Establishing Causality With Whitened Cross-Correlation Analysis

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***Abstract*—In many biomedical applications, it is important to determine whether two recorded signals have a causal relationship and, if so, what the nature of that relationship is. Many advanced techniques have been proposed to characterize this relationship, but in practice simple techniques such as cross-correlation analysis are used. Unfortunately, the traditional cross-correlation analysis is influenced by the autocorrelation of the signals as much as it is by the relationship between the signals. Practically, this results in the cross correlation suggesting that the signals are correlated over a broad range of lags. Prewhitening the signals overcomes this limitation and reveals the essentially causal relationship between the signals. This is a simple method that can also easily generalize cross-correlation analysis to nonstationary signals, which are frequently encountered in biomedical applications. This technique has been used in other fields, but remains mostly undiscovered in biomedical research. In the case of a purely causal relationship, we show that whitened cross-correlation analysis is equivalent to directly estimating the all-pass component of the transfer function that relates the signals. We give examples of this type of analysis applied to several biomedical applications to demonstrate some of the new insights and information that can be produced by this type of analysis.**

***Index Terms*—Adaptive filter, arterial blood pressure, causality analysis, cross correlation, heart rate, intracranial pressure, Kalman filter, prewhitening, prediction error filter, time delay estimation.**

I. Introduction

UNDERSTANDING the relationship between two stochastic processes is of interest in many biomedical problems. There are many signal-processing and time-series analysis techniques for statistically characterizing this relationship. Popular techniques include cross-correlation analysis, transfer function estimation, parametric modeling, and coherence analysis [1]. However, there are only a few techniques that have been developed to determine whether there is a causal relationship between the two processes and the properties of the relationship.

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Causality cannot generally be determined from signal analysis alone. However, if we accept the premise that a causal relationship, say $x(n)$ causes $y(n)$, implies that $y(n)$ is only correlated with past and present values of $x(n)$, then we may be able to statistically distinguish between several possible causal relationships with cross-correlation analysis. For example, if the estimated cross correlation between two stationary stochastic processes $x(n)$ and $y(n)$

$$\hat{r}_{yx}(\ell) \approx \mathrm{E}\left[y(n)x(n-\ell)\right] \tag{1}$$

is only significant at positive lags ($\ell > 0$), then $y(n)$ is not correlated to present and future values of $x(n)$ and we can rule out the hypothesis that $y(n)$ is causing $x(n)$. The range of lags (ℓ) in which there is significant cross correlation may give further insights about delays in the relationship between the signals. However, if the processes are correlated at both positive and negative lags, then the processes do not have a clear causal relationship and we cannot make any conclusions. Unfortunately, this often occurs even when the processes are known to have a simple causal relationship.

Establishing causality is useful in many scientific and biomedical studies in which researchers wish to determine the direction in which communication or control signals occur. For example, it might be used to determine whether nerve fibers are transmitting efferent or afferent information. It can also be used to identify and isolate the complicated web of influences on the autonomic nervous system. Among numerous applications, causality analysis has been applied to determine the source of neural activity in epileptic seizures [2], to determine local field potential (LFP) propagation between brain structures in different behavioral states [3], to investigate electroencephalogram (EEG) activity propagation in different sleep stages [4], and to describe interactions between cardiovascular and cardiorespiratory variability signals [5]–[7].

Researchers have used many different approaches to understand the causality and timing of the relationship between two stochastic signals. Wiener recognized the importance of the temporal ordering in the inference of casual relations from a pure statistical point of view [8]. Granger utilized Wiener's concept and formulated his widely known Granger's causality measure based on vector autoregressive models [9]. Several further measures of causality in the frequency domain were developed based on Granger's concept. Saito decomposed coherence into two directed coherencies; representing feedforward and feedback aspects of the interaction between two signals [10]. Baccala introduced partial directed coherence based on Saito's directed coherence (DC) and applied it to

study the information flow between the cortex and the hippocampus [11]. Kaminski proposed a multivariate spectral measure called the directed transfer function (DTF) [12]. In a more recent study, he showed that the DTF and Saito's DC can be interpreted within the framework of Granger causality [13].

Traditional measures based on linear statistical process models are also widely used. This includes cross-correlation and coherence analysis. However, coherence analysis only reveals a measure of the degree of correlation as a function of frequency; it does not provide any information about the type or timing of the relationship. Treating the signals as though they are related by a linear time-invariant (LTI) system and then using the properties of this system to understand the relationship has also been widely used. Group delay, defined as the first derivative of the phase with respect to frequency, is often used to estimate the time delay of a system as a function of frequency. A negative group delay means that there is a group advance and, generally, fluctuations in the output signal will appear to precede fluctuations in the input signal. However, even a simple causal LTI system, such as a bandpass filter, can have a negative group delay over most frequencies, which would suggest the wrong relationship between the signals [14]. Phase delay, which is defined as the negative ratio between the phase response of the system and frequency [15], suffers from similar problems.

Many methods have also been proposed to estimate a pure delay between two stochastic processes. This is usually based on the following statistical model of the signals:

$$x(n) = s(n) + v(n) \tag{2}$$

$$y(n) = As(n-d) + w(n) \tag{3}$$

where $x(n)$ and $y(n)$ are the observed signals, $v(n)$ and $w(n)$ are mutually uncorrelated white noise processes, $s(n)$ is the originating signal, and d is the delay of interest [16]–[18]. To study the time delay between neurophysiological signals, the Hilbert transform can be used to estimate the phase of a linear system and its log gain [19]. However, the direction of the relationship between the signals has to be known in advance. More general statistical models that incorporate linear filters on one of the signals

$$x(n) = s(n) + w_x(n) \tag{4}$$

$$y(n) = h(n) * s(n-d) + w_y(n) \tag{5}$$

where $h(n)$ is the impulse response of an unknown LTI system and $*$ denotes convolution have also been examined [20], [21].

Cross-correlation analysis is the simplest and possibly most widely applied technique to determine whether a causal relationship exists, but it often fails—even when the relationship is known. This problem usually occurs when a signal has a strong predictable component and is correlated with itself over long lag times. Many biomedical signals, and especially cardiovascular signals, have this property because they are measures of nearly periodic rhythms, such as the cardiac or respiratory cycles. A simple solution to this problem is to apply whitening filters to each of the stochastic signals prior to cross-correlation analysis. This effectively removes the autocorrelation of the signals, but retains the essential cross correlation. The practical consequence of prewhitening is that the cross correlation contains peaks that are less broad and more indicative of the actual delay and causal relationship between the signals [22]–[24].

The concept of whitened cross correlation has been used in the econometrics literature for identifying dynamic regression models [25] and for checking the adequacy of transfer function models [24]. However, this analysis has rarely been used in biomedical applications.

The following sections explain the theoretical basis for whitened cross-correlation analysis and give three biomedical application examples. These examples demonstrate the insights that can be gained by studying the causal relationship between intracranial pressure (ICP) and heart rate (HR), the relationship between electrocardiogram (ECG) and arterial blood pressure (ABP), and the relationship between ICP and the arterial blood pressure (ABP). In an earlier paper, we presented additional examples of this method applied to ICP and HR [26].

II. Theory

A. Linear Random Signal Models

Let $x(n)$ and $y(n)$ be two simultaneously-recorded, stochastic processes. We assume without loss of generality that they have zero mean. We also assume that they are jointly wide sense stationary, though we will relax this assumption later. To simplify the presentation, we assume the signals are real valued.

The cross correlation is defined as the joint second-order moment

$$r_{yx}(\ell) = \mathrm{E}\left[y(n)x(n-\ell)\right] \tag{6}$$

where ℓ is the lag and $\mathrm{E}[\cdot]$ denotes the expected value [27]. A very common estimator of the cross correlation is

$$\hat{r}_{yx}(\ell) = \begin{cases} \frac{1}{N}\sum_{n=0}^{N-\ell-1} y(n+\ell)x(n), & 0 \le \ell \le N-1 \\ \frac{1}{N}\sum_{n=0}^{N+\ell-1} y(n)x(n-\ell), & -(N-1) \le \ell \le -1 \end{cases} \tag{7}$$

where N is the number of observed samples. This is often normalized to a range of $-1 \le \hat{r}_{yx}(l) \le 1$ and expressed as the the cross-correlation function (CCF)

$$\hat{\rho}_{yx}(\ell) = \frac{\hat{r}_{yx}(\ell)}{\sqrt{\hat{\sigma}_x^2 \hat{\sigma}_y^2}} \tag{8}$$

where $\hat{\sigma}_x^2$ is the sample variance of the observed signal $x(n)$

$$\hat{\sigma}_x^2 = \frac{1}{N}\sum_{n=0}^{N-1} x(n)^2. \tag{9}$$

If the two processes are independent or uncorrelated, their CCF is zero for all lags. If $\hat{\rho}_{yx}(\ell)$ is close to 1 at only a specific lag $\ell = d$, this implies that there is a pure delay of d samples between the two processes.

The consequences of prewhitening the signals prior to cross-correlation analysis can be understood by modeling the stochastic processes with linear random signal models. These models essentially assume that the second-order statistical

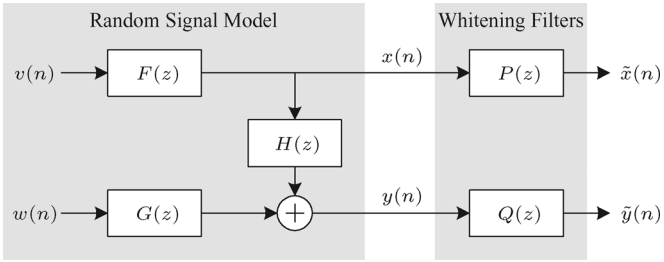

Fig. 1. Block diagram of the random signal models used to develop the theory and properties of whitened cross-correlation analysis. The signals $w(n)$ and $v(n)$ are white noise processes with zero mean and unit variance. All of the LTI systems are assumed to be causal and stable. The systems $F(z)$ and $G(z)$ are also assumed to be minimum phase. In this case, $x(n)$ causes some of the variation in $y(n)$, but not vice versa.

properties can be explained by assuming the signals arise from white noise processes that have been applied to unknown LTI systems. These signal models are widely used in biomedical applications and can represent stochastic processes with almost any aperiodic correlation structure or continuous power spectral density. These models include the familiar autoregressive (AR), moving average (MA), and autoregressive moving average (ARMA) random signal models as special cases.

Fig. 1 shows a block diagram of the random signal models used to develop the theory and properties of whitened cross-correlation analysis. The systems are represented and completely defined by their transfer functions, which are defined as the z transform of their impulse responses. For example

$$H(z) = \sum_{n=-\infty}^{\infty} h(n) z^{-n} \tag{10}$$

where $h(n)$ is the impulse response and z is a complex-valued variable. In most cases the systems $F(z)$ and $G(z)$ completely determine the autocorrelation or, equivalently, power spectral densities of the processes $x(n)$ and $y(n)$. Since it is impossible to distinguish between minimum, mixed, and maximum phase systems based on the second-order statistical properties of the signal alone, $F(z)$ and $G(z)$ are usually assumed to be minimum phase systems. A minimum phase system is causal and stable and has a causal and stable inverse [27]. If a minimum phase system has a rational transfer function, all of the poles and zeros are located within the unit circle.

Since we can observe both $x(n)$ and $y(n)$, we could try to estimate the relationship between these processes directly. However, we would not know *a priori* whether to estimate the transfer function from $x(n)$ to $y(n)$, or vice versa. If we estimated both transfer functions, we would still lack a normalized measure of the degree of correlation and a simple means of determining whether the correlation was statistically significant. The whitened cross-correlation analysis overcomes these limitations and does not require a direct estimate of the transfer function between the processes.

For the random signal model in Fig. 1, the cross correlation between $x(n)$ and $y(n)$ is given by

$$r_{yx}(\ell) = h(\ell) * r_x(\ell) \tag{11}$$

where $r_x(\ell)$ is the autocorrelation of $x(n)$

$$r_x(\ell) = \mathrm{E}\left[x(n)x(n-\ell)\right]. \tag{12}$$

Because the cross correlation depends on both $r_x(\ell)$ and $h(\ell)$, the cross correlation is affected by the autocorrelation of $x(n)$ as much as it is affected by the system $H(z)$. In many biomedical applications, the signal autocorrelations are significant over a long range of lags and this blurs the cross correlation. This is the primary limitation of cross-correlation analysis. However, if the process $x(n)$ is a white noise process such that $r_x(\ell) = \delta(\ell)$, where $\delta(\cdot)$ is the Kronecker delta function, then $r_{yx}(\ell) \propto h(\ell)$ and fully characterizes the relationship that we are interested in.

This partly motivates whitening the signals $x(n)$ and $y(n)$ prior to estimating the cross correlation. These whitening filters are shown as $P(z)$ and $Q(z)$ in Fig. 1. However, we must determine how the cross correlation between the whitened signals $\tilde{x}(n)$ and $\tilde{y}(n)$ is related to the causal relationship between $x(n)$ and $y(n)$.

Prediction error filters are identical to whitening filters [27] and have a straight-forward design. These filters produce an output signal that is defined as the difference between the observed signal and its value predicted from a linear combination of past observations, $\tilde{x}(n) = x(n) - \hat{x}(n)$. These filters are minimum phase.

Since $F(z)$ in Fig. 1 is minimum phase by assumption and the whitening filter $P(z)$ is minimum phase by construction, we know that $P(z) = F^{-1}(z)$ and $\tilde{x}(n) = v(n)$. The whitening filter $Q(z)$ is more difficult discern since it depends on both white noise processes, $v(n)$ and $w(n)$, as well as all three systems in the random signal model. Since $Q(z)$ is minimum phase and produces a whitened signal $\tilde{y}(n)$, it can be shown that

$$Q(z) = \left\{ \frac{1}{F(z)F^*(z)H(z)H^*(z) + G(z)G^*(z)} \right\}_{\mathrm{mp}} \tag{13}$$

where * denotes complex conjugation and $\{\cdot\}_{\mathrm{mp}}$ denotes the minimum phase portion of the expression. If all of the systems have rational transfer functions, then $\{\cdot\}_{\mathrm{mp}}$ produces only the poles and zeros that are located inside the unit circle.

In this general case, the relationship of the whitened cross correlation $r_{\tilde{y}\tilde{x}}(\ell)$ to $H(z)$ is complicated. However, if most of the variation in $y(n)$ is caused by either $w(n)$ or $x(n)$, we can use reasonable approximations to better understand this relationship. In the first case, $G(z) \gg F(z)H(z)$ and $Q(z) \approx G^{-1}(z)$, so we have $r_{\tilde{y}\tilde{x}}(\ell) \approx 0$ for all lags ℓ, as expected.

A more interesting relationship is obtained when most of the variation in $y(n)$ is caused by $x(n)$. If we assume that $H(z)$ is a stable system with a rational transfer function with no zeros on the unit circle, then it can be factored as

$$H(z) = H_{\min}(z) H_{\mathrm{ap}}(z) \tag{14}$$

where $H_{\min}(z)$ is minimum phase and $H_{\mathrm{ap}}(z)$ is all pass. An LTI system is all pass if

$$\left| H_{\mathrm{ap}}(\exp^{j\omega}) \right| = 1 \text{ for all } \omega. \tag{15}$$

If $F(z)H(z) \gg G(z)$ so that most of the variation in $y(n)$ is caused by $x(n)$, then

$$Q(z) \approx \left\{ \frac{1}{F(z)F^*(z)H(z)H^*(z)} \right\}_{\text{mp}} \tag{16}$$

$$= F^{-1}(z)H_{\min}^{-1}(z) \tag{17}$$

since $F(z)$ is minimum phase by construction. It then follows that

$$\tilde{y}(n) = q(n) * y(n) \tag{18}$$

$$\approx \left[f^{-1}(n) * h_{\min}^{-1}(n) \right] * [h(n) * f(n) * v(n)] \tag{19}$$

$$= h_{\min}^{-1}(n) * h(n) * v(n) \tag{20}$$

$$= h_{\text{ap}}(n) * \tilde{x}(n). \tag{21}$$

The whitened cross correlation is then given by

$$r_{\tilde{y}\tilde{x}}(\ell) = h_{\text{ap}}(\ell) * r_{\tilde{x}}(\ell) = h_{\text{ap}}(\ell). \tag{22}$$

Thus, the whitened cross correlation is equal to the all-pass portion of the system impulse response when a causal relationship exists between two random processes.

This is a satisfying and useful result. The minimum phase component of $H(z)$ is causal and stable and has a causal and stable inverse. Thus, if $H(z)$ is minimum phase, it is impossible to determine the nature of the causal relationship between $x(n)$ and $y(n)$ based on second-order statistics alone. However, if there is a delay of d samples in cascade with the minimum phase system, that is

$$H(z) = H_{\min}(z)z^{-d} \quad h(n) = h_{\min}(n-d) \tag{23}$$

then the all-pass component of $H(z)$ consists of only the delay and this is fully represented in the whitened cross correlation

$$r_{\tilde{y}\tilde{x}}(\ell) = \delta(d) \tag{24}$$

as desired. Thus, the all-pass component essentially represents the portion of the relationship between $x(n)$ and $y(n)$, which is distinctly causal. Additionally, it eliminates the confounding effect of the autocorrelation of $x(n)$ and $y(n)$ on cross-correlation analysis.

In the more general case, when the variation in $y(n)$ due to $w(n)$ and $x(n)$ is comparable, the whitening filter $Q(z)$ will no longer serve as an exact inverse for $F(z)$ and $H_{\min}(z)$. Generally, the resulting whitened cross correlation is still much narrower than the traditional cross correlation and, more clearly, indicates the nature of the relationship between the $x(n)$ and $y(n)$, but it is blurred across a larger range of lags due to the inexact cancellation in (19).

Whitened cross-correlation analysis permits one to study the causal relationship between two random processes without having to directly estimate the transfer function or make assumptions about the nature of their relationship. The practical consequence is that the whitened cross-correlation estimates are statistically significant over a more narrow range of lags that more accurately and precisely characterizes the causal relationship between the two processes.

B. Statistical Significance

Establishing exact confidence intervals or estimates of the higher order moments of whitened cross-correlation analysis is impossible in practice because, even in simplifying case when $v(n)$ and $w(n)$ have a Gaussian distribution, the distribution of $r_{\tilde{y}\tilde{x}}(\ell)$ depends on the true cross correlation, $r_{yx}(\ell)$, which is unknown. However, we can adopt the same asymptotic estimates based on white noise processes that are used with traditional cross-correlation analysis to establish critical values for the normalized whitened CCF [28]. In this case, $\hat{\rho}_{\tilde{y}\tilde{x}}(\ell)$ is approximately normally distributed with zero mean and a variance of $1/N$. We use this approximation to calculate a 95% critical region which would encompass the estimated cross correlation of uncorrelated processes over 95% of the lags, on average. If the estimated CCF markedly differs from the critical region over a range of lags, we interpret these values as being significantly different than zero.

C. Whitening Filter Design

The heart of a whitening filter is a one-step forward linear predictor that estimates $x(n)$ as a linear combination of the past samples $\{x(n-1), x(n-2), \ldots, x(n-M)\}$ [29]. The whitened signal is then calculated as $\tilde{x}(n) = x(n) - \hat{x}(n)$, which is sometimes called the innovations process. Intuitively, the innovations represent the variation in $x(n)$ that is not predictable from past observations. In this sense, it conveys the new information that is presented at each sample time n.

There are many methods that could be used to design the one-step linear predictor. In most cases, the predictor is an FIR filter to simplify estimation of the filter coefficients and implementation. If the process is wide sense stationary and not significantly non-Gaussian, this naturally leads to a least squares approach to estimating the coefficients.

In many biomedical applications, the processes are known to be nonstationary. If the processes are known to be locally stationary with second-order statistical properties that drift slowly over time, an adaptive filter approach is more suitable. The drift is considered to be slow if the statistics do not change significantly over many periods (say >20) of the lowest, significant frequency components in the signals.

This generalizes the random signal model shown in Fig. 1 to the case where $F(z)$ and $G(z)$ are slowly time-varying systems. However, the whitened cross-correlation analysis retains the assumption that $H(z)$ is time-invariant. If $H(z)$ is also time-varying, then a moving-window with appropriate weighting of the samples could be used to create an estimate of the time-varying whitened cross-correlation analysis in the same manner as many time-frequency analysis methods, such as the spectrogram.

1) Kalman Filter Adaptive Linear Predictor: There are many adaptive filter algorithms that are well suited to nonstationary signals with slowly varying statistical properties. For the applications discussed in subsequent sections, we used an adaptive filter design based on the Kalman filter recursions.

TABLE I
USER-SPECIFIED PARAMETERS AND SAMPLE RATES FOR THE ADAPTIVE KALMAN FILTER LINEAR PREDICTOR

Signal	γ	P	f_s (Hz)
HR	10	25	1
ICP	10	25	1
ABP	0.5	60	125
ICP	100	60	125
ECG	10	85	125

In this case, the state vector is the set of time-varying filter coefficients $f(n,\ell)$. The stochastic process $x(n)$ is modeled as

$$x(n) = \sum_{\ell=0}^{P-1} f(n,\ell)x(n-\ell) + v(n) \tag{25}$$

where $f(n,\ell)$ is the finite impulse response of the system $F(z)$ at time n. The Kalman filter also requires a statistical model of the state vector. To account for the time varying nature of the coefficients we used a random walk model

$$f(n+1,\ell) = f(n,\ell) + u_\ell(n) \tag{26}$$

where $u_\ell(n)$ is a white noise process. We used the same noise variance for all of the filter coefficients, σ_u^2. The ratio of the process and observation noise variances, $\gamma = \sigma_v^2/\sigma_u^2$, determines the tradeoff between variance of the estimates and how quickly the filter can adapt to changing statistics (i.e., bias).

Once the user specifies the filter order (P), the initial state covariance, and the variance ratio (γ), the Kalman filter recursions provide estimates of both the innovations and the filter coefficients [30]. If the statistical model is true, the Kalman filter provides the optimal coefficients in the mean square error sense. In all of the examples that follow, we used an initial state covariance of 1. Table I lists the variance ratio and filter order for each of the four signals that we examined. The variance ratio was chosen empirically and the model order was chosen based on the range of lags over which the partial autocorrelation function was statistically significant [26].

2) Signal Bandwidth and Time Resolution: In practice, most biomedical signals have a finite bandwidth. Even signals that have a broad bandwidth often have the bandwidth truncated with an analog lowpass filter prior to sampling to prevent aliasing. Whitening filters attempt to amplify frequency components with low signal power to attain a flat spectrum. However, if there is no significant signal power at high frequencies due to either a finite bandwidth or anti-aliasing filters, the whitening filters cannot achieve a flat spectrum at frequencies higher than the largest significant spectral component. If we denote the highest significant frequency component as $f_{\max}$, then the whitening filter will only achieve a flat spectrum and uncorrelated samples if the sample rate is $2f_{\max}$ and the sampling interval is $T_s = 0.5f_{\max}^{-1}$. This limits the time resolution of whitened cross-correlation analysis. If a higher sample rate is used, the whitened cross-correlation analysis will appear as though it has been filtered with a lowpass filter. For example, systems with a pure lag, $H(z) = z^{-d}$, will be be estimated as the impulse response of an ideal lowpass filter (i.e., a sinc function), centered at the time of the lag. Thus, the actual lag resolution cannot be improved by increasing the sample rate. Rather, it is inherently limited by the bandwidth of the signals that the analysis is applied to.

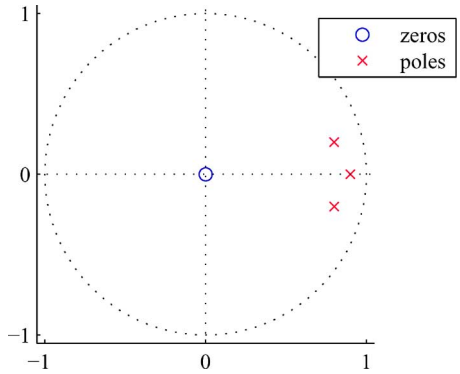

Fig. 2. Poles and zero of the minimum phase system $F(z)$. The system had three poles at $0.8 \pm j0.2$ and 0.9.

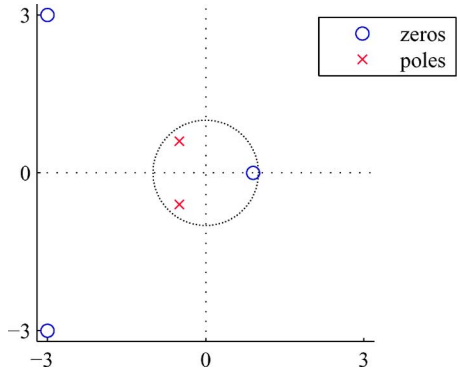

Fig. 3. Poles and zero of the nonminimum phase system $H(z)$. The system had three zeros at $-3 \pm j3$ and 0.9 and two poles at $-0.5 \pm j$ 0.6.

III. APPLICATION EXAMPLES

A. Synthetic Example

The random signal model shown in Fig. 1 was applied to synthetic white Gaussian noise signals. We used a purely causal relationship between $x(n)$ and $y(n)$ with $G(z) = 0$. Fig. 2 shows a pole-zero diagram of the minimum phase system $F(z)$ and Fig. 3 shows a pole-zero diagram of the nonminimum phase system $H(z)$.

The filters $P(z) = F^{-1}(z)$ and $Q(z) = F^{-1}(z)H_{\min}^{-1}(z)$ were used to whiten the signals $x(n)$ and $y(n)$, respectively. The impulse response of the all-pass component of $H(z)$ is shown in Fig. 4 along with an estimate of the whitened CCF. We used 10 000 samples of synthetic white noise signals to generate the estimate of the cross-correlation. As expected, the whitened CCF function is proportional to the impulse response of the all-pass component of $H(z)$.

Fig. 5 provides a comparison between the CCF of the signals before and after whitening. While the cross correlation between the whitened signals correctly suggests that the signal $y(n)$ lags, and possibly is caused by, $x(n)$, the traditional estimate of the cross correlation suggests that the signal $y(n)$ precedes, and possibly causes, $x(n)$. The gray region represents the 95% estimated confidence intervals of uncorrelated white Gaussian noise process [28].

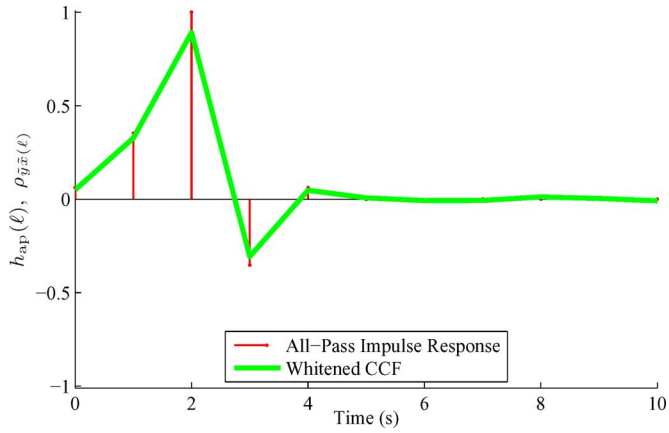

Fig. 4. Normalized impulse response of the all-pass system and the CCF between the whitened signals $\bar{y}(n)$ and $\bar{x}(n)$. The output signal $y(n)$ lags the input $x(n)$ by two time samples.

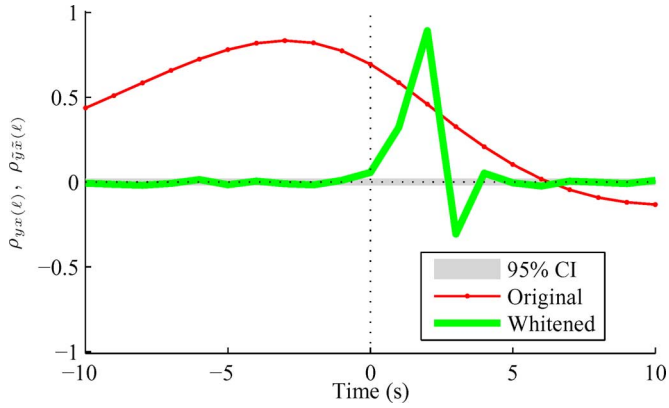

Fig. 5. Original ($\rho_{yx}(\ell)$) and whitened ($\rho_{\bar{y}\bar{x}}(\ell)$) CCFs. The traditional CCF incorrectly suggests $x(n)$ primarily leads $y(n)$ with a mean negative lag of 3.40 s. The whitened CCF correctly suggests that $x(n)$ lags $y(n)$ and correctly suggests a causal relationship (i.e., $x(n)$ causes $y(n)$) with a mean positive lag of 2.00 s. The gray region represents the 95% significance threshold, which is based on the confidence intervals of uncorrelated white Gaussian signals.

B. Intracranial Pressure and Heart Rate

Traumatic brain injury (TBI) is the leading cause of death and disability in children in the United States [31]. It has been demonstrated that the severity of TBI affects efferent autonomic neural pathways to the sinoatrial (SA) node in the heart [32]. We used whitened cross-correlation analysis to determine whether the variation in the heart rate is likely to cause or caused by fluctuations in the mean intracranial pressure (ICP).

The mean ICP and instantaneous heart rate (HR) signals used in this analysis were obtained from 2-h records of the ICP ($f_s = 125$ Hz) and ECG ($f_s = 500$ Hz) of a sedated pediatric TBI patient in the intensive care unit at Oregon Health and Science University (OHSU) [33]. We used a zero-phase (noncausal) elliptic lowpass filter with cutoff frequency $f_c = 0.3$ Hz to compute the mean ICP. A 1-min segment of an ICP signal and its mean ICP are shown in Fig. 6.

To calculate the instantaneous heart rate, we used an automatic detection algorithm to detect the R waves of the ECG signal. The instantaneous heart rates were computed as the inverse of the interbeat interval and assigned to the center of these intervals. This yields a nonuniformly sampled series. We

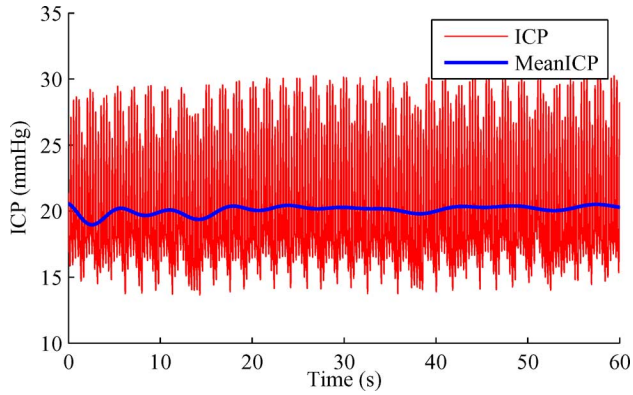

Fig. 6. One-minute segment of an ICP signal and lowpass filtered mean ICP.

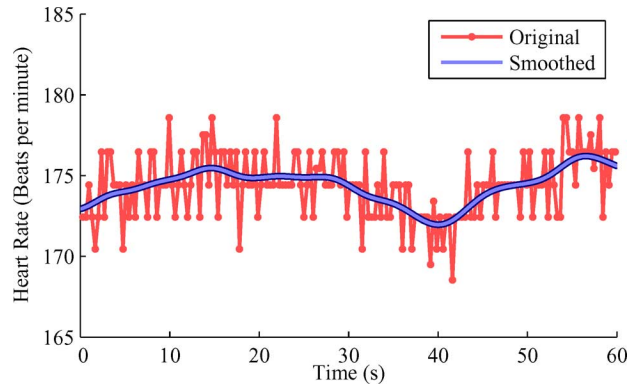

Fig. 7. Segment of instantaneous heart rate (60 s) and smoothed estimate. The heart rate is higher than for an adult because it was acquired from a pediatric patient.

smoothed and interpolated this series to uniform sampling rate of $f_s = 125$ Hz using a Gaussian kernel smoother. This reduces quantization error caused by the sample rate of the ECG, as shown in Fig. 7. This is described in greater detail in [34]. To reduce computation, both ICP and HR were lowpass filtered and decimated to 1 Hz before applying the whitening filter. This did not compromise the time resolution of the whitened cross-correlation estimates since most heart rate fluctuations have a bandwidth of less than 0.5 Hz.

The autocorrelation estimate of the mean ICP, represented as a dotted line in Fig. 8, shows that the signal has a long memory. The signal has a high degree of correlation among its samples and has a significant, lasting autocorrelation function. In contrast the autocorrelation estimate of the whitened mean ICP, represented as a solid line, shows a maximum lag at zero. Surprisingly, the signal also has a significant autocorrelation at a lag of one sample due to the inability of the whitening filter to completely whiten the signal. This is consistent with the method used to calculate the mean ICP by attenuating frequency components greater than the cutoff frequency of 0.3 Hz. The heart rate had a similar autocorrelation function (not shown).

Fig. 9 shows the traditional and whitened CCFs for the mean ICP and HR signals. The traditional CCF shows significant correlation over a broad range of lags, which is primarily due to the long memory of these processes, as illustrated by their autocorrelation functions. In contrast, the whitened CCF gives a much

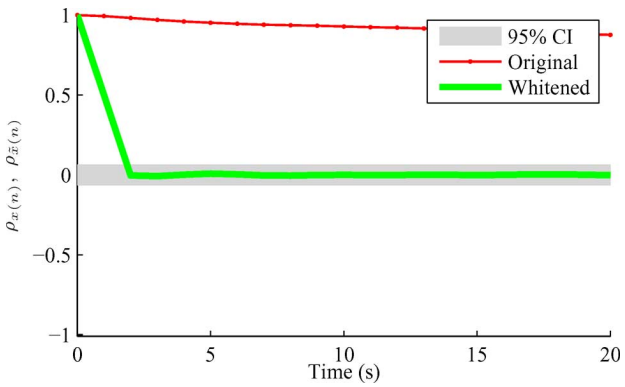

Fig. 8. Autocorrelation of the mean ICP. The mean ICP has a long memory. Samples beyond a lag of 1 s are not significantly correlated for the whitened mean ICP and lie inside the gray region representing a 95% confidence interval for a white noise process.

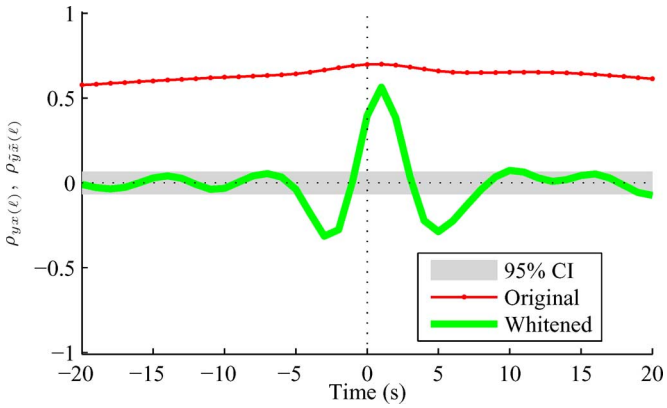

Fig. 9. Traditional and whitened cross correlation between mean intracranial pressure (ICP) and the instantaneous heart rate (HR). The mean delay was 0.604 s with the heart rate lagging the mean ICP, on average.

more precise representation of the relationship between ICP and HR. Specifically, this analysis shows that, on average, the HR fluctuations lag the ICP fluctuations and their causal relationship shows significant correlation at lags ranging from −5 to 10 s. The shape of the autocorrelation function closely resembles a sinc function. This suggests that the whitened cross-correlation analysis was blurred by the limited bandwidth of the signals and that the actual causal relationship may span an even shorter range of lags. None of these insights could be discerned from the traditional cross-correlation analysis.

The hypothesis that fluctuations in the mean ICP cause significant fluctuations in the HR is in agreement with [35]. Using causal coherence analysis, [35] demonstrated that there was a significant correlation within the low frequency range from 0.04 to 0.15 Hz. They also demonstrated that there was a feedback effect from ICP to RR interval that was enhanced during occurrence of B-waves.

C. Arterial Blood and Intracranial Pressures

The following example shows the result of applying the whitened cross-correlation analysis to arterial blood pressure (ABP) and ICP signals obtained from another traumatic brain injury patient at OHSU [33].

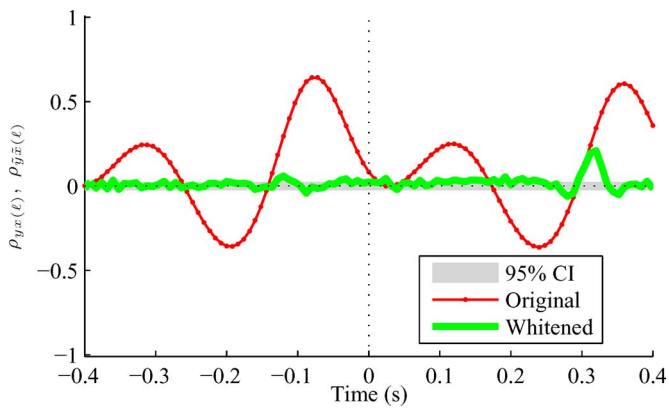

Fig. 10. Traditional and whitened CCFs between ICP and ABP. The whitened CCF clearly shows a causal relationship with a nearly pure delay of approximately 0.3 s.

Fig. 10 shows the traditional and whitened cross-correlation analysis. The traditional CCF is quasi-periodic with a very long memory. The whitened cross correlation shows only one significant value at a positive lag, suggesting that fluctuations in the arterial blood pressure are causing fluctuations in the ICP. In fact, this is consistent with the known physiology since fluctuations in the blood pressure are transmitted through the cerebral vasculature to the brain tissue and cerebral spinal fluid. The assumption that ABP causes fluctuations in ICP has been assumed and used in previous studies [36].

D. Electrocardiogram and Arterial Blood Pressure

The ABP signal contains valuable information about the cardiovascular system and it can be used to asses the properties of the arterial vessel wall [37]. Pulse wave velocity describes how quickly a blood pressure pulse travels from one point to another in the human body and is commonly used to provide an estimate of the condition of the cardiovascular system [38]. The ECG and ABP signals are closely related in terms of their timing, and the delay time between these signals is closely related to the pulse wave velocity [39].

We applied the whitened cross-correlation analysis to ABP and ECG signals obtained from the MIMIC database 40, part of Physionet [41]. The database consists of long-term recordings of cardiovascular signals (e.g., electrocardiogram, arterial blood pressure, impedance plethysmography, pulse oximetry) recorded in an intensive care setting from a patient monitor. All of the signals were sampled at 125 Hz, except the electrocardiogram, which was sampled at 500 Hz. The example below was obtained from patient record number 240. This was obtained from a 30.6-h segment recorded from a 68-year-old male with angina.

A significant correlation between the whitened ECG and ABP at a positive lag can be seen in Fig. 11. This suggests that fluctuations in ECG precede those in ABP, as expected. The QRS features of the ECG correspond to contraction of the ventricles. These features are transmitted at a rate near the speed of light to the surface electrodes. The velocity of the corresponding pressure pulse travels at a rate of 3–5 m/s in the aorta, 7–10 m/s in the larger arteries, and 15–35 m/s in the small arteries

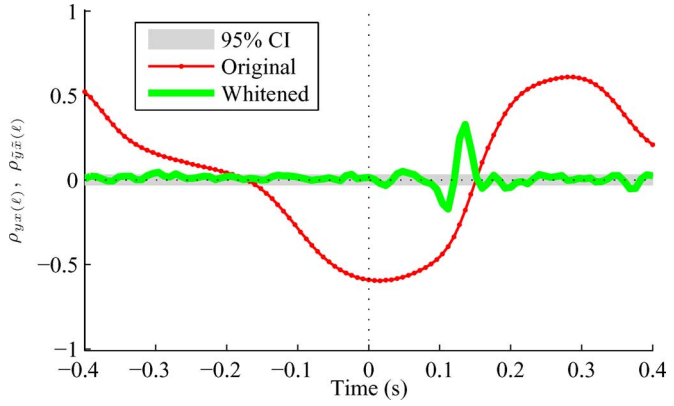

Fig. 11. Traditional and whitened CCFs between ECG and ABP. The whitened CCF correctly suggests a causal relationship with a brief delay interval of approximately 0.1–0.2 s. The traditional CCF suggests a significant correlation over a broad range of positive and negative lags.

[42]. The delay of 0.1–0.2 s is in accord with these propagation rates and consistent with the delay estimated by detection techniques [43]. However, it is indiscernible from the traditional cross correlation.

IV. Conclusion

Whitened cross-correlation analysis can be used to isolate the essentially causal component between two random processes. Unlike the traditional CCF, it is mostly unaffected by the degree of autocorrelation of the signals that it is applied to. It can be used to identify or rule out possible causal relationships and often leads to new insights that are impossible to discern from the traditional cross-correlation analysis. It can be easily generalized to nonstationary applications in which the statistical relationship and properties of the signals are known to drift over time. It has been applied in other fields and should be applied more often in biomedical applications.

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