellow in the Nell Hodgson Woodruff School of Nursing at Emory University, Atlanta, Georgia. Address for correspondence: Autumn Schumacher, PhD, RN, Emory University, Nell Hodgson Woodruff School of Nursing, 1520 Clifton Rd., Suite 305, Atlanta, GA 30322-4207; e-mail: aschuma@emory.edu.

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and Cooper 1974). Within this definition, the cardiovascular system is composed of cellular and systemic components working together to deliver oxygen to the tissues amid a variety of activities. A *dynamic system* is a system that evolves over time by accepting, then operating on, an original signal to produce a new set of signals (Strogatz 1994). All physiological systems are dynamic systems. *Signals* represent the means by which energy is propagated through a system and may depict any variable within a system (McGillem and Cooper 1974). In this context, the electrocardiographic (ECG) signal represents cardiac cell activation by electrical energy, whereas the ECG waveform represents the propagation of electrical activity along a myocardial pathway during the cardiac cycle. Thus, both the ECG signal and waveform describe how the cardiac system's electrical behavior qualitatively and quantitatively changes as a function of time. A *time series* data set is a collection of observations (data points) made sequentially over time (Chatfield 1989). For example, the value of one discrete observation would be the amount of time elapsing from one R-wave to the next R-wave in an ECG. A time series would consist of all R-to-R wave time intervals (R-R intervals) contained in an ECG recording. Time series analysis and signal analysis are considered conceptually synonymous (Kaplan 1994).

Linear Signal Analysis

The linear numerical description of time series data consists of a first-power mathematical equation; that is, the equation contains no exponents (McGillem and Cooper 1974). The equation describing a line, $y = a + bx$, is an example of a simple linear first-power system whereby a given amount of input stimulus (x) produces a proportional corresponding magnitude in output response (y) (Hilborn 1994). A linear system's component characteristics do not change as a result of the stimulus's magnitude; only the magnitude of the response changes. The stimulus produces a response without regard for initial conditions. Statistics is the modus operandi for describing a linear relationship between stimuli (independent) and response (dependent) variables (Chatfield 1989).

Also considered theoretically linear, power spectrum analysis (PSA) techniques transform time series data into frequency domain data. PSA presents another perspective with which to view variable relationships within a data set (Chatfield 1989). Fast Fourier transform (FFT) and autoregressive modeling are 2 common PSA techniques (Kay 1988). The autoregressive modeling technique is mathematically superior, but the FFT is simpler to use. The reader is referred to Berntson and others (1997) along with Kay (1988) for further discussion concerning specific similarities and differences between these spectral methods. All PSA techniques transform a time series data set into its frequency components by decomposing the original signal into a series of sinusoidal waves, analogous to a prism separating light into its corresponding colors (Bracewell 1989). Each individual sinusoidal wave possesses a unique amplitude and phase that corresponds to a specific frequency. Graphing the amplitude versus the frequency for each sinusoidal wave creates a PSA plot. The PSA plot not only identifies the specific frequencies contained in the signal but also indicates the amount (power) each frequency has contributed to the original signal.

The term *heart rate variability* (HRV) refers to the variability in timing between heartbeats. Clinicians and researchers use both linear and nonlinear analysis techniques to assess this physiological signal. Theoretically, heart rate is determined by both autonomic modulation of sinus node activity and stretch receptor responses to venous return (the Bainbridge reflex). HRV assessment therefore reveals information encompassing all the influences (input stimulus) on heart rate (output response) at a given point in time (Fetsch and others 2000). A comprehensive review of the historical emergence of HRV as a physiologically meaningful measure can be found in the 2 HRV standards papers: Berntson and others (1997) and Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology ([Task Force], 1996). A practical review of HRV can be found in McMillan (2002).

R-R interval distribution within a given ECG recording is characterized via descriptive statistics in the time domain. These time domain measures do not correlate with physiological processes and differ slightly between human and all animal species due to differences in heart rate (Schumacher 2001). Commonly used time domain HRV measures are listed in Table 1 with brief explanations. Research into this aspect of HRV has revealed that R-R interval variability typi-

Table 1. Common Heart Rate Variability (HRV) Measures in the Time Domain

Variable	Description	Normal Values
Mean R-R interval	The average time interval between heartbeats within a data set. R-R intervals are measured in milliseconds (ms) and are also called heart periods.	> 750 ms
SDNN (standard deviation of normal-to-normal beats)	The calculated standard deviation for all R-R intervals within a data set. SDNN estimates overall HRV and is dependent on length of ECG recording. In 24-h electrocardiographic (ECG) recordings, values below 50 ms are considered too low.	141 ± 39 ms
SDANN (standard deviation of average normal-to-normal beats)	The standard deviation of mean R-R interval times for all 5-min segments of an entire ECG recording. 24-h ECG recordings are divided into 5-min data sets, 12 per hour. SDANN estimates long-term HRV and allows for comparisons over time.	127 ± 35 ms
RMSSD (root mean square of squared differences)	The time difference between consecutive R-R intervals is calculated. The value is then squared and averaged, and the square root value is obtained. The RMSSD estimates short-term HRV and accounts for sequential order of R-R intervals.	27 ± 12 ms

NOTE: This information is summarized from Berntson and others (1997), Crawford and others (1999), and Task Force (1996). Normal values given are for human adults.

cally decreases with age and is a predictor of sudden death in post–myocardial infarction patients (Kleiger and others 1987).

Frequency domain analysis of R-R interval data via PSA extracts specific frequency components (Fig. 1A) that are related to autonomic physiological processes (Kamath and Fallen 1993). Common HRV frequency domain measures are listed in Table 2 with brief explanations. As with time domain measurements, frequency domain measurements differ slightly between human and all animal species due to differences in heart rate (Schumacher 2001). The relationship between the spectral frequencies and the autonomic nervous system was initially recognized in animal studies whereby spectral changes were observed during pharmacologic and/or surgical blockade of the autonomic divisions (Akselrod and others 1981; Pagani and others 1986; Cerutti and others 1991). This relationship was confirmed in human subjects (Pomeranz and others 1985; Malliani and others 1991; Bigger and others 1992). Figure 1B illustrates a PSA plot that could be generated with R-R interval data obtained from an isolated heart. This PSA plot essentially lacks power in the high and low frequencies because the isolated heart exhibits little variability among the R-R intervals due to the lack of respiratory, hormonal, or autonomic modulatory influences on the sinus node (Schumacher 2001).

A number of assumptions are necessary when applying linear analysis techniques to R-R interval data to ensure meaningful interpretation of the data. For example, the data must be stationary: that is, the data set must exhibit a stable mean and variance (Chatfield 1989). Data sets are therefore conditioned to meet these assumptions. R-R interval data is analyzed only from sinus rhythm containing few ectopic beats. After the ectopic beats are removed, interpolated sinus beats are inserted in place of the ectopy. Also, only analyzed R-R interval time series of the same duration are compared since results are dependent on the length of the data sets (Berntson and others 1997).

The cardiac system is dynamic, nonlinear, and nonstationary, with performance continually fluctuating on a beat-to-beat basis as extrinsic and intrinsic stimuli simultaneously influence the state of the system (Christini and others 2001; Zbilut and others 2002). Due to the assumptions and conditioning requirements, linear analyses may not account for all aspects of cardiac performance, particularly the subtle interactions between the control mechanisms that regulate cardiac function (Malpas 2002). Analysis techniques arising from nonlinear dynamics systems theory were therefore developed to ascertain the multidimensional processes that control the cardiac system (Akay 2001).

Table 2. Heart Rate Variability Measures in the Frequency Domain

Variable (Unit)	Description	Normal Values
Total power (ms^2/Hz)	The total area under the curve in a power spectrum plot. The ms^2/Hz unit is considered an absolute unit of measure.	3466 ± 1018 ms^2/Hz
ULF (ultra low frequency)	The peak frequency found in this defined range; obtained from 24-h recordings and may be a graphical representation of direct current (DC).	0.00-0.003 Hz
VLF (very low frequency)	The peak frequency found in this defined range. The physiological significance is unknown but may correspond to thermoregulation. VLF power affected by mathematical algorithms of trend (baseline) removal.	0.003-0.04 Hz
LF (low frequency)	The peak frequency found in this defined range. Both parasympathetic and sympathetic activity influences this component, which may reflect baroreflex-mediated modulatory activity.	0.04-0.15 Hz
LF power (ms^2/Hz)	The area under the spectral curve within this frequency range.	1170 ± 416 ms^2/Hz
LF power (nu)	Measure represents relative proportional value of LF power to total power; calculated as (LF power/(total power – VLF power)) × 100. Power in normalized units should be reported in conjunction with absolute units. Normalization minimizes the effect of change in total power dependent on the individual frequency components.	54 ± 4 nu
HF (high frequency)	The peak frequency found in this defined range, which is influenced by both respiratory and parasympathetic activity.	0.15-0.4 Hz
HF power (ms^2/Hz)	The area under the spectral curve within this frequency range.	975 ± 203 ms^2/Hz
HF power (nu)	Measure represents relative proportional value of HF power to total power; calculated as (HF power/(total power – VLF power)) × 100.	29 ± 3 nu
LF/HF ratio	Calculated as LF power/HF power. This controversial measure is considered an assessment of sympathovagal balance.	1.5-2.0

NOTE: nu = normalized unit. This information is summarized from Berntson and others (1997), Crawford and others (1999), and Task Force (1996). Normal values given are for human adults for stable 5-min electrocardiographic recordings, which is the recommended data set/time series length for power spectrum analysis.

Nonlinear Signal Analysis

A nonlinear system is mathematically defined as a 2nd- or higher-power system: that is, the independent variable in the mathematical equation contains an exponent (McGillem and Cooper 1974). For example, the equation for a parabola, $y = x^2$, describes a simple nonlinear system (Denton and others 1990). In a linear system, the variables produce an output response, whereas in a nonlinear system, the variables contribute to the output response. Although a linear system can be decomposed into its component parts, in a nonlinear system, the parts interfere, cooperate, or compete with each other (Strogatz 1994). A small change dramatically alters the nonlinear system because the initial condition of all variables along with the input stimulus influences the output response (Hilborn 1994).

Nonlinear dynamics systems theory allows for the mathematical reconstruction of an entire system from one known variable since the reconstructed dynamics are geometrically similar to the original dynamics (Kaplan and Glass 1995). Chaos theory,[1] popularized by Gleick's (1987) best-selling book, is a specialized subtheory of nonlinear dynamics that describes systems that are low dimensional (i.e., systems containing 3-5 variables), have defined boundaries, and exhibit sensitive dependence on initial conditions (Crutchfield and others 1986). This theory alerted scientists to the value of mathematical error and physiological noise when describing a system's behavior (Glass and Mackey 1988). Chaos theory demonstrated that random (stochastic) appearing systems actually contained deterministic[2] behavior. The random behavior observed in chaotic systems arises from the extreme sensitivity to initial conditions, which significantly influences the state of a system.

Theoretical limitations have become evident in the use of chaos theory per se to describe cardiac dynam-

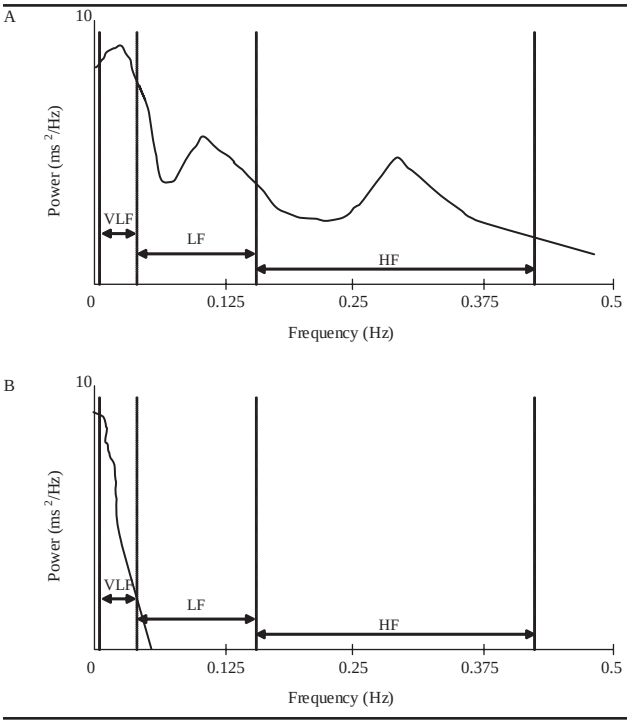

Figure 1. Fictional representative drawings depicting power spectrum analysis (spectral) plots for a human subject (A) and an isolated heart (B). In humans, the very low frequency (VLF) ranges from 0.003 to 0.04 Hz, the low frequency (LF) ranges from 0.04 to 0.15 Hz, and the high frequency (HF) ranges from 0.15 to 0.4 Hz.

ics. Function not only arises from a multitude of initial conditions but also requires noise for homeostasis (Zbilut and others 2002). Also, with sinus rhythm, deterministic behavior is exhibited during a cardiac cycle and stochastic behavior between cardiac cycles (Chillemi and others 1997; Zak and others 1997). Consequently, analysis techniques based on the broader nonlinear dynamics systems theory have been used to explain and account for the nonlinearity of the high-dimensional cardiac system. Numerous nonlinear analysis techniques exist; a few common ones are listed and briefly explained in Table 3. Examples of HRV studies employing nonlinear analysis techniques include Woo and others (1992, 1996), in which investigators detected diminished HRV in congestive heart failure patients; Pikkujamsa and others (1999), which investigated aging effects; and Goldberger and others (2002), which assessed alterations in aging and disease.

A nonlinear analysis technique favored by this author is recurrence quantification analysis (RQA) (Webber and Zbilut 1994, 1996; Zbilut and others 1998; Thomasson and others 2001; Zbilut and others 2002). Originally described in the physics literature by Eckmann and others (1987), RQA characterizes physiological systems by detecting the subtle rhythmic patterns produced by a system as it continually adapts to maintain homeostasis. RQA searches for repeating data sequences, which allows the data to be reconstructed as a time-ordered sequence of vectors.[3] The resulting vector matrices are then indexed and compared on all possible *I*, *J* vector coordinate combinations, producing the qualitative recurrence plot (see Fig. 2). The recurrence plot is a visual representation of the vectored data sequences, illustrating changes in the system as it evolves in time. In the recurrence plot, 2 points are considered recurring if their distance apart is less than a preset radius. The plot's diagonal lines denote trajectories: 2 vectors (data sequences) starting from 2 close points remain close together over a subsequent time period. In other words, the trajectory of 1 vector parallels the other over that distance in time. Recurrence plots dramatically illustrate one's data. However, since statistical analysis is necessary for experimentation, RQA quantifies the information contained within the recurrence plots. To this end, only the upper triangle is used for variable calculations since the recurrence plot is symmetrical. (The central line of identity splits the 2 triangular halves.) Alongside each recurrence plot is a list of the parameter values used to generate the individual plot, the resulting variable values, and a histogram showing the various lengths of the line segments (see Fig. 2). As summarized in Table 4, RQA produces 5 variables: %recurrence, %determinism, entropy, maxline, and trend. Once a time series has been analyzed with RQA, statistical analysis is performed on these variables to examine the relationships with other pertinent variables or the significance of experimental results.

Studies using RQA to assess cardiac function in human and animal models include Dabire and others (1998), Giuliani and others (1998), Mestivier and others (1997, 1998), and Zbilut and others (1992). These studies demonstrated the sensitivity of RQA in uncovering nonlinear structure and behavior patterns of the neurocardiac control mechanisms when analyzing R-R interval data. Although RQA results are not intuitive from a physiological perspective and are difficult to interpret (Schreiber 1999), the detection of changes

Table 3. Common Nonlinear Signal Analysis Techniques

Technique	Definition
Poincaré plot	This scatter plot visually reconstructs a system by plotting data point (x) against point ($x + 1$) for all data points in the time series. Also called a first return map, the Poincaré plot qualitatively represents the data without an associated quantitative variable.
Lyapunov exponent	This instability measure quantitates the degree to which a system exhibits sensitive dependence on initial conditions by measuring the exponential separation of 2 trajectories. The Lyapunov (Liapunov) exponent λ must be positive for a system to be classified as chaotic.
Fractal dimension	This self-similarity measure quantitates the self-likeness of a geometrical system over time. Fractals are subunits resembling the general structure of the original form, regardless of the subunit scale. The fractal-scaling exponent α represents this measure, whereby a larger α value means greater self-similarity and loss of complexity.
Approximate entropy	This complexity measure quantifies the regularity of a system by calculating the logarithmic likelihood that runs of patterns close to contiguous observations will remain close on subsequent incremental comparisons. Accounts for sequential order of data in a time series. The ApEn acronym represents this measure, whereby a time series from a sinusoidal-shaped periodic signal exhibits a low ApEn value.
Surrogate data analysis	This analysis technique is a method for checking whether a particular time series contains nonlinear components. Surrogate data are shuffled data generated to contain the same descriptive statistics and spectral components as the original time series. Surrogate data are consistent with the null hypothesis. Thus, the original time series will not be consistent with the null hypothesis if it contains nonlinear elements.

NOTE: This information is summarized from Goldberger and others (2002), Kantz and Schreiber (1997), Kaplan and Glass (1995), Pincus (2001), Schreiber (1999), and Strogatz (1994).

Table 4. Recurrence Quantification Analysis Variables

Variable (Unit)	Plot Element Quantified	Significance
%recurrence (percentage)	Number of recurrent points occurring in triangle versus total number of points	Periodic systems have higher %recurrence values compared to aperiodic systems
%determinism (percentage)	Number of recurrent points forming upward diagonal lines versus total number of points	Deterministic and structured systems have high % determinism values
Entropy (bits per histogram bin)	Shannon entropy[a] measure calculated from the line-length distribution in the histogram	Describes amount of regularity within an aperiodic system
Maxline (data's unit of measure)	Length of longest diagonal line in a plot	Inversely proportional to largest positive Lyapunov exponent in a chaotic system
Trend (% local recurrence per 1000 points)	Linear slope of the %recurrent points per unit distance away from central diagonal line	Values hovering around zero denote a dynamically stationary system

NOTE: This information is summarized from Thomasson and others (2001), Webber and Zbilut (1994, 1996), and Zbilut and others (1998, 2002).

a. The Shannon entropy is a measure of uncertainty first described by Shannon (1948) as a central theorem of information theory.

in dynamic behavior may be clinically useful as a marker in evaluating the disease process.

Isolated Heart Model

Analysis of identical R-R interval data sets from 3 different experimental conditions in the same isolated rat heart demonstrates the methodological differences between PSA and RQA in Figure 3 (Schumacher 2001). The purpose of the study was to examine intrinsic cardiac signal variability and to determine if PSA or RQA better detected autonomic-induced changes in cardiac function in the isolated heart model. ECG signals were acquired from isolated rat hearts before and after autonomic pharmacologic agents were added to the perfusate during retrograde (Langendorff) perfusion. Autonomic antagonists were added in the perfusate prior to the agonists to ensure inhibition of the opposing autonomic division. R-R interval data sets from 2-min ECG recordings were obtained before and after

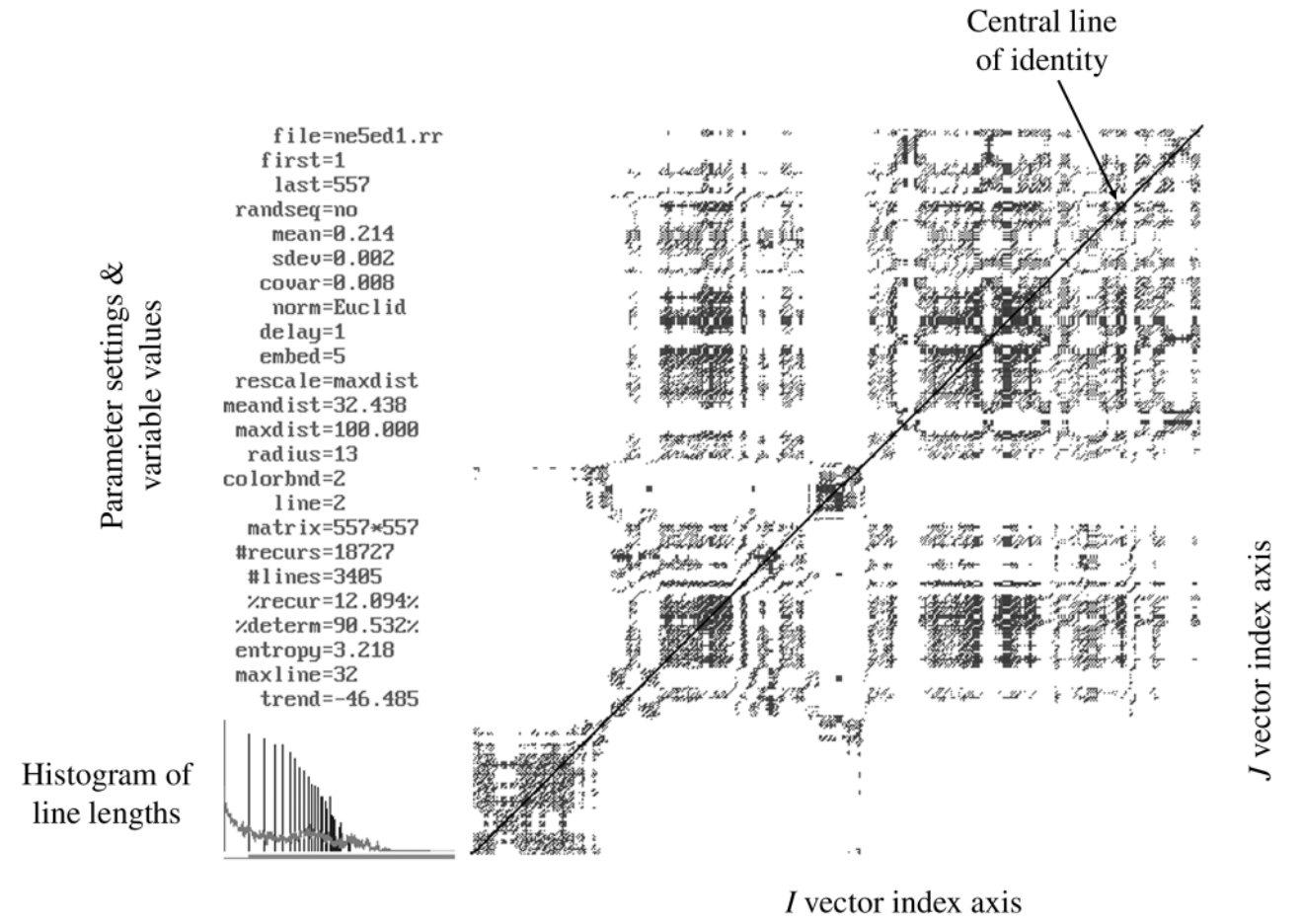

Figure 2. A representational recurrence quantification plot produced with R-R interval data from an isolated rat heart. Along the left side of each plot is listed the file name and parameter values used to generate the individual plot: first point, last point, randomization (randseq), mean of points in data set (mean), standard deviation of points in data set (sdev), covariate of points in data set (covar), normalization used (norm), amount of delay used, embedding dimension used (embed), type of rescaling (rescale), size of radius, colors for plot (colorbnd), number of points defining a line, matrix size (number of points by number of points in data set), number of recurrences found in plot (#recurs), and number of line segments found in plot (#lines). The resulting variable values are also listed along with each plot: %recurrence (%recur), %determinism (%determ), entropy, maxline, and trend. In the lower left corner is a histogram showing the various lengths of all line segments found in the plot.

each pharmacologic treatment and then analyzed with PSA and RQA. Figures 3A and 3B compare the PSA and RQA plots generated from the R-R interval data during the baseline/no-drug period, Figures 3C and 3D after the addition of the parasympathetic muscarinic antagonist atropine, and Figures 3E and 3F after the addition of the sympathic adrenergic agonist norepinephrine. Note how each RQA plot's visual appearance and most variable measurements changed with each experimental condition, whereas the PSA plots and variable measurements were scarcely altered with each condition. This particular example demonstrates the sensitivity of RQA to identify small changes in a time series not detectable with PSA.

Conclusion

Both the clinician and the researcher analyze physiological signals in their scopes of practice. The clinician monitors patients with technology typically based on linear systems theory. With improved technology based on nonlinear dynamics systems theory, it may be possible to indirectly detect cellular-level changes and clinically intervene prior to catastrophic alter-

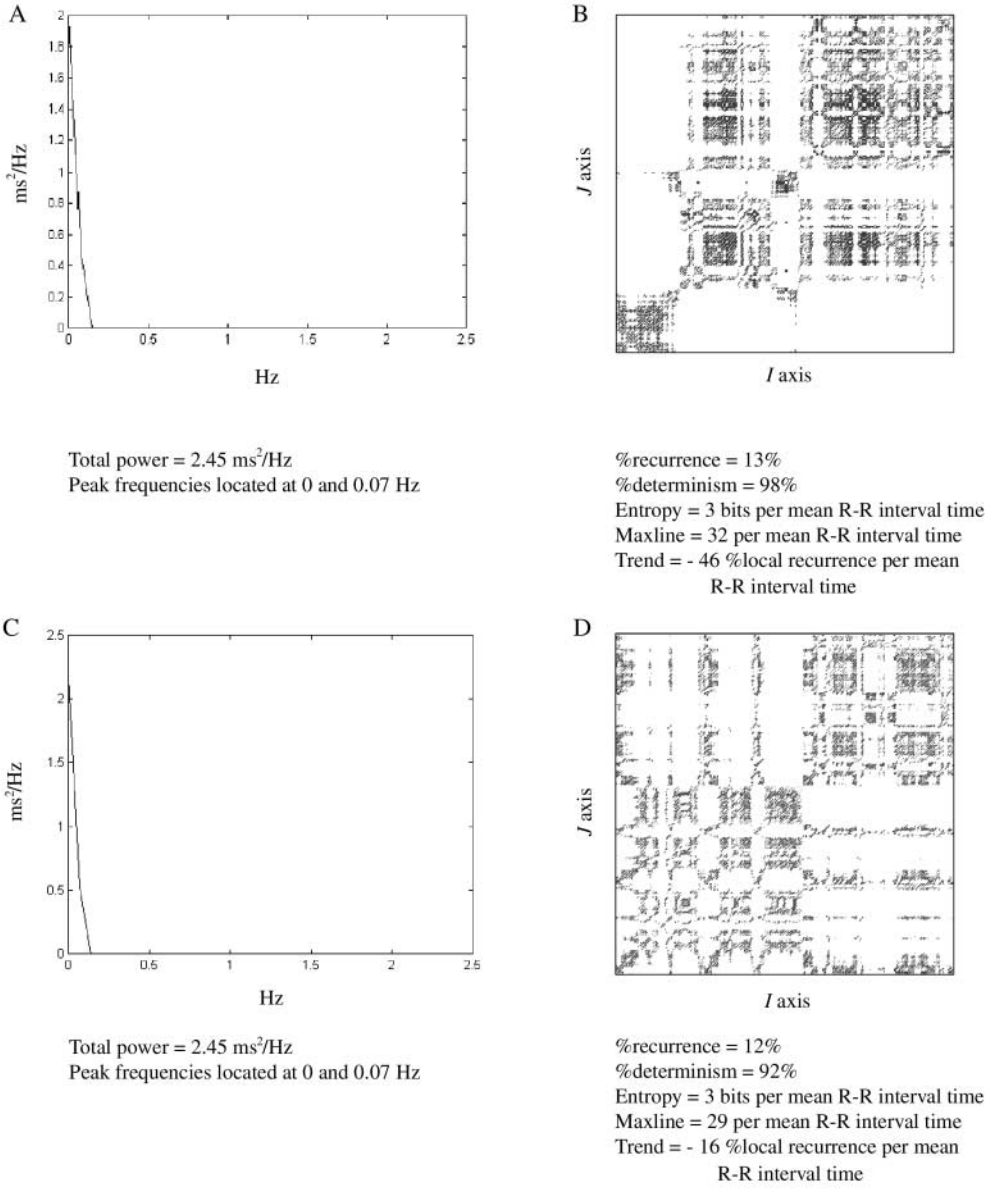

Figure 3. Power spectrum analysis plots (A,C,E) and recurrence quantification plots (B,D,F) produced with identical R-R interval data sets from one isolated rat heart. Plots A and B were generated with data obtained during the baseline/no-drug period. Plots C and D were generated with data obtained after the addition of the parasympathetic muscarinic antagonist atropine. Plots E and F were generated with data obtained after the addition of the sympathic adrenergic agonist norepinephrine.

ations in a patient's vital signs (Goldberger 1996). The researcher typically analyzes data with techniques also based in linear systems theory. Although linear techniques such as statistics and PSA have led to the recognition and understanding of HRV and its associated neurocardiac relationships, analysis techniques based on nonlinear dynamics systems theory are proving to be more sensitive tools with which to detect the complex autonomic, baroreceptor, and respiratory control mechanisms influencing cardiac function si-

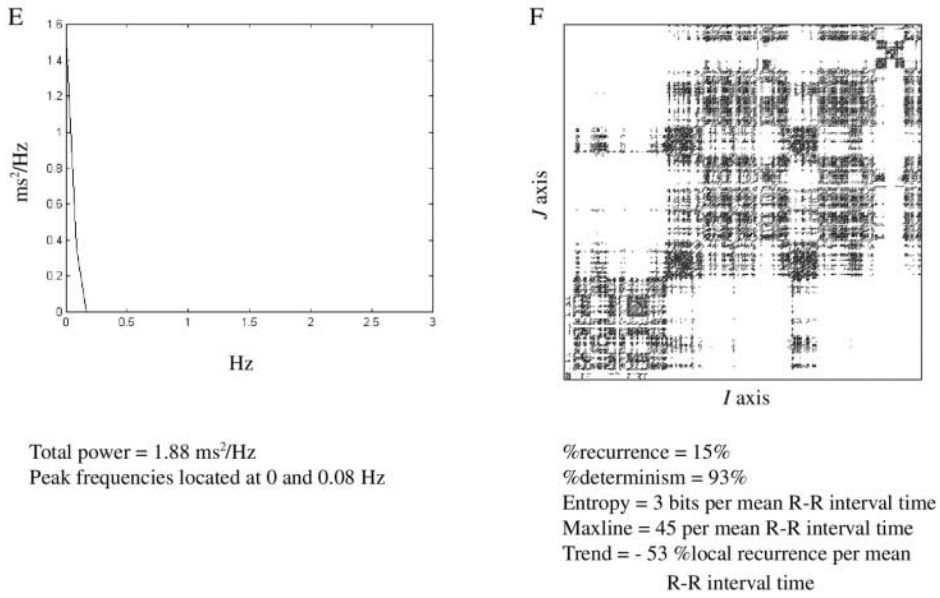

Figure 3. (continued)

multaneously to maintain homeostasis (Malpas 2002). Understanding the theoretical basis for applying the various signal analysis techniques is important for proper interpretation of the data.

Cardiac research using linear and nonlinear R-R interval time series (i.e., HRV) analysis proliferated over the past 2 decades due to improved computer capabilities. This noninvasive research has enhanced the understanding of the mechanisms underlying autonomic control of heart rate in healthy and pathological conditions. However, HRV is neither a direct measure of autonomic tone nor a measure of autonomic influence over all cardiac structures (Malik and Camm 1993). Control of cardiac function is a complex phenomenon involving multiple mechanisms at different structural and functional levels. HRV reflects sinus node activity and is a marker, not a mechanism, of cardiac electrical function (Fetsch and others 2000).

When assessing cardiac function, differentiation between parasympathetic and sympathetic activity may never be possible due to the ubiquitous nature of the autonomic nervous system. Instead, one may need to consider the modulation of sympathetic-parasympathetic interactions and the influence this autonomic modulation has on the multilevel control mechanisms (feedback loops). In other words, how well do the sympathetic and parasympathetic nervous systems modulate each other, such that the control mechanisms can operate within the neurocardiac milieu and maintain homeostasis? Pathology may result when the control mechanisms cannot operate optimally due to loss of neurocardiac modulation when one autonomic division dominates the other, such as in heart failure. Neurocardiac regulation may be nonlinear in structure due to the multilevel nature of the interactions between the autonomic nervous system and the various control mechanisms. Therefore, nonlinear techniques may offer advantages over linear techniques in identifying and quantifying the modulation of interactions among neurocardiac control mechanisms.

Notes

1. *Chaos theory* and *nonlinear dynamics systems theory* are frequently used as interchangeable terms despite their technically different meanings.

2. Mathematically, *deterministic* means that one data point will govern the value of the next data point when describing a system. Theoretically, *deterministic* means that random or noisy stimuli do not affect a system (Strogatz 1994).

3. A vector is a mathematical description of direction and magnitude. For example, a car traveling northeast at 60 miles per hour has properties of a vector.

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