

# Statistical Approach to Quantify the Presence of Phase Coupling Using the Bispectrum

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**Abstract**—The bispectrum is a method to detect the presence of phase coupling between different components in a signal. The traditional way to quantify phase coupling is by means of the bicoherence index, which is essentially a normalized bispectrum. The major drawback of the bicoherence index (BCI) is that determination of significant phase coupling becomes compromised with noise and low coupling strength. To overcome this limitation, a statistical approach that combines the bispectrum with a surrogate data method to determine the statistical significance of the phase coupling is introduced. Our method does not rely on the use of the BCI, where the normalization procedure of the BCI is the major culprit in its poor specificity. We demonstrate the accuracy of the proposed approach using simulation examples that are designed to test its robustness against noise contamination as well as varying levels of phase coupling. Our results show that the proposed approach outperforms the bicoherence index in both sensitivity and specificity and provides an unbiased and statistical approach to determining the presence of quadratic phase coupling. Application of this new method to renal hemodynamic data was applied to renal stop flow pressure data obtained from normotensive ( $N = 7$ ) and hypertensive ( $N = 7$ ) rats. We found significant nonlinear interactions in both strains of rats with a greater magnitude of coupling and smaller number of interaction peaks in normotensive rats than hypertensive rats.

**Index Terms**—Bicoherence, bispectrum, cross bispectrum, nonlinear interactions, quadratic phase coupling, surrogate data.

## I. INTRODUCTION

THE BISPECTRUM is a useful tool for identifying a process that is either non-Gaussian or is generated by nonlinear mechanisms. Application of the bispectrum has been especially popular in biological systems because of the ubiquity of inherently nonlinear characteristics of biological mechanisms. One such characteristic is the presence of nonlinear interactions that have been detected in neural [1]–[4], renal [5], [6], and cardiovascular [7], [8] systems, in particular. Detection of nonlinear interactions has been particularly useful in neural system studies because the bispectrum has been used effectively to

detail changes in interactions with the level of anesthesia and sedation [9]–[11]. Furthermore, it has been used in an attempt to detect and predict epileptic seizure events [12].

While nonlinear interactions can be identified in many forms, including phase coherence, the bispectrum is ideally suited to detecting phase coupling between two components of a process [13]. The power spectrum suppresses phase relations; thus, it cannot be used for detection of phase coupling.

Quantification of phase coupling via the bispectrum is obtained by estimating the bicoherence index (BCI), which is essentially a normalized bispectrum obtained by dividing the bispectrum by the power spectra of the signal [13]. The theoretical values of the BCI correspond to a range from insignificant to highly significant phase-coupled peaks. Phase coupling implies both frequency and phase coupling, in which the third frequency peak and its phase are the sum of the first two frequency peaks and phases. The BCI is designed to consider only phase-coupled components, eliminating bispectral peaks resulting from frequency locking alone that should not be present in a bispectrum but are often represented. However, due to technical considerations such as using an insufficient number of segments to compute the bispectrum, frequency-coupled peaks will sometimes appear in the BCI. Further, for finite-length data sets, the high variability present in the bicoherence index will cause theoretically Gaussian processes to have a nonzero value.

To avoid making erroneous decisions about the presence of phase coupling based on the BCI, a method was proposed by Elgar and Guza [14] that is based on modeling the significance level for zero bicoherence. In this work, the level of significance was based primarily on the number of segments used in the calculated bicoherence. We have recently proposed an autoregressive bispectrum combined with surrogate data method to test the statistical significance of the obtained quadratic phase-coupled peaks [6]. This approach allows better detection of phase-coupled peaks, even with noise contamination. While this approach, known as *S*-statistics, is certainly an improvement over the BCI itself, the method still suffers from low specificity due to a normalization procedure that can allow insignificant bispectral peaks to become significant. In addition, in certain instances, the BCI values are greater than one when a small amount of time variance was introduced into the data. This further complicates the interpretation of results, as most physiological data inherently have some degree of time variance. To compensate for this problem, Pinhas *et al.* [15] introduced a method that statistically removes these erroneous peaks. However, this method suffers from the fact that it is based on the central limit theorem, which requires a large amount of data that may be difficult to obtain with physiological data.

Manuscript received August 23, 2007. This work was supported by the National Institutes of Health under Grant HL069629. Asterisk indicates corresponding author.

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Digital Object Identifier 10.1109/TBME.2007.913418

Given the aforesaid problems associated with the detection of phase coupling with the use of the BCI as well as  $S$ -statistics, the aim of the present work is to circumvent the limitations of both methods. The approach we propose does not involve the use of the BCI, rather, it uses bispectrum estimation followed by testing the significance of the results against surrogate data realizations. The goal of the surrogate data transformation is to destroy the nonlinear dynamics in the data. This leaves a time series with only linear properties; thus no phase coupling should be detected. As a result, only bispectral peaks remaining must arise from harmonic components and are insignificant. The efficacy of our new method, based on the use of the bispectrum estimation followed by the use of a surrogate data technique, will be compared to the traditional BCI as well as combination of the BCI and the  $S$ -statistics method.

## II. METHODS

### A. Bispectral Analysis

There are two nonparametric approaches, direct and indirect, to compute the bispectrum. The indirect method involves computation of the third-order cumulant followed by the 2-D Fourier transform of the third-order cumulant. For our analysis, we use the direct method, which is estimated by taking the average of triple products of the Fourier transform over  $K$  segments

$$BS(f_1, f_2) = \frac{1}{K} \sum_{k=1}^K X_k(f_1) X_k(f_2) X_k^*(f_1 + f_2) \quad (1)$$

where  $X_k(f)$  is the Fourier transform of the  $k$ th segment and  $*$  indicates the complex conjugate. Note that as the size of each segment decreases, the frequency resolution will also decrease. Therefore, it is important to choose the proper segment size so that there is sufficient resolution to resolve the dynamics in the signal while retaining enough segments to properly reduce variance in the bispectrum for the detection of phase coupling. This tradeoff between time and frequency resolution also pertains to the indirect method and to a lesser extent to parametric approaches. In addition, while our estimation results are all based on the direct method of computing the bispectrum, our approach of statistically quantifying the presence of phase coupling equally applies to both indirect and parametric (model based) approaches to estimating the bispectrum.

### B. Necessity of Statistical Analysis in Bispectral Analysis

To illustrate the necessity of complementing bispectral estimation with statistical analysis, a simple simulation example is provided. The simulation consists of two test signals, both involving three frequencies, as shown next:

$$y_{1,2}(t) = \sin(2\pi f_1 t + \theta_1) + \sin(2\pi f_2 t + \theta_2) + A \sin(2\pi f_3 t + \theta_3) \quad (2)$$

where  $f_1$  and  $f_2$  are set to 0.1 Hz and 0.2 Hz, respectively. For both test signals, the third frequency,  $f_3$ , is set to  $f_1 + f_2 = 0.3$  Hz in order to achieve the frequency coupling. Phases associated with the first two frequencies ( $\theta_1$  and  $\theta_2$ ) are randomly generated

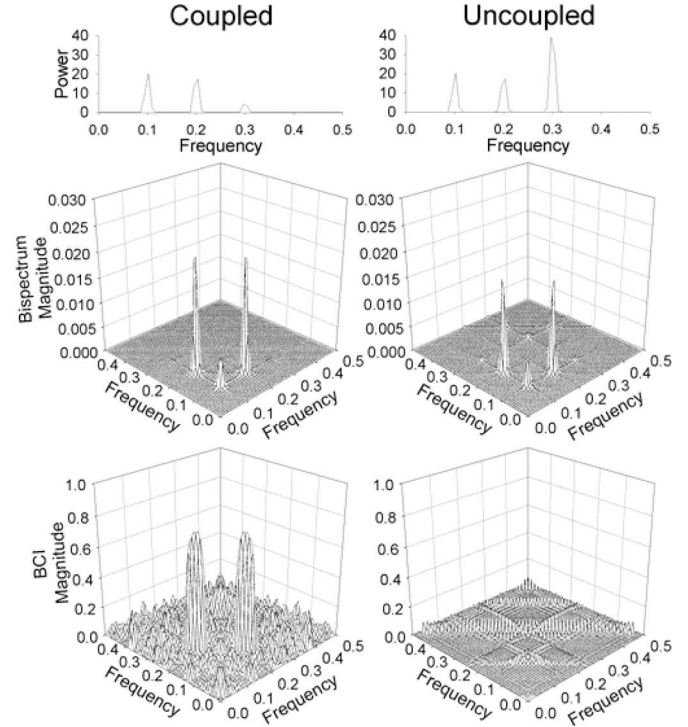


Fig. 1. Bispectra (middle panels) and bicoherence (bottom panels) with (left panels) and without (right panels) phase coupling. Note the similar phase coupling magnitudes for both phase uncoupled and coupled system.

between  $-\pi$  and  $\pi$  with a uniform distribution. For the first test signal ( $y_1(t)$ ), the third frequency is also phase coupled such that  $\theta_3 = \theta_1 + \theta_2$ . The second test signal ( $y_2(t)$ ) is not phase coupled so that  $\theta_3$  is also randomly generated to be between  $-\pi$  and  $\pi$ . The amplitude  $A$  is set to 0.5 for the phase-uncoupled signal whereas it is set to 1.5 for the phase-coupled signal. The amplitude of the phase-uncoupled signal is set to a high value to simulate a condition, where high bispectral values can be obtained from frequency-matching components alone. Both test signals were generated at 1-Hz sampling rate and contained 2048 data points. For both test signals, 32 segments, each containing 64 data points, with no overlapping segments, were used to estimate the bispectrum.

The resulting bispectra (middle panels) and the BCI (bottom panels) for the phase-coupled and uncoupled signals with their respective power spectra (top panels), are shown in the left and right panels of Fig. 1. The power spectra of the phase-coupled and uncoupled signals are indistinguishable in terms of frequency information, albeit the amplitude of the phase-coupled spectrum is lower especially at 0.3 Hz. Although the phase-coupled signal has lower spectral amplitude than the phase-uncoupled spectral peak, we observe a similar bispectral peak magnitude at the frequency pair (0.1, 0.2) Hz in these two systems. This example demonstrates an important issue. Due to inherent limitations associated with the bispectrum estimation, it is possible to obtain a bispectral peak for the phase-uncoupled signal under certain frequency and amplitude combinations. That is, frequency coupling alone is sufficient to generate peaks in the bispectrum. Hence, a statistical method is needed to distinguish

true peaks resulting from frequency and phase coupling from erroneous peaks resulting from frequency coupling alone. The bottom panel shows the bicoherence of the test signals. As shown on the bottom right panel, the BCI was able to correctly eliminate the phase-uncoupled peaks as these peaks have values lower than the threshold value of 0.306, as derived by Elgar and Guza [14]. However, note the inadequate frequency resolution especially on the bottom left panel as compared to the figure shown on the top left panel. In addition, this simulation is based on noise-free and relatively long data records, conditions which are seldom met with experimental data. The limitations of the BCI will be further illustrated in Section III.

### C. Traditional Statistical Methods

Traditionally, determination of phase-coupled peaks in the bispectrum required the calculation of a normalized bispectrum, called the bicoherence index (BCI). The BCI is calculated by

$$\text{BCI}(f_1, f_2) = \frac{\text{BS}(f_1, f_2)}{\sqrt{P(f_1)P(f_2)P(f_1 + f_2)}} \quad (3)$$

where  $P(f)$  is the power spectrum of the signal.

From the BCI, one would then need a method for determining significance in the peaks observed. The method developed by Elgar and Guza [14] for determining significance in the BCI based on describing the significance levels for zero bicoherence was used here. Specifically, it was found that the 95% significance level for zero bicoherence is approximately  $\sqrt{6/2m}$ , where  $m$  is the number of segments. Further, the  $S$ -statistical method [6], based on surrogate data, was also used here for comparison. While the  $S$ -statistics method was developed for use with autoregressive-model-based bispectral estimation, we adopt this technique for the direct method of computing the bispectrum.

Surrogate data are a modified form of the original data that eliminates nonlinear properties while retaining linear statistical properties. Randomization of phases accomplishes the elimination of nonlinearity and since randomization can be performed in many ways, we can obtain multiple realizations of surrogate data from a single time series. This is useful in the statistical testing of nonlinearity, as one can then use the generated surrogate data as the null condition to be tested against. We chose the iteratively refined surrogate data technique (IRSDT) [9]. The IRSDT will destroy any nonlinearity in the signal, and has been shown to be more accurate than the amplitude-adjusted Fourier transform technique [16] because it iteratively corrects for deviations in the spectrum as well as maintains the correct distribution of the signal.

The  $S$ -statistic approach involves generation of multiple realizations ( $\sim 100$  suffice) of surrogate data. The BCI is calculated for each realization of surrogates as well as for the original data. The  $S$  value, which tests for the 95% significance of the detected quadratic phase coupling, is based on the assumption that the distribution of the surrogates follows a normal distribution. In the current work, the threshold for  $S$ -statistics is set as the 95th percentile of the distribution of the BCI estimated on the 100 realizations of surrogate data. The threshold value is then

subtracted from the BCI value of the original data. Values above zero are considered significant for the  $S$ -statistics.

We will show using simulation examples that the BCI and  $S$ -statistics lack sensitivity and specificity, respectively. Due to the inherent limitations of these traditional methods, a new approach for evaluating quadratic phase coupling, based on surrogate data of the bispectral estimate and completely bypassing the computation of the BCI, is described in the following section.

### D. Proposed Approach: Surrogate Data Threshold Method Applied to the Bispectrum and Not BCI

The bispectrum with surrogate (BWS) method is similar to  $S$ -statistics, being also based on surrogate data. However, a key distinction is the fact that it does not utilize BCI but only the bispectrum estimate, since its statistical determination of the presence of phase coupling uses surrogate data realizations. The procedure involves generating 100 realizations of surrogate data from the original data. The bispectrum of each of the surrogates, as well as the original data, is calculated. The mean and standard deviation of all 100 surrogates' bispectral estimates are calculated. The 95% statistical threshold values are defined as the mean plus 2 standard deviations. To accentuate specificity, we used a single threshold value (determined as the largest among all candidate threshold values) for all frequencies instead of having different threshold values for each frequency. If higher sensitivity is desired, varying threshold values can be used for different frequencies. Note that the statistical threshold of the BWS, based on the normality assumption, is verified using the Kolmogorov–Smirnov goodness-of-fit test [17]. Any bispectral peaks estimated from the original data that are above these threshold values are considered to have significant frequency and phase coupling. Therefore, the difference between the bispectrum value from the original data and the threshold value is then calculated. Difference values above 0 will indicate a bispectrum value above the threshold, and are therefore, considered significant.

### E. Simulation Conditions

The three methods, the BCI,  $S$ -statistics, and our proposed approach (BWS) were tested by using simulated data under different conditions. Unless otherwise noted, the test signal used consisted of a phased-coupled triplet as described earlier, at a 1-Hz sampling rate with 2048 data points. The frequencies used were  $f_1 = 0.1$ ,  $f_2 = 0.2$ , and  $f_3 = 0.3$ . The bispectra was also calculated as described before with segment size of 64, but 128 points were used for the fast Fourier transformation (64 points zero padding), and there were no overlapping segments.

To guard against counting the same bispectral peak twice (especially possible if the frequency resolution is not high), each peak was checked against its eight nearest neighbors. If the magnitude of a peak was higher than any of its neighbors, it was then considered a peak. We repeated this process for the entire bispectrum. We then tested the peaks for significance of using the three methods.

### F. Application of the BWS to Renal Blood Flow

The BWS was applied to experimental renal hemodynamic data to demonstrate its efficacy. All experiments were performed under protocols approved by The Institutional Animal Care and Use Committee at Stony Brook and The University of South Florida. The data were collected from a previous study in which stop flow pressure (SFP) recordings from a single nephron were measured in Sprague–Dawley (SDR, 240–300 g,  $n = 7$ ) and spontaneously hypertensive rats (SHR, 12-week old,  $n = 7$ ) [18]. Surgical preparation and the stop flow pressure measurements are detailed in our previously published study [6]; thus, they will only be briefly described here. Animals were anesthetized with halothane administered in an oxygen–nitrogen mixture and artificially ventilated after the administration of a muscle relaxant. Tubular flow was interrupted with bone wax in a selected proximal tubule, and intratubular hydraulic pressure proximal to the wax block was measured via a 1–3  $\mu\text{m}$  diameter micropipette attached to a servo-nulling pressure circuit. Data was recorded on a TEAC R-61 4-channel cassette data recorder for offline analysis. The recorded data were replayed through an electronic low-pass filter with a roll-off frequency of 1.5 Hz and sampled digitally at 4 Hz. Before bispectral analysis, the data were further filtered by a digital low-pass filter with a cutoff frequency of 0.5 Hz, and downsampled to 1 Hz.

## III. RESULTS AND DISCUSSION

### A. Test for Normality

Our statistical threshold, based on the normality assumption, was verified using the Kolmogorov–Smirnov goodness-of-fit test [17]. The calculated  $P$  value was  $>0.05$ , which confirms that this set is drawn from a normally distributed population.

### B. Test of Robustness Against Noise Corruption

We tested the three methods for robustness against noise-corrupted data. The generated signal was corrupted by additive Gaussian white noise (AGWN) such that the SNR ranged from 25 to  $-25$  dB. Ten independent realizations of Gaussian white noise at each noise level were generated to corrupt the signal in order to achieve a statistical result. The bispectrum was then calculated for each realization of the noise-corrupted signal to examine how robust each method was in detecting only the true phase-coupled peak. To test the sensitivity of each method, the calculated value of each method at the generated frequencies were recorded for each realization and averaged. Further, to test for specificity, the total number of significant detected peaks across the entire bispectrum was also recorded for each realization. The mean of sensitivity and the median of specificity results are reported in the top and bottom panels of Fig. 2, respectively. Note that for the BCI, the thresholding method proposed by Elgar and Guza was used [14], while for the  $S$ -statistics and the BWS methods, a threshold value of 0 was used as this represents the difference between the bicoherence value of the data and surrogate data results. All of these threshold values are noted as dashed lines.

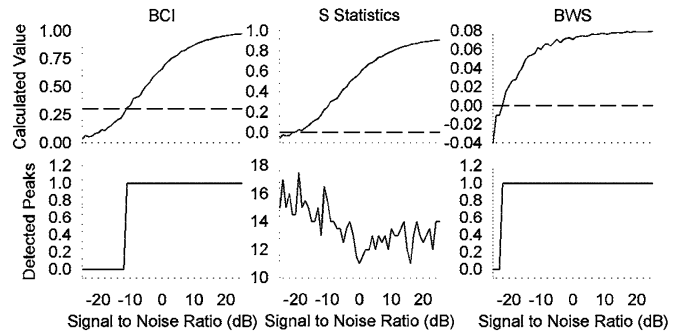


Fig. 2. Comparison of three bispectral methods with noise contamination. The data were corrupted by a variable amount of Gaussian white noise. The top panels show the calculated value of each method at the generated frequencies. The bottom panels show the median number of significant peaks detected at each noise level.

As shown in the top panels of Fig. 2, the BCI is most susceptible to noise corruption as it needs an SNR greater than  $-11$  dB to detect the true peak. The  $S$ -statistics method is able to tolerate a greater amount of noise as it remains robust even with SNR at  $-\mu-20$  dB (robust in the sense that it always detects the phase-coupled peak, even if it also detects extraneous peaks). The performance of the BWS is the best out of the three, being able to detect the frequency peak at a noise level as low as  $-22$  dB.

Comparison of the specificity information for the three methods is shown in the bottom panels of Fig. 2. We observe that the  $S$ -statistics method is nonspecific, as it detects an average of 14 additional nonphase-coupled peaks over the range of SNR that we have used. The BCI and BWS methods have high specificity, detecting only the phase-coupled peak up until the noise level at which these methods fail. This simulation shows that the BWS has the optimal combination of specificity and sensitivity in the case of varying amounts of noise in the data. Further, it should be noted that the degree of coupling in the test signal was not varied. Therefore, ideally the calculated values should not change with noise corruption. The top panel of Fig. 2 shows that all three methods' average calculated values decrease with increasing noise. However, the BWS is most resistant to this effect, with a relatively unchanging calculated value up until approximately 0 dB. This suggests that the calculated values from the BWS used to assess coupling strength are the most accurate, as the BWS method is the least affected by noise corruption. Further supporting evidence to this effect is shown in the next few sections.

### C. Test of Amount of Phase Coupling

This example was designed to determine each method's fidelity in discriminating uncoupled phases. The amount of phase coupling was varied by injecting a number of data points that had uncoupled phases. The amount of phase coupling varied from 0% to 100% at an increment of 1%. For each level of phase coupling, 100 realizations of the test signals were generated. Each realization of the test signal was corrupted by 0 dB AGWN. For sensitivity testing, the calculated value for each method was recorded at the known phase-coupled frequency. For specificity, the total number of significant detected peaks in

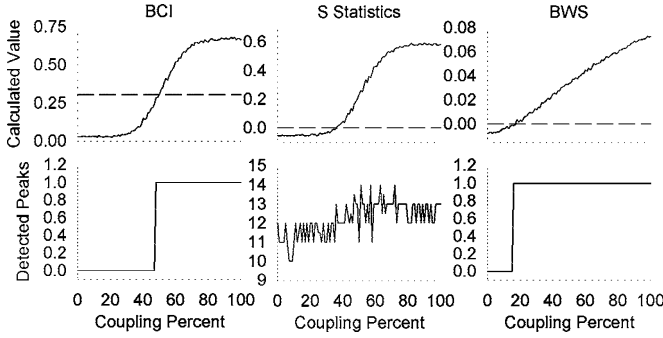


Fig. 3. Comparison of three bispectral methods with varying amounts of coupling. Plotted on the top panels are the calculated values at the known phase-coupled frequency for each of the three methods. The dotted lines show the significant threshold levels for each of the three approaches.

the entire bispectrum was recorded and the median between the realizations is reported. These values are shown in Fig. 3 as a function of varying percent of phase coupling.

As shown in the top panels of Fig. 3, the percent of coupling that each method was sensitive to was approximately 50%, 35%, and 18% for the BCI, *S*-statistics, and the BWS, respectively. The bottom panels show the specificity of the three tests. The trend here is the same as the prior example, where the specificity for the BCI and BWS is very high, while it is poor for the *S*-statistics method. This example provides evidence that the BWS has the best combination of sensitivity and specificity in detecting low levels of phase coupling. Further, it should be noted that the calculated value for the BWS linearly increases with increasing coupling percent for values above 18%, thereby suggesting that the BWS method provides a good quantification of the actual amount of phase coupling present in the system. The BCI and the *S*-statistics, however, show a more sigmoidal relationship with only a small window of linearity from approximately 40% to 70% coupling. The problem here is that it would be difficult to distinguish between two signals with high coupling strengths with the BCI and the *S*-statistics, as they will show up with similar values. This suggests that the BCI and *S*-statistics are less able to distinguish relative degrees of coupling when signals are strongly coupled.

#### D. Effects of Segment Number

Varying the number of segments is tested, as it has been demonstrated that only by having a sufficient number of segments will one detect the presence of phase coupling, if it exists [13]. The size of each segment was kept constant at 64 data points. The number of segments was varied from 1 to 32 at an increment of one. For example, 1 segment means there are 64 data points and 32 segments correspond to 2048 data points in total, still 64 in each segment. For each segment, 100 realizations of the test signal were generated. Each realization was corrupted by 0 dB AGWN. Similar to previous simulations, the calculated value of the three tests and the number of detected peaks will be recorded for sensitivity and specificity, respectively. The result of this simulation is shown in Fig. 4.

The top panels of Fig. 4 show the calculated values of each method as a function of segment number. It should be noted

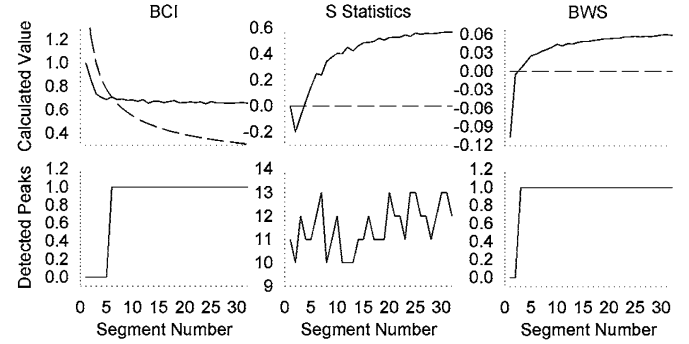


Fig. 4. Comparison of three bispectral methods with varying number of segments. The top panels show the calculated value of each method at the known phase-coupled frequency. The dotted lines in the top panels show the threshold levels for each method: 0.5 for the BCI, 2 for the *S*-statistics, and 0 for the BWS. The bottom panels show the number of detected peaks for the three methods.

TABLE I  
COMPARISON OF THE THREE BISPECTRAL METHODS' ABILITIES TO TOLERATE A SMALL AMOUNT OF TIME VARIANCE IN THE DATA

	BCI	S-Statistics	BWS
Triplet 1	1.00	0.93	0.0940
Triplet 2	31.92	31.83	0.0029

The simulation used a signal with two frequency triplets, where both of the triplets are both frequency and phase coupled. However, triplet 2 only exists in the last segment of data, whereas triplet 1 exists in all data. Reported here are the calculated values from the three methods for triplets 1 and 2.

here that the threshold for the BCI, shown as the dashed curve, changes with the segment number according to the method by Elgar and Guza [14]. It can be seen from the top panels that the minimum number of segments needed to detect significant peaks for the BCI, *S*-statistics, and BWS are 6, 4 and 3, respectively. This corresponds to 384, 256, and 192 points, respectively. The specificity analysis in the bottom panel shows a similar trend as in previous tests, where the BCI and the BWS have the highest specificity, while the *S*-statistics method detects many erroneous peaks. From these results, it could be concluded that the BWS has the best tolerance to small amounts of data.

#### E. Test of Small Amount of Time Variance

In this simulation, we test the problem of having a small amount of time variation (nonstationarity) in the data while using the time-invariant bispectrum for analysis. This problem was originally reported by Pinhas *et al.* [15]. The simulated test signal consisted of 2048 data points at a sampling rate of 1 Hz. This signal contains 32 segments of 64 data points each. Two frequency triplets are used in the signal. The first frequency triplet contains frequencies 0.05, 0.1, and 0.15 Hz. The second frequency triplet contains frequencies 0.2, 0.25, and 0.45 Hz. Both frequency triplets are fully phase coupled. The second frequency triplet exists only in the last segment of the data, while the first frequency triplet exists in all data. This simulates a signal, where a small portion of it is different from the rest. One hundred realizations of the test signal were generated in this simulation, and the results are averaged. The three methods are compared and the results are summarized in Table I.

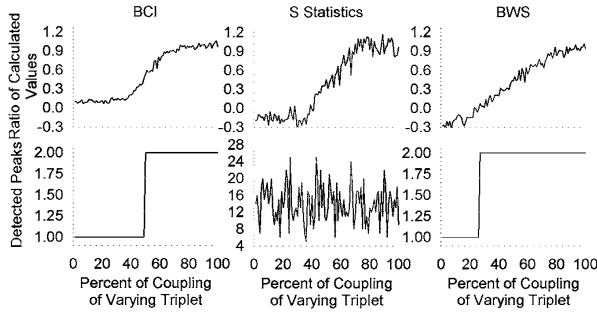


Fig. 5. Comparison of three bispectral methods with two triplets of varying amounts of phase coupling. In this simulation, the first triplet was fully phase coupled, while the second triplet had a varying amount of phase coupling ranging from 2 to 100%, in 1% increments. The calculated values for each method for the two triplets were recorded, and the ratio between the calculated values of the two triplets is shown in the top panels. The bottom panels show the number of detected peaks from the three methods.

As shown in Table I, the calculated values for the BCI and  $S$ -statistics show a much higher value for the second triplet compared to the first triplet. This is an erroneous result, as the second triplet only exists in a small amount of data, which should, in theory, lead to a smaller magnitude of coupling. For the BWS, the calculated value of the second triplet is lower than the first. Further, the value of the first triplet is 32.35 times that of the second. This matches very well to the 32:1 ratio (# of segments between the first and the second frequency triplets) between the first and second triplet, which may suggest that the calculated value of the BWS accurately quantifies the degree of coupling that is in the signal. It is important to note here that for the BCI and the  $S$ -statistics, the calculated values also show a 32 to 1 ratio, except in the opposite direction (the value for the second triplet is 32 times that of the first). This phenomenon is further investigated in the next section.

#### F. Test of the Relative Magnitudes of the Calculated Values

In this simulation, the three methods were tested for their ability to quantify the relative coupling strengths between multiple coupling processes in a signal. The simulation signal used was the additive sum of two different frequency triplets, resulting in a signal with six frequency components. Each frequency triplet was generated in the same manner as described in Section II-B. The specific frequencies used were  $f_1 = 0.05$  Hz,  $f_2 = 0.1$  Hz,  $f_3 = f_1 + f_2 = 0.15$  Hz,  $f_4 = 0.2$  Hz,  $f_5 = 0.25$  Hz,  $f_6 = f_4 + f_5 = 0.45$  Hz. The coupling percent of the  $f_4 f_5 f_6$  triplet was varied between 0% and 100% at an increment of 1%, while the  $f_1 f_2 f_3$  triplet was fully phase coupled. The signal was generated at a 1-Hz sampling rate with 2048 data points. One hundred realizations of the test signal were generated, and the averaged results are shown. The calculated values at the two simulated frequency triplets, and the total number of detected peaks in the entire bispectrum, were recorded. Further, the ratio between the calculated values of the two triplets was also calculated. This ratio should ideally change linearly with coupling percent if the calculated values represent the actual strength of coupling.

The top panels of Fig. 5 show the plot of the ratio between the calculated values of the two triplets. Similar to the previous

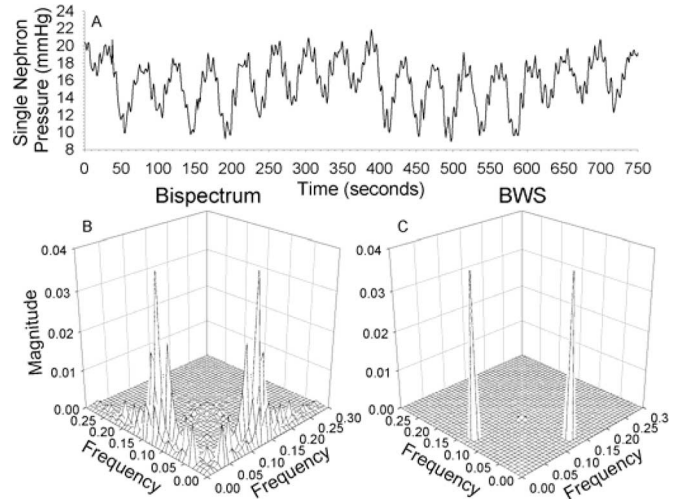


Fig. 6. Stop-flow pressure tracing (A) and the corresponding bispectrum without (B) and with surrogate data (C). Note the elimination of many peaks in (B) with the use of the BWS.

simulation, the BCI and the  $S$ -statistics both have a linear region at the start of their detectable range. However, the ratio quickly saturates to the value of 1. For the BWS, the ratio remains relatively linear over its entire range. Linear regression of the ratio from the BWS yields an  $R^2$  of 0.97. This linear behavior of the ratio is important when multiple components exist in a signal, and one wishes to quantitatively compare the degree of coupling between the mechanisms. For the BCI and the  $S$ -statistics, this will be difficult at best since the ratio between the calculated values of 70% to 100% shows a very similar value. The BWS, on the other hand, shows a linear relationship across its detectable range, allowing for a meaningful quantitative comparison between the different components in the signal.

The bottom panels of Fig. 5 show the number of detected peaks from the three methods. The trend in this simulation is similar to all the other examples, where the BCI and the BWS are very sensitive and detect the correct number of peaks for their detectable range, while the  $S$ -statistics method is not specific and detects a high number of peaks over all ranges.

In summary, the two simulations presented in this section show that the BWS is able to correctly determine the relative magnitude of different coupling components in the same signal. The other two methods, on the other hand, are less effective in quantifying the degree of coupling between dynamics.

#### G. Application of the BWS to Renal Data

Our previous data analysis involving autoregressive bispectrum revealed quadratic phase coupling at the prescribed myogenic (MYO: 0.1–0.3 Hz) and tubuloglomerular feedback (TGF: 0.02–0.05 Hz) frequency ranges [6]. Thus, the purpose of this section is to demonstrate the presence of such quadratic phase coupling using the BWS method, as well as its ability to discriminate only the significant phase coupling peaks. A typical BWS result is shown in Fig. 6. Panel A of Fig. 6 shows the time series of a typical single nephron stop flow pressure. Note both fast and slow oscillations in the stop flow pressure data, which

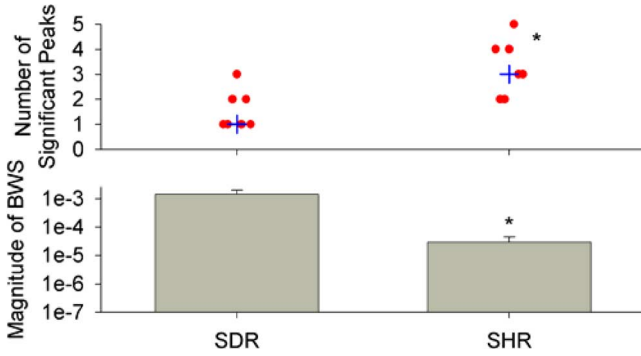


Fig. 7. Summary of the application of the BWS on renal stop flow pressure measurements on both SDR ( $n = 7$ ) and SHR ( $n = 7$ ). The top panel shows the number of significant peaks between the two strains, with the blue + representing the median. Both the magnitude and the number of peaks are significantly different ( $P < 0.05$ ), with the SHR showing a lower magnitude as well as a greater number of peaks. Bottom panel shows the average BWS magnitude of significant peaks between the TGF and MYO mechanisms in log scale.

reflect the activity of the two autoregulatory mechanisms. Panel B shows the bispectral estimation without the use of surrogate data on the data shown in panel A. The largest peak is at the prescribed frequency pair (TGF: 0.0234 Hz, MYO: 0.1328 Hz) associated with the TGF and MYO mechanisms. In addition to the largest peak, there are many smaller peaks present in the bispectral plot. It is difficult to discern whether these smaller peaks are the result of true phase-coupled peaks or if they simply arise from frequency coupling alone, measurement noise, or estimation error. Panel C shows the bispectrum of the same time tracing after using the BWS method to eliminate the erroneous peaks. The smaller peaks shown in panel B have mostly been eliminated, preserving only the phase-coupled peak. Summarized results for both SDR ( $n = 7$ ) and SHR ( $n = 7$ ) are shown in Fig. 7. As shown in the top panel of Fig. 7, we observe nonlinear interactions between MYO and TGF in all SDR and SHR and this result is consistent with past studies [6], [19], [20]. In addition, we found that there was a greater number of significant nonlinear interaction peaks with SHR than SDR. However, the strength of interactions is significantly greater in SDR than SHR ( $P < 0.05$ ) as shown in the bottom panel of Fig. 7. The magnitude result is shown in log scale due to the SDR having a BWS magnitude of more than an order of magnitude larger than that of the SHR.

#### IV. DISCUSSION

The simulation examples presented generally show that our proposed approach, BWS, offers the best combination of sensitivity and specificity under all of the tested conditions. Further, the BWS in general is more sensitive than the BCI and the  $S$ -statistics method in detecting coupling. The  $S$ -statistics method detects many spurious peaks; the culprit is the normalization procedure inherent in the computation of the BCI. The  $S$ -statistics method is reliable and appropriate to use when there is *a priori* information about the presence of quadratic phase coupling at specific frequencies. Furthermore, the use of  $S$ -statistics is more appropriate with parametric approaches to

bispectral estimates, as the process of finding the proper number of autoregressive terms limits introduction of spurious peaks [6]. Otherwise, the use of  $S$ -statistics via the direct method to computing the bispectrum is not advised. Finally, the BWS provides more accurate quantitative measure of the degree of coupling strength than either the BCI or  $S$ -statistics methods do, as shown in Figs. 3 and 5. It should be noted, however, that the BWS does not provide a normalized indicator for coupling strength; thus, the BWS will be more appropriate for comparison between different conditions.

Although not specifically shown in this paper, the BWS can also be applied to the cross bispectrum. In the cross bispectrum, phase coupling that may exist between two signals is detected. A similar method can be used, where surrogate data realizations are generated for each of the two signals, and the cross bispectra are calculated between the surrogates in order to obtain a statistical threshold. Moreover, while the results presented are based on the direct method of calculating the bispectrum, both indirect and model-based bispectra are equally applicable to the BWS.

In this paper, a statistical method based on surrogate data was introduced to analyze bispectral data. Our approach completely bypasses the use of the bicoherence index. As shown in our results, the normalization factor in the computation of the bicoherence index is the main culprit in providing less sensitive and less specific results. The BWS, because it does not use the BCI at all, provides results far superior to either the BCI or  $S$ -statistics. It should be noted that the bispectrum detects not only quadratic phase-coupled phenomenon but it also provides information regarding nonlinearity, and deviation from Gaussian process. Therefore, with the BWS approach, one can obtain statistical quantification regarding the phase coupling, nonlinearity, and deviation from normality.

The BWS, BIC, and  $S$ -statistics were all based on nonparametric bispectral estimation. However, all of the methods are also applicable to parametric bispectral estimation. In fact, the  $S$ -statistics method was already used with an autoregressive bispectral approach [6]. Given the fact that the BWS outperforms the  $S$ -statistics and BIC, we surmise that the BWS will also be applicable as an accurate approach for determining the statistical threshold levels of the parametric bispectrum. The advantages of using the parametric over the nonparametric bispectrum are higher frequency resolution and its ability to retain the accuracy for data with short data records. However, the main disadvantage of the parametric approach is the determination of model order, which can be complex.

As in our previous study [6], we observe consistent phase coupling in tubular pressure recordings from both SDR and SHR with the application of the BWS. The BWS revealed that the SHR has a significantly greater number of MYO and TGF interaction peaks, but the strength of coupling is smaller than SDR. This may be due to either more transient behavior or the TGF frequency shifting, both of which we have previously reported [5], [21]. These results are also consistent with a recent modeling study [22], which suggests that the TGF mechanism in the SHR switches between different dynamic modes. This shifting of modes can lead to the increased amount of peaks



detected in the SHR as each mode would show up as a separate peak. Furthermore, the shifting of modes would decrease the amount of time of each mode in the total time record, leading to a decrease in the magnitude of coupling observed.

The significance of detecting the presence of phase coupling in renal blood flow is that perhaps this can be used as a marker in differentiating normal versus disease conditions that may arise because of autoregulatory dysfunction in kidneys. It can be speculated that with progressive renal autoregulatory dysfunction, the presence of quadratic phase coupling, which is needed for efficient autoregulation in normal conditions, may dissipate. However, further studies are needed to determine if such a scenario occurs. We are currently evaluating nephron-to-nephron interactions and how they may differ in both normotensive and hypertensive rats using the cross BWS, and we hope to report our findings in the near future.

## REFERENCES

- [1] G. Pfurtscheller, A. Stancak, Jr., and G. Edlinger, "On the existence of different types of central beta rhythms below 30 Hz," *Electroencephalogr. Clin. Neurophysiol.*, vol. 102, pp. 316–325, Apr. 1997.
- [2] L. Huang, Y. Wang, J. Liu, and J. Wang, "Evaluation of ischemic states using bispectrum parameters of EEG and neural networks," in *Proc. Conf. IEEE Eng. Med. Biol. Soc.*, 2004, vol. 1, pp. 582–585.
- [3] K. Schwab, M. Eiselt, C. Schelenz, and H. Witte, "Time-variant parametric estimation of transient quadratic phase couplings during electroencephalographic burst activity," *Methods Inf. Med.*, vol. 44, pp. 374–83, 2005.
- [4] B. Schack, N. Vath, H. Petsche, H. G. Geissler, and E. Moller, "Phase-coupling of theta-gamma EEG rhythms during short-term memory processing," *Int. J. Psychophysiol.*, vol. 44, pp. 143–163, May 2002.
- [5] R. Raghavan, X. Chen, K. P. Yip, D. J. Marsh, and K. H. Chon, "Interactions between TGF-dependent and myogenic oscillations in tubular pressure and whole kidney blood flow in both SDR and SHR," *Amer. J. Physiol. Renal. Physiol.*, vol. 290, pp. F720–F732, Mar. 2006.
- [6] K. H. Chon, R. Raghavan, Y. M. Chen, D. J. Marsh, and K. P. Yip, "Interactions of TGF-dependent and myogenic oscillations in tubular pressure," *Amer. J. Physiol. Renal. Physiol.*, vol. 288, pp. F298–F307, Feb. 2005.
- [7] J. Jamsek, A. Stefanovska, and P. V. McClintock, "Nonlinear cardiorespiratory interactions revealed by time-phase bispectral analysis," *Phys. Med. Biol.*, vol. 49, pp. 4407–4425, 2004.
- [8] A. Al-Fahoum and L. Khadra, "Combined bispectral and bicoherency approach for catastrophic arrhythmia classification," in *Proc. Conf. IEEE Eng. Med. Biol. Soc.*, vol. 1, pp. 332–336, 2005.
- [9] G. Widman, T. Schreiber, B. Rehberg, A. Hoeft, and C. E. Elger, "Quantification of depth of anesthesia by nonlinear time series analysis of brain electrical activity," *Phys. Rev. E. Stat. Phys. Plasmas Fluids Relat. Interdiscip. Topics*, vol. 62, pp. 4898–4903, Oct. 2000.
- [10] E. Wodey, O. Tirel, J. Y. Bansard, A. Terrier, C. Chanavaz, R. Harris, C. Ecoffey, and L. Senhadji, "Impact of age on both BIS values and EEG bispectrum during anaesthesia with sevoflurane in children," *Br. J. Anaesth.*, vol. 94, pp. 810–820, Jun. 2005.
- [11] J. P. Roustan, S. Valette, P. Aubas, G. Rondouin, and X. Capdevila, "Can electroencephalographic analysis be used to determine sedation levels in critically ill patients?," *Anesth. Analg.*, vol. 101, pp. 1141–1151, Oct. 2005 (table of contents).
- [12] T. H. Bullock, J. Z. Achimowicz, R. B. Duckrow, S. S. Spencer, and V. J. Iragui-Madoz, "Bicoherence of intracranial EEG in sleep, wakefulness and seizures," *Electroencephalogr. Clin. Neurophysiol.*, vol. 103, pp. 661–678, Dec. 1997.
- [13] C. L. Nikias and A. P. Petropulu, *Higher-Order Spectral Analysis: A Nonlinear Signal Processing Framework*. Englewood Cliffs, NJ: Prentice-Hall, 1993.
- [14] S. Elgar and R. T. Guza, "Statistics of bicoherence," *IEEE Trans. Acoust., Speech Signal Process.*, vol. 36, no. 10, pp. 1667–1668, Oct. 1988.
- [15] I. Pinhas, E. Toledo, D. Aravot, and S. Akselrod, "Bicoherence analysis of new cardiovascular spectral components observed in heart-transplant patients: Statistical approach for bicoherence thresholding," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 10, pp. 1774–1783, Oct. 2004.
- [16] J. Theiler, S. Eubank, A. Longtin, B. Galdrikian, and J. D. Farmer, "Testing for nonlinearity in time series: The method of surrogate data," in *Proc. Conf. Interpretation Time Series Nonlinear Mech. Syst.*, Warwick, U.K., 1992, pp. 77–94.
- [17] J. H. Zar, *Biostatistical Analysis*, 4th ed. Upper Saddle River, NJ: Prentice-Hall, 1999.
- [18] Y. M. Chen, K. P. Yip, D. J. Marsh, and N. H. Holstein-Rathlou, "Magnitude of TGF-initiated nephron–nephron interactions is increased in SHR," *Amer. J. Physiol.*, vol. 269, pp. F198–F204, Aug. 1995.
- [19] O. V. Sosnovtseva, A. N. Pavlov, E. Mosekilde, N. H. Holstein-Rathlou, and D. J. Marsh, "Double-wavelet approach to study frequency and amplitude modulation in renal autoregulation," *Phys. Rev. E Stat. Nonlin. Soft. Matter. Phys.*, vol. 70, pp. 031915-1–031915-8, Sep. 2004.
- [20] K. H. Chon, Y. M. Chen, V. Z. Marmarelis, D. J. Marsh, and N. H. Holstein-Rathlou, "Detection of interactions between myogenic and TGF mechanisms using nonlinear analysis," *Amer. J. Physiol.*, vol. 267, pp. F160–F173, Jul. 1994.
- [21] L. Feng, K. Siu, L. C. Moore, D. J. Marsh, and K. H. Chon, "A robust method for detection of linear and nonlinear interactions: Application to renal blood flow dynamics," *Ann. Biomed. Eng.*, vol. 34, pp. 339–353, Feb. 2006.
- [22] A. T. Layton, L. C. Moore, and H. E. Layton, "Multistability in tubuloglomerular feedback and spectral complexity in spontaneously hypertensive rats," *Amer. J. Physiol. Renal. Physiol.*, vol. 291, pp. F79–97, Jul. 2006.



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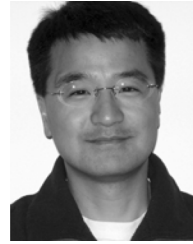
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