Lecture 6
Establishing Causality Between Biomedical Signals

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I. INTRODUCTION

- Establishing causality is useful in many scientific and biomedical studies.

  (1) To determine whether nerve fibers are transmitting efferent or afferent information;

  (2) To identify and isolate the complicated web of influences on the autonomic nervous system;

  (3) To determine the source of neural activity in epileptic seizures [2];

I. INTRODUCTION

- Establishing causality is useful in many scientific and biomedical studies.

  (4) To determine local field potential (LFP) propagation between brain structures in different behavioral states [3];

  (5) To investigate electroencephalogram (EEG) activity propagation in different sleep stages[4];

  (6) To describe interactions between cardiovascular and cardiorespiratory variability signals [5]–[7].

I. INTRODUCTION

- There are many signal-processing and time-series analysis techniques for statistically characterizing the relationship between two stochastic processes.

  Cross-correlation analysis

  Transfer function estimation

  Parametric modeling

  Coherence analysis

However, a few of techniques can be applied to determine whether there is a causal relationship between the two processes.

I. INTRODUCTION

To determine whether there is a causal relationship.

(1) Wiener recognized the importance of the temporal ordering in the inference of casual relations from a pure statistical point of view [8].

(2) Granger's causality measure based on vector autoregressive models [9] and improved Granger methods.

I. INTRODUCTION

Causality cannot generally be determined from Signal analysis alone;

However, we may be able to statistically distinguish between several possible causal relationships with cross-correlation analysis.

For example

- A causal relationship, say $x(n)$ causes $y(n)$, implies that $y(n)$ is only correlated with past and present values of $x(n)$, that is,

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

is only significant at positive lags (l>0), then $y(n)$ is not correlated to present and future values of $x(n)$.

So, the hypothesis that $y(n)$ is causing $x(n)$ can be ruled out.

I. INTRODUCTION

- 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.

The exsiting causality analysis methods

(1) Wiener's pure statistical point of view [8].

(2) Granger's causality measure based on vector auto regressive models.

(3) Saito decomposed coherence into two directed coherencies.

(4) Baccala introduced partial directed coherence based on Saito's directed coherence(DC).

(5) Kaminski proposed a multivariate spectral measure called the directed transfer function (DTF)[12].

(6) Group delay.

About the delay method

- The statistically model of the signals:

$$x(n) = s(n) + v(n) \quad (2)$$

$$y(n) = As(n-d) + w(n) \quad (3)$$

x(n) , y(n): observed signals;

v(n),w(n): mutually uncorrelated white noise processes.

s(n): original signal. d: the delay of interest.

About the delay method

- More general statistical model:

$$x(n) = s(n) + w_x(n) \quad (4)$$

$$y(n) = h(n) * s(n-d) + w_y(n) \quad (5)$$

h(n): the impulse response of an unknown LTI system.

The direction bewteen signals should be known in advance.

Cross-correlation

- Cross-correlation analysis often fails in determining the causality.
- The problem usually occurs when a signal has a strong predictional component and is correlated with itself over long lag time.
- A simple solution to this problem is to apply whiting filters to each of the stochastic signals prior to corss-correlation analysis.

II. Theory

- Computing cross-correlation:

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

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

- Normalized Cross-correlation function (CCF)

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

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

II. Theory

- What is uncorrelated or correlated?

(1) CCF is zero for all lags, two processes are independent or uncorrelated;

(2) CCF is close to 1 at only a specific lag

l=d, there is a pure delay d samples between the two processes.

II. Theory

Why is the whiting necessary?

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

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

(1） The cross-correlation depend on both $r_x(l)$ and $h(l)$;

(2) The cross-correlation is affected by $r_x(l)$ as much as it is affected by the system H(z);

II. Theory

- Why is the whiting necessary?

  If $x(n)$ is a white noise process such that

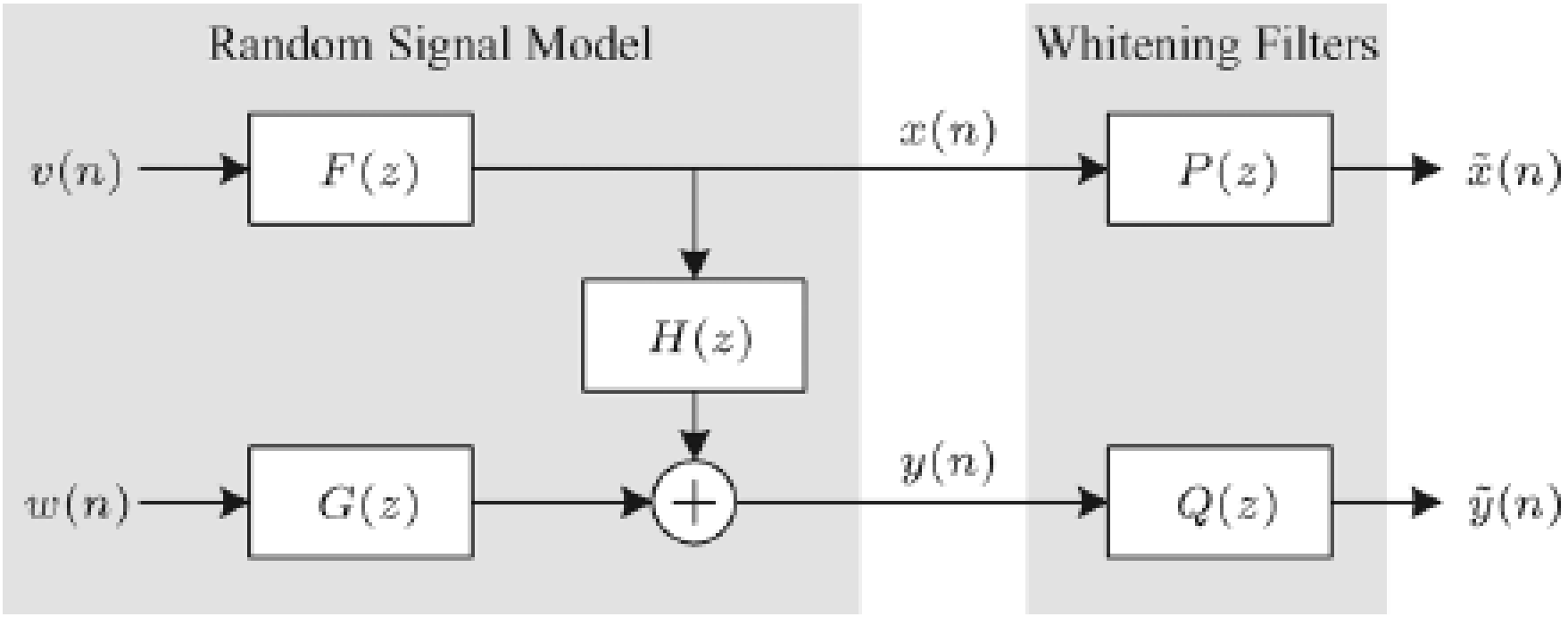
$$r_x(\ell) = \delta(\ell)$$

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

Then $$r_{yx}(\ell) \propto h(\ell)$$

The cross-correlation fully characterizes the relationship that we are interested in.

Whitening method [27] (Fig. 1)



- Including AR, MA and ARMA random signal models.

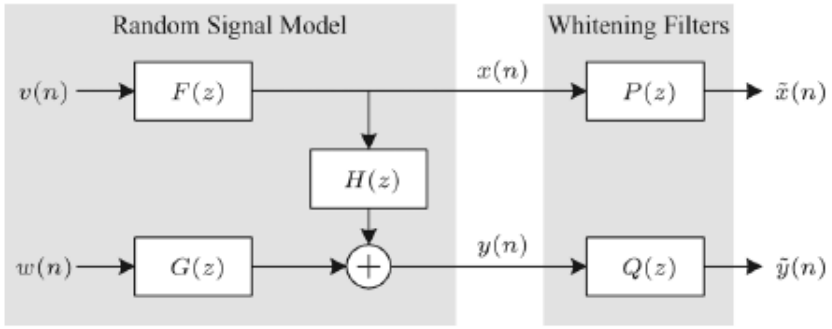
Causality

- How is the cross-correlation between

$$\tilde{x}(n) \text{ and } \tilde{y}(n)$$

is related to the causal relationship between x(n) and y(n)?

Analysis



$$P(z) = F^{-1}(z) \text{ and } \tilde{x}(n) = v(n)$$

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

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.

Analysis

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

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

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

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

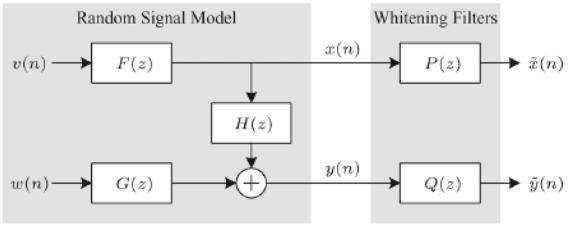
Analysis

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

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

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

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



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

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

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

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

$$H(z) = H_{\text{min}}(z)H_{\text{ap}}(z)$$

Analysis

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

The whitened cross correlation is then given by

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

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.

Analysis

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

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

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.

Analysis

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.

III. APPLICATION EXAMPLES

- A. Synthetic Example
- B. Intracranial Pressure and Heart Rate
- C. Arterial Blood and Intracranial Pressures

D. Electrocardiogram and Arterial Blood Pressure

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 $H(z)$.

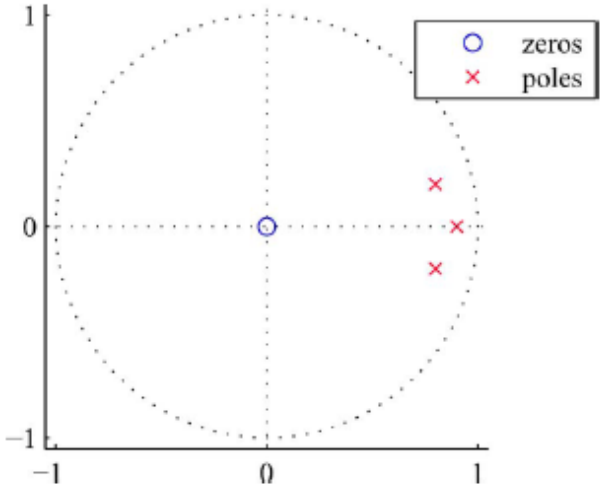


Fig. 2. Poles and zero of the minimum phase system $F(z)$. The system had three poles at $0.8 \pm j0.2$ and 0.9.

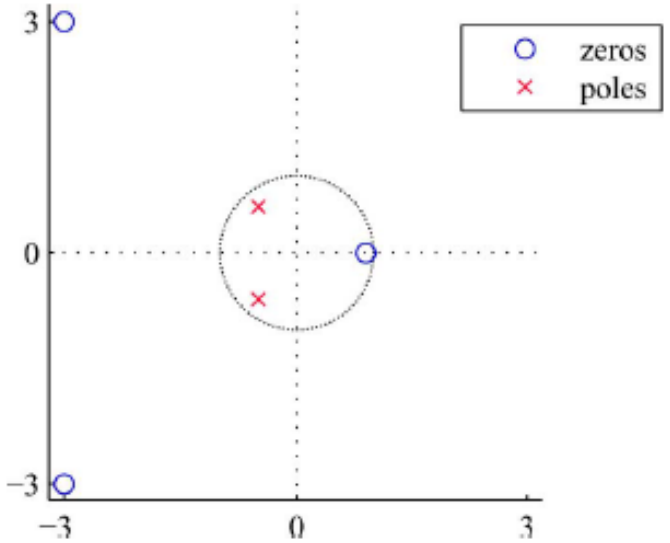


Fig. 3. Poles and zero of the nonminimum phase system $H(z)$. The system had three zeros at $-3 \pm j3$ and 0.9 and two poles at $-0.5 \pm j$ 0.6.

A. Synthetic Example

The impulse response of the all-pass component of $H(z)$ is shown in Fig. 4

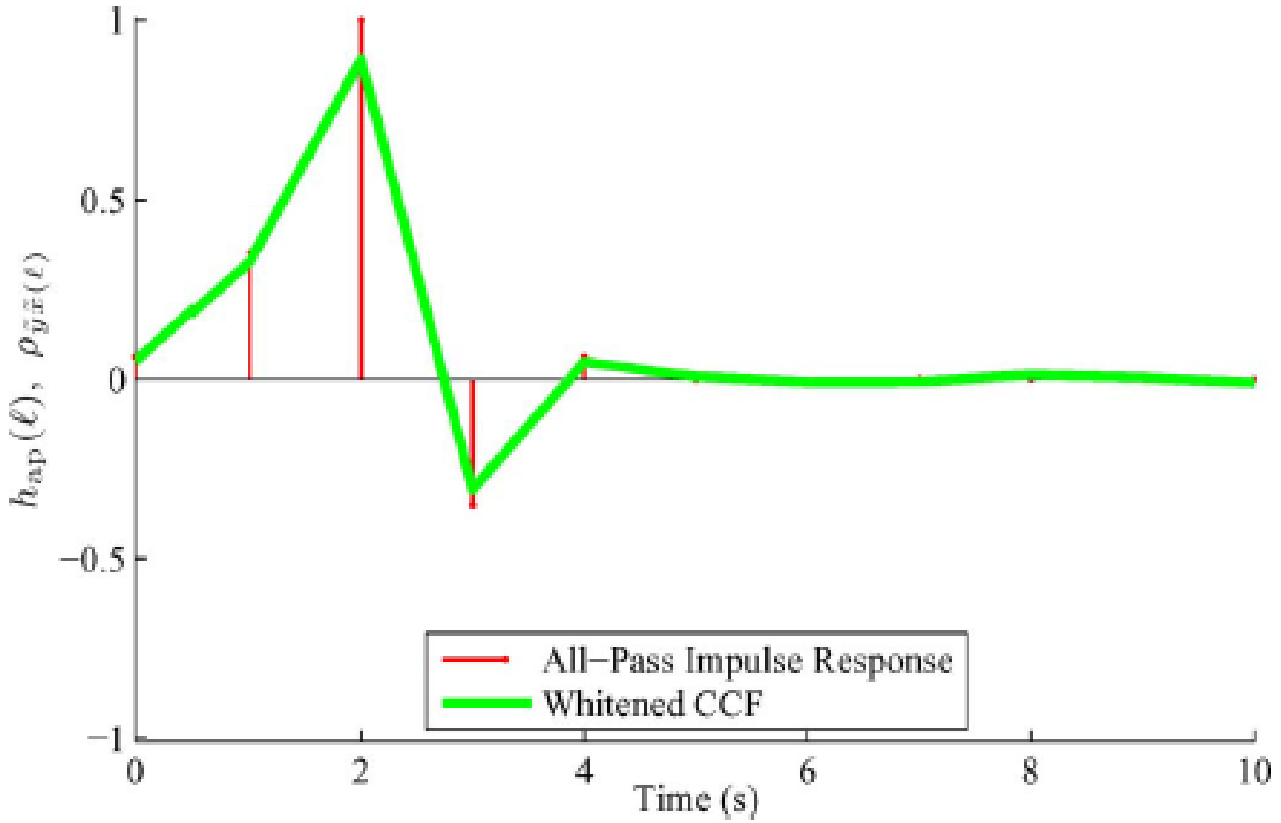


Fig. 4. Normalized impulse response of the all-pass system and the CCF between the whitened signals $\tilde{y}(n)$ and $\tilde{x}(n)$. The output signal $y(n)$ lags the input $x(n)$ by two time samples.

A. Synthetic Example

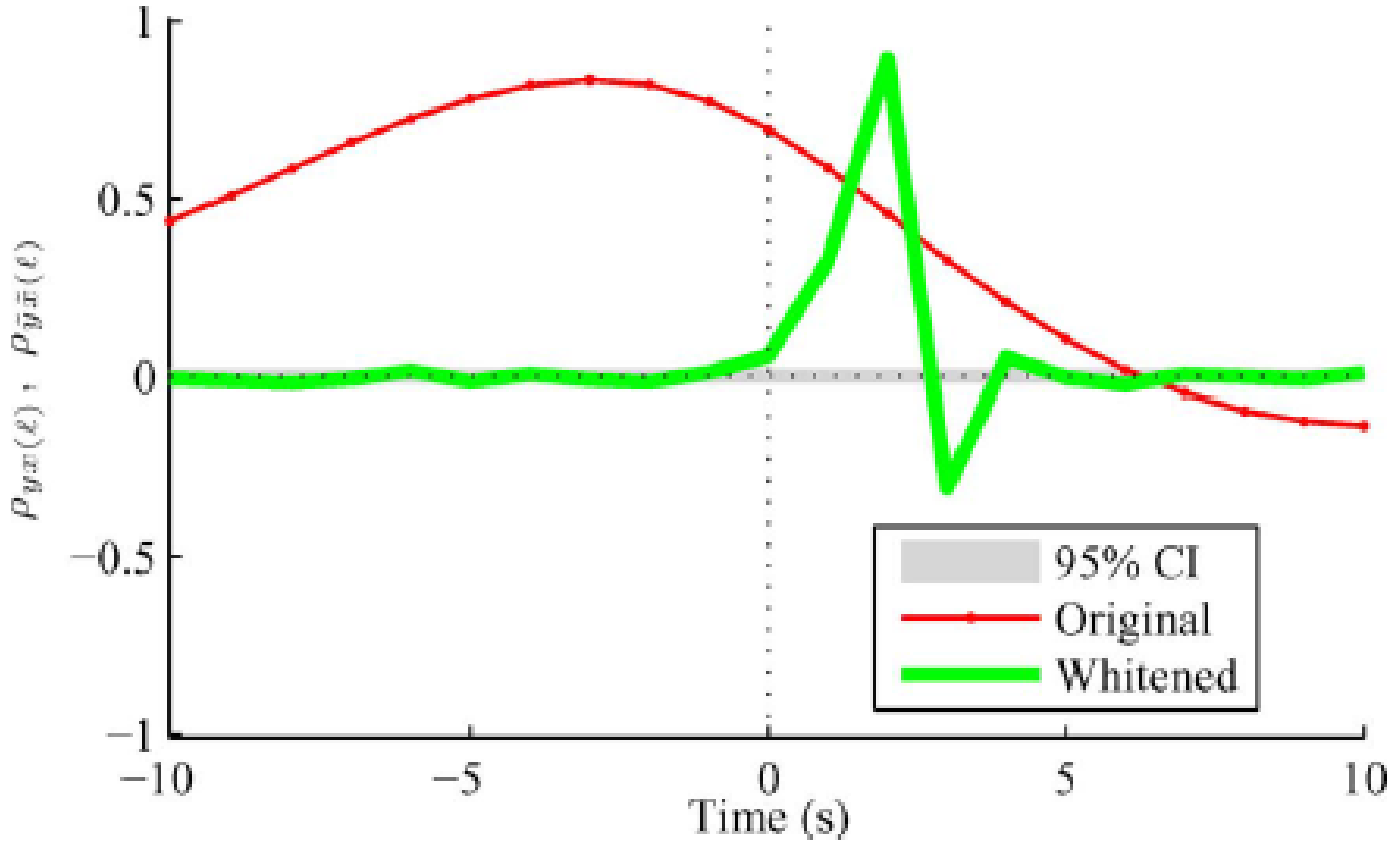


Fig. 5. Original ($\rho_{yx}(\ell)$) and whitened ($\rho_{y\bar{x}}(\ell)$) CCFs. The traditional CCF incorrectly suggests $x(n)$ primarily leads $y(n)$ with a mean negative lag of 3.40 s. The whitened CCF correctly suggests that $x(n)$ lags $y(n)$ and correctly suggests a causal relationship (i.e., $x(n)$ 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

- Research Motivation

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).

B. Intracranial Pressure and Heart Rate

- **Data: (1) Intracranial Pressure**

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.

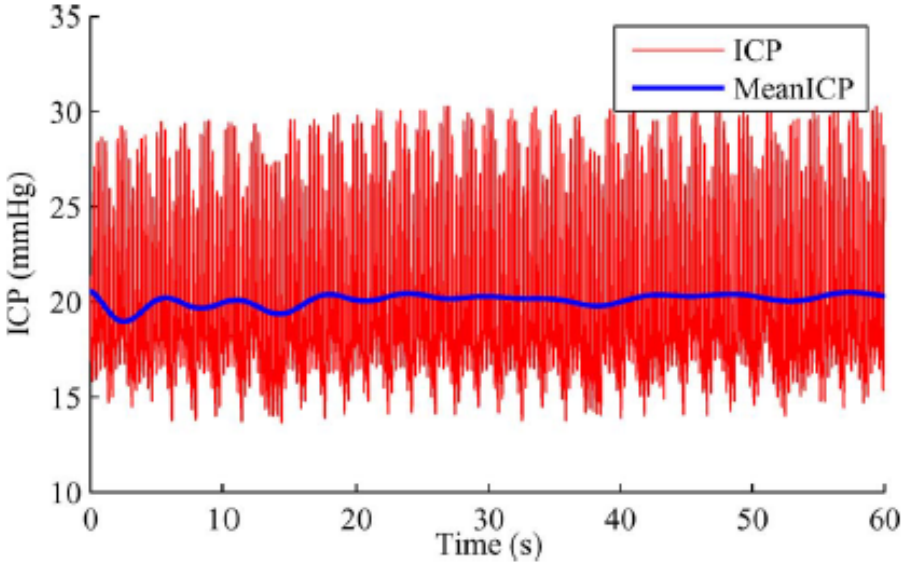


Fig. 6. One-minute segment of an ICP signal and lowpass filtered mean ICP.

B. Intracranial Pressure and Heart Rate

Data: (2) **Heart Rate**

- **To detect R waves of the ECG signal**
- **RR interval = RRI**
- **To compute the heart rate using the inverse of RRI, a nonuniformly sampled series**
- **To smooth and interpolate this series to uniform sampling rate of fs=125Hz using a Gaussian kernel smoother.**
- **The result is shown in Fig. 7**

B. Intracranial Pressure and Heart Rate

Data: (2) **Heart Rate**

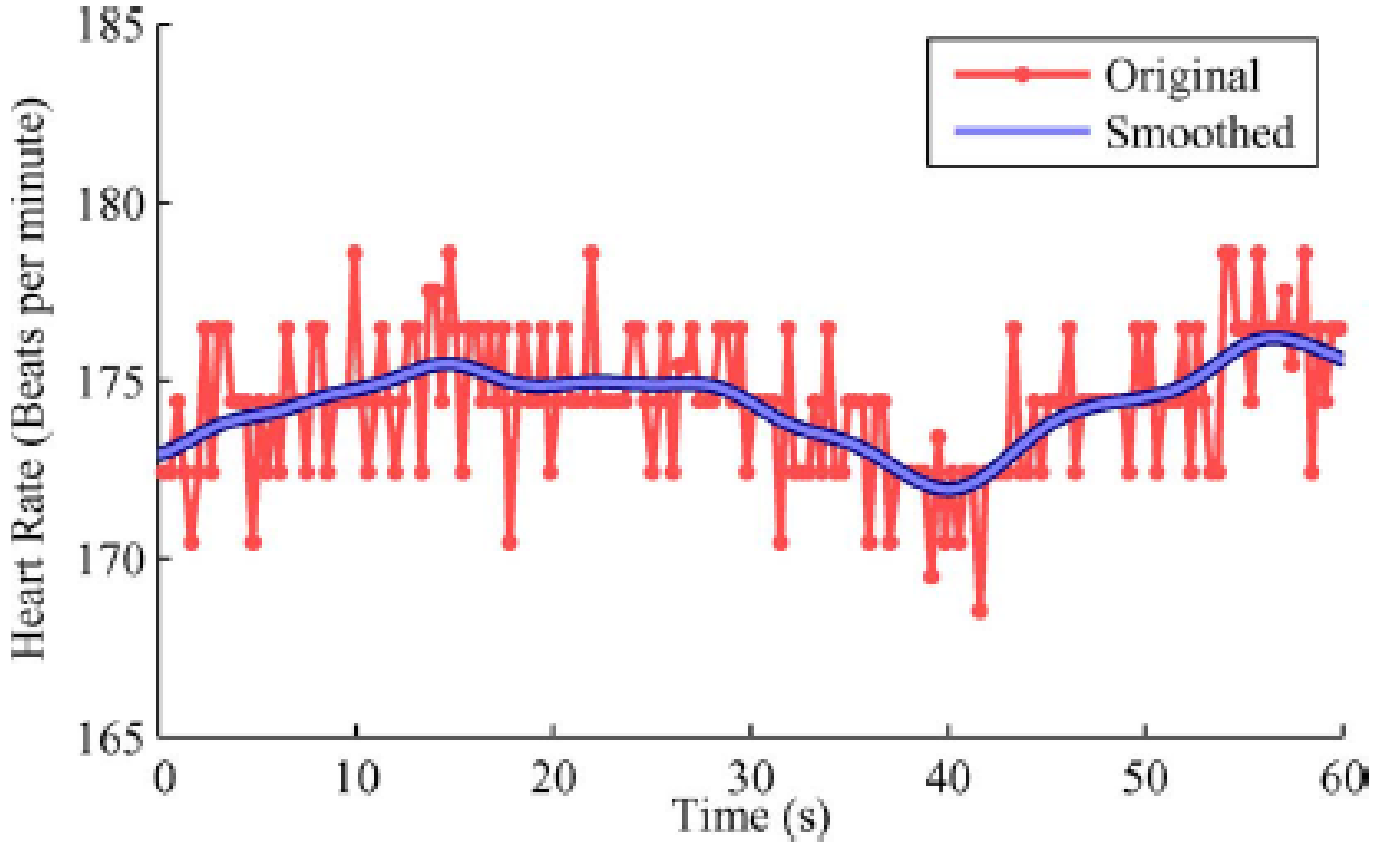


Fig. 7. Segment of instantaneous heart rate (60 s) and smoothed estimate. The heart rate is higher than for an adult because it was acquired from a pediatric patient.

B. Intracranial Pressure and Heart Rate

- **Results:**

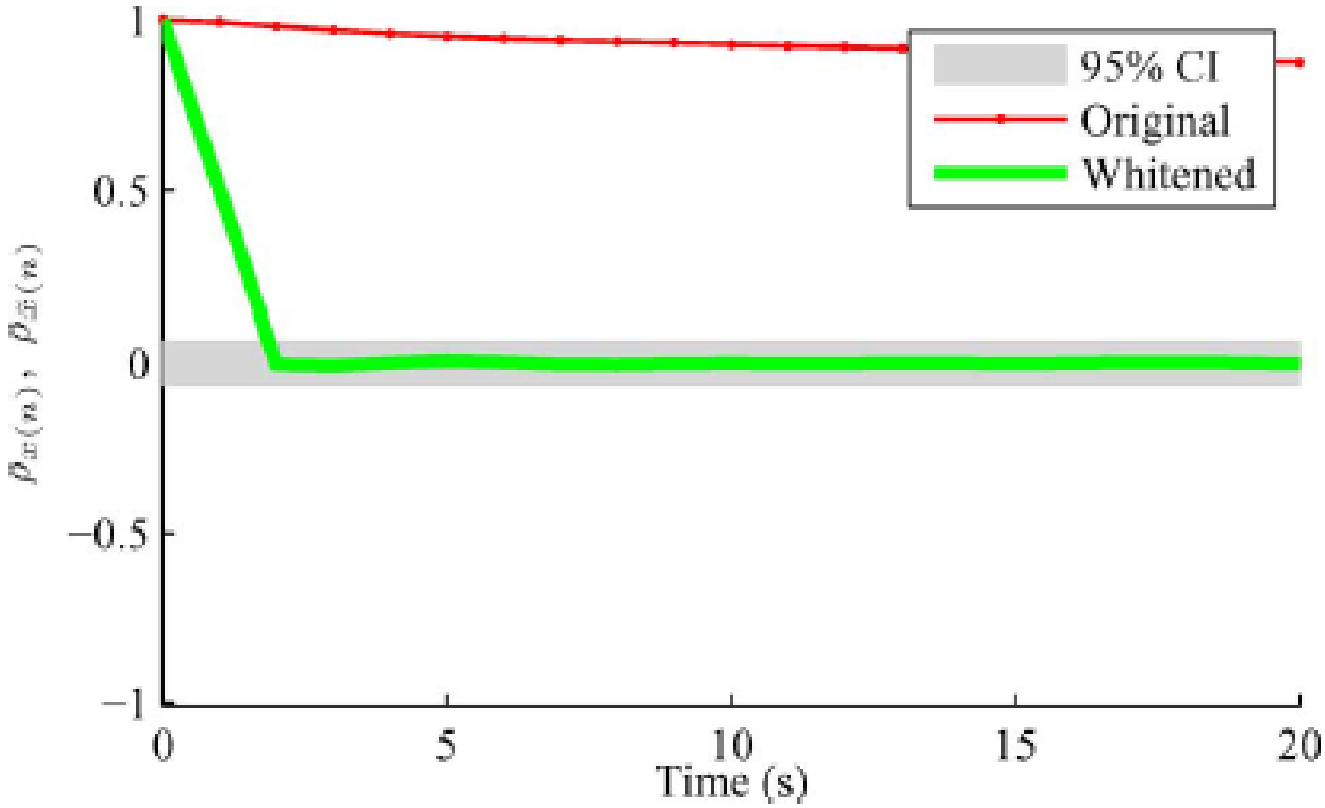


Fig. 8. Autocorrelation of the mean ICP. The mean ICP has a long memory. Samples beyond a lag of 1 s are not significantly correlated for the whitened mean ICP and lie inside the gray region representing a 95% confidence interval for a white noise process.

B. Intracranial Pressure and Heart Rate

- **Results:**

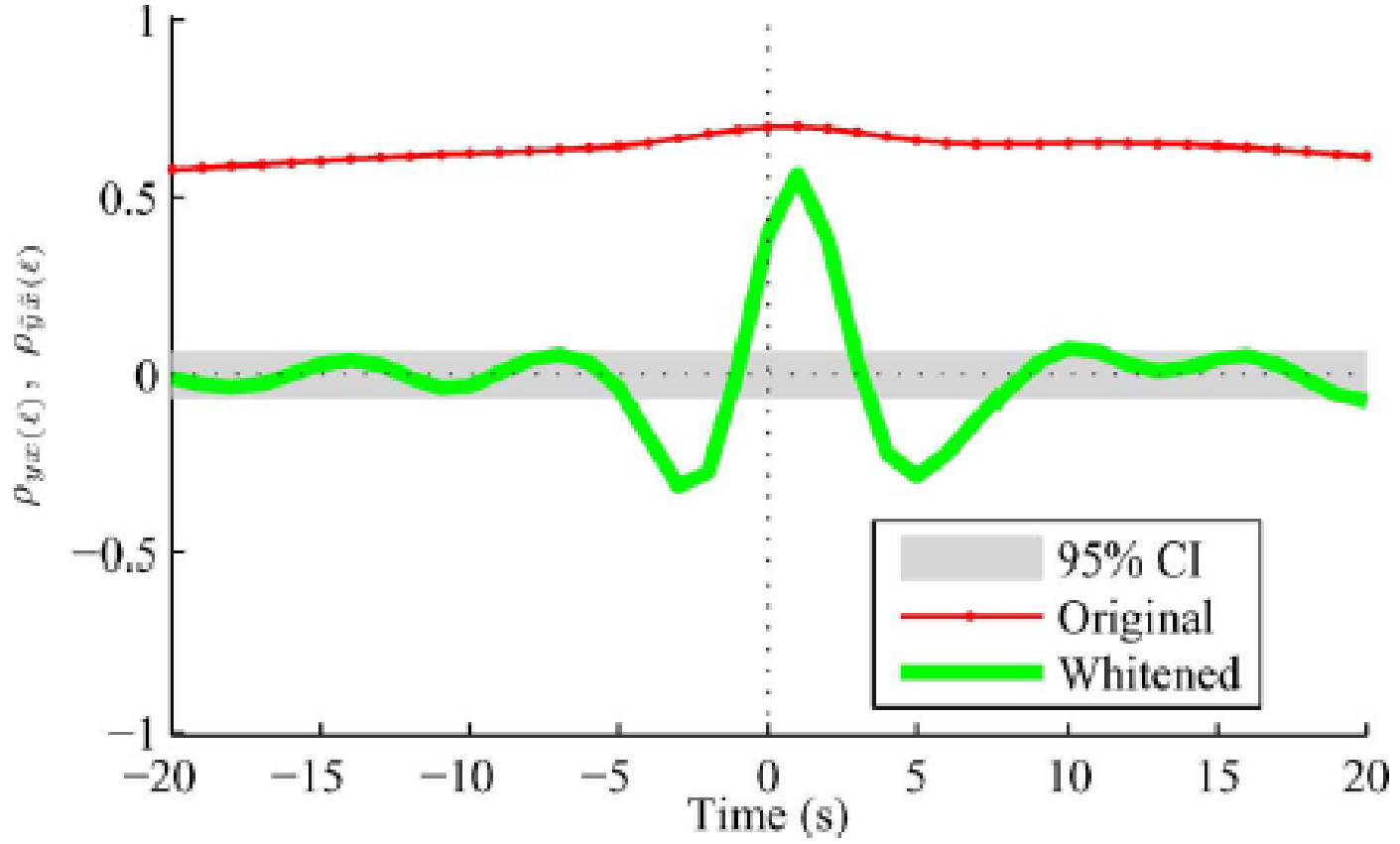


Fig. 9. Traditional and whitened cross correlation between mean intracranial pressure (ICP) and the instantaneous heart rate (HR). The mean delay was 0.604 s with the heart rate lagging the mean ICP, on average.

B. Intracranial Pressure and Heart Rate

- **Conclusions:**

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

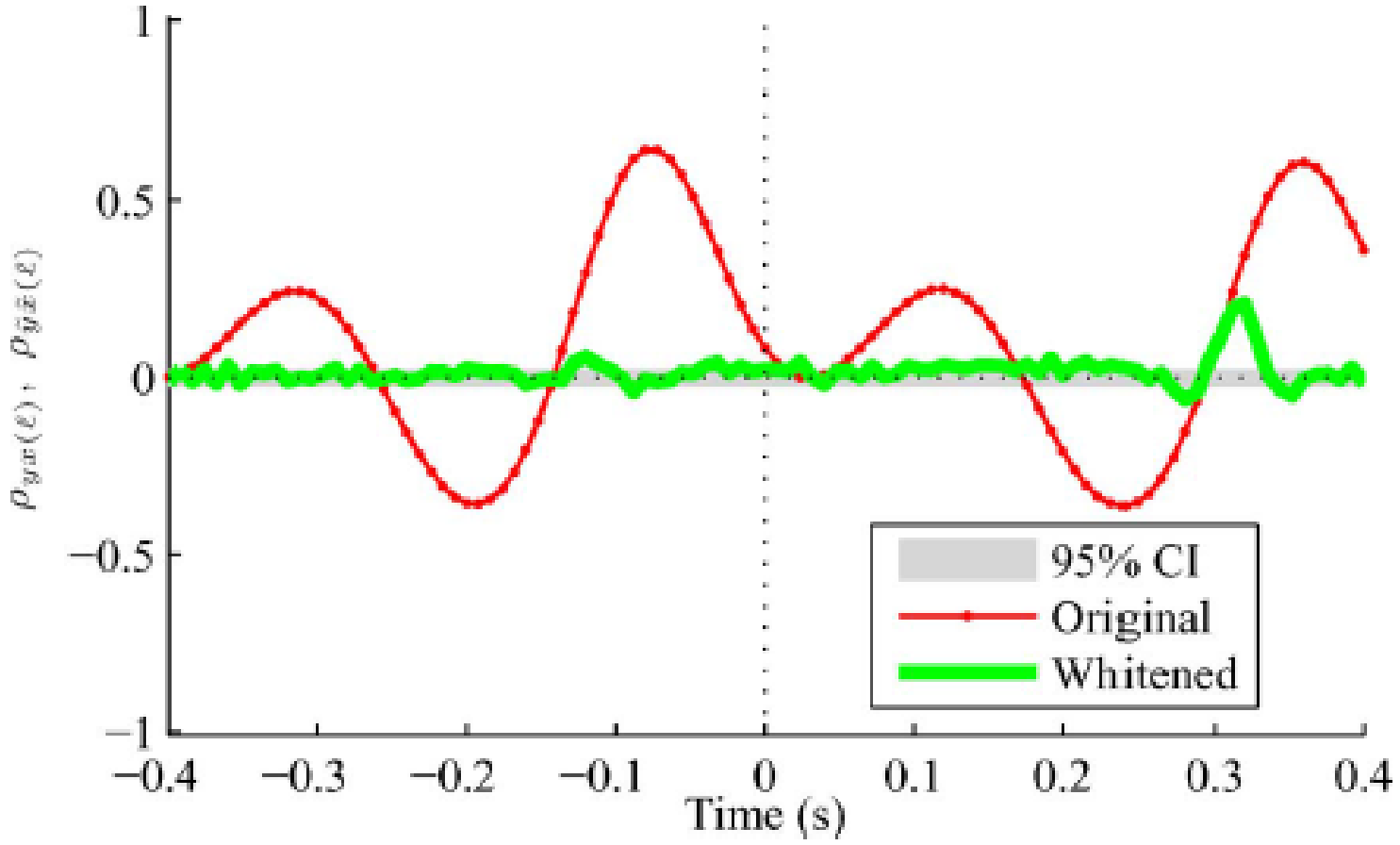


Fig. 10. Traditional and whitened CCFs between ICP and ABP. The whitened CCF clearly shows a causal relationship with a nearly pure delay of approximately 0.3 s.

C. Arterial Blood and Intracranial Pressures

- **Conclusions:**

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

- Motivation:

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].

D. Electrocardiogram and Arterial Blood Pressure

- ECG data collection:

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.

D. Electrocardiogram and Arterial Blood Pressure

- Results:

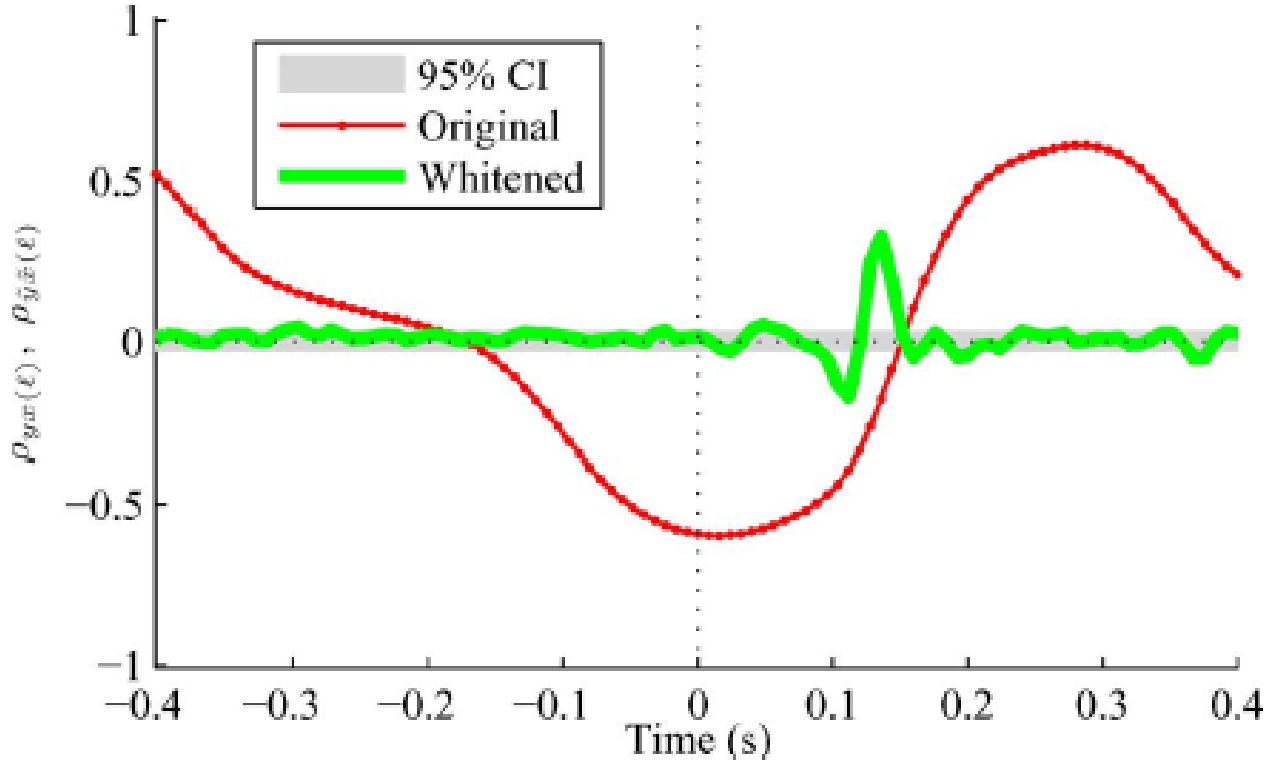


Fig. 11. Traditional and whitened CCFs between ECG and ABP. The whitened CCF correctly suggests a causal relationship with a brief delay interval of approximately 0.1–0.2 s. The traditional CCF suggests a significant correlation over a broad range of positive and negative lags.

D. Electrocardiogram and Arterial Blood Pressure

- **Conclusions:**

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 [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.

Thanks a lot!