Robust Causality Analysis of Non-Stationary Multivariate Physiological Time Series

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Abstract—An important research area in biomedical signal processing is that of quantifying the relationship between simultaneously observed time series and to reveal interactions between the signals. Since biomedical signals are potentially non-stationary and the measurements may contain outliers and artifacts, we introduce a robust time-varying generalized partial directed coherence (rTV-gPDC) function. The proposed method, which is based on a robust estimator of the time-varying autoregressive (TVAR) parameters, is capable of revealing directed interactions between signals. By definition, the rTV-gPDC only displays the linear relationships between the signals. We therefore suggest to approximate the residuals of the TVAR process, which potentially carry information about the nonlinear connectivity structure by a piece-wise linear time-varying moving-average (TVMA) model. The performance of the proposed method is assessed via extensive simulations. To illustrate the method’s applicability to real-world problems, it is applied to a neurophysiological study that involves intracranial pressure (ICP), arterial blood pressure (ABP), and brain tissue oxygenation level (PtiO2) measurements. The rTV-gPDC reveals causal patterns that are in accordance with expected cardiac mechanisms and potentially provides new insights regarding traumatic brain injuries (TBI).

Index Terms—Biomedical signal processing, connectivity analysis, directed coherence, Kalman filter, multivariate autoregressive modeling, time-varying autoregressive (TVAR), time-varying moving-average (TVMA), partial directed coherence (PDC), generalized partial directed coherence (gPDC), intracranial pressure (ICP), arterial blood pressure (ABP), traumatic brain injuries (TBI).

I. INTRODUCTION

In multivariate biomedical signal processing, an important and frequently asked question is whether the underlying time series interact and whether they are causally connected. Answering this question is of interest in many applications, for example in the case of non-invasive brain activity measurements, such as electroencephalography (EEG) or functional magnetic resonance imaging (fMRI), where the neural connectivity is characterized [1]–[10]. Also in cardiological studies one is interested, for example, in the relation between cardiovascular and cardiorespiratory data [11]–[15].

A traditional approach to analyze the relation between multivariate biomedical signals is to use the coherence function [16], the partial coherence [17], or time-varying extensions of the coherence based approaches [15], [18]. However, coherence is not a directional measure, i.e., it does not provide the direction of the information flow. Therefore, several techniques based on linear multivariate autoregressive (MVAR) models have been proposed to quantify causality in the frequency domain. One of the most frequently applied methods is the directed transfer function (DTF), that was introduced by Kaminski and Blinowska [19] as a multivariate measure of the intensity of activity flow in brain structures. A further multivariate approach for the estimation of causality between time series is the directed coherence (DC), a terminology introduced in [20] and reviewed by Baccalá et al. in [2], which was first applied to analyze neural data. The partial directed coherence (PDC) and the re-examined definition of the generalized partial directed coherence (gPDC) were introduced by Baccalá et al. [21], [22]. The PDC is a conceptional generalization of the DC, whereas the gPDC is a natural generalized definition of the PDC. It allows to perform a multivariate analysis that is capable of detecting the interactions between two signals after removing the contribution of all the other signals. gPDC also has the advantage of being scale invariant and more accurate for short time series as compared to the PDC. Thus, the gPDC is able to distinguish between direct and indirect connections. To overcome the limitation of stationarity, Milde et al. [23] presented a technique to estimate high-dimensional time-variant autoregressive (TVAR) models for interaction analysis of simulated data and high-dimensional multi-trial laser-evoked brain potentials (LEP). Systematic investigations on the approach to use a Kalman filter for the estimation of the TVAR models were performed by Leistritz et al. [24]. A mathematical derivation of the asymptotic behaviour of the gPDC has been presented by Baccalá et al. [25]. Omidvarnia et al. [26] modified the time-varying generalized partial directed coherence (TV-gPDC) method by orthogonalization of the strictly causal multivariate autoregressive model coefficients. The generalized orthogonalized PDC (gOPDC) minimizes the effect of mutual sources and was applied on event-related directional information flow from flash-evoked responses in neonatal EEG. All the above-mentioned multivariate measures rely on the concept of Granger causality between time series [27] and can be interpreted as frequency domain representations of this very popular concept of
causality.

However, a severe challenge in estimating the parameters of MVAR models is the sensitivity of classical estimators towards artifacts or outliers in the measurements [5], [28]–[35]. The presence of artifacts or outliers was frequently reported, e.g., in fMRI [36] or ECG [35] measurements. Researchers often must exclude contaminated signal parts [5], [28], [29], [31]–[33] which can lead to a significant loss of data. Finally, since MVAR models are bound to describe linear relations between time series, they fail to detect nonlinear causalities, which can be present in real biomedical signals [37]–[39].

Our contributions are as follows: We propose a new directed coherence measure called the robust time-varying generalized partial directed coherence (rTV-gPDC). The parameters of the gPDC are estimated using a Kalman filter. In this way, the assumption of stationarity is dropped. Based on robust statistics [34], [40], [41], we introduce a computationally attractive one-step reweighting algorithm that is incorporated into the Kalman filter to handle artifacts. We adapt a method by Chowdhury [42] to approximate the unknown nonlinear function with the help of a family of piece-wise linear functions using a TVMA model. With this TVMA model, we extend the gPDC to nonlinear causality patterns to reveal nonlinear relations between multivariate time series. We evaluate our method numerically both in terms of accuracy and robustness and compare it to an existing method [43]. Further, we apply our method to clinically collected traumatic brain injury data and display the interactions between intracranial pressure (ICP), arterial blood pressure (ABP) and brain tissue oxygenation level (PtiO2) signals.

The paper is organized as follows. Section II briefly revisits some important existing methods. Section III introduces a novel time-varying frequency domain approach to assess causality between time series based on TVAR and TVMA models as an extension of the gPDC. The new approach is validated on simulated TVAR data in Section IV, whereas Section V is devoted to an application of the approach to a real clinically collected multivariate biomedical time series. Section VI discusses the approach based on the achieved results and addresses the advantages and drawbacks, before Section VII concludes the paper.

II. BACKGROUND ON MEASURING CAUSALITY IN THE FREQUENCY DOMAIN

This Section briefly reviews the TVAR model and the frequency domain causality measures including the gPDC.

A. Multivariate Autoregressive (MVAR) Model

Let \( \mathbf{x}(n) = [x_1(n), x_2(n), \ldots, x_M(n)]^T \) denote an \( M \)-dimensional multivariate time series whose consecutive measurements contain information about the underlying processes. A common attempt to describe such a time series is to model the current value as a linear summation of its previous values plus an innovation term. This very popular time series model is called the MVAR model and is given by

\[
\mathbf{x}(n) = \sum_{p=1}^{P} \mathbf{A}_p \mathbf{x}(n-p) + \mathbf{v}(n),
\]

where \( P \) is the model order, \( \mathbf{v}(n) = [v_1(n), v_2(n), \ldots, v_N(n)]^T \) is a white noise vector, and \( \mathbf{A}_p \) are the parameters that define the time series:

\[
\mathbf{A}_p = \begin{bmatrix}
a_{11} & \cdots & a_{1M} \\
\vdots & \ddots & \vdots \\
a_{M1} & \cdots & a_{MM}
\end{bmatrix}.
\]  

Here, \( a_{ij} \) reflects the linear relationship from channel \( j \) to channel \( i \), where \( i, j = 1, \ldots, M \).

B. Frequency Domain Causality Measures

1) Granger Causality: The economist Sir Clive W. J. Granger defined the concept of causality by exploiting the temporal relationships between time series [27], [44]. In his definition, the general idea of causality is expressed in terms of predictability: If a signal \( X \) causes a signal \( Y \), the knowledge of the past of both \( X \) and \( Y \) should improve the prediction of the presence of \( Y \) as opposed to the knowledge of the past of \( Y \) alone.

Granger causality is based on assuming stationarity and requires a good fit of the underlying AR model to the data at hand. More recently, time-varying approaches of Granger causality have been proposed, such as in [45], [46], by incorporating TVAR models with time-dependent parameters and time-dependent estimates of the variances of the prediction errors. In addition to the time-variation, also nonlinear approaches of Granger causality have recently been published [38], [46]. However, Granger causality is unable to distinguish between direct and indirect causality in the case of multivariate time series. A recent survey of Granger causality from a computational viewpoint was published by Liu and Bahadori [47].

2) Generalized Partial Directed Coherence: Based on Granger causality and MVAR models, several frequency domain based measures have been introduced to determine the directional influence in multivariate systems. One of the recently proposed methods is the PDC, introduced in the context of analyzing neural data by Baccalá in [21]. It reveals the information flow between isolated pairs of time series.

A re-examined and improved modification of the PDC was proposed by Baccalá in [22]: the generalized partial directed coherence. The gPDC aims at improving the performance under scenarios that involve severely unbalanced predictive modeling errors and it features hugely reduced variability for short time series, which is required for bootstrap-based connectivity testing approaches [22], [48], [49].

In the original definition of the gPDC, time-invariance and stationarity of the data are required. It is based on the MVAR parameters comprised in (2), which have to be transformed.
into the frequency domain by

$$A(f) = IM - \sum_{p=1}^{P} A_p e^{-i2\pi fp}, \quad (3)$$

where $i$ is the imaginary unit and $f$ is the normalized frequency in the interval $[-0.5, 0.5]$. The gPDC [22] is defined as

$$\pi_{ij}(f) = \frac{\frac{1}{\sigma_i} \bar{A}_{ij}(f)}{\sqrt{\sum_{m=1}^{M} \frac{1}{\sigma_i} A_{mj}(f) A_{mij}^*(f)}}, \quad (4)$$

where $\frac{1}{\sigma_i}$ refers to the standard deviation of the innovations processes $v_i(n)$ and * refers to complex conjugate.

### III. ROBUST TIME-VARYING GENERALIZED PARTIAL DIRECTED COHERENCE (rTV-gPDC)

This Section is dedicated to describing and analyzing our proposed methodological approach to robustly assess the causality between time series based on a new method called the robust time-varying generalized partial directed coherence (rTV-gPDC).

#### A. TVAR and TVMA Models for Nonlinearity Approximation

For non-stationary multivariate time series, an explicit description of the variation is necessary due to the time-dependent MV AR parameters $A_p(n)$. This is realized by extending Eq. (1) to the TVAR model

$$x(n) = \sum_{p=1}^{P} A_p(n) x(n-p) + v(n), \quad (5)$$

where $v(n)$ is assumed to be a white noise process.

The TVAR model is based on linear equations; thus, it is only able to describe linear relationships between time series. However, most physiological systems are subject to more complex and nonlinear forms [50]. For example, for cerebral hemodynamics, the Blood Oxygen Level Dependent (BOLD) signal responses to stimulus temporally in a nonlinear manner, and nonlinearity has also been observed, when two identical stimuli induced close together in time produce a net response with less than twice the integrated response of a single stimulus alone [51]. It was also reported that intracranial pressure (ICP), an important indicator for secondary brain insult for traumatic brain injury (TBI) patients, is associated with the cerebral blood volume based on a nonlinear mechanism of auto-regulation [52].

To reveal nonlinear relationships, we propose to extend the model in order to approximately model nonlinear relationships. Since we usually do not have any prior knowledge about the nonlinear relation between biomedical signals, we do not assume a specific form of the nonlinear function.

In [42], Chowdhury proposed a method to approximate the unknown nonlinear function with the help of a family of piecewise linear functions. She argues that, at each discrete time step, a linear system can match the input-output data of the nonlinear plant. When $v(n)$ is not white but colored noise, Chowdhury suggests to approximate it by

$$v(n) \approx \sum_{q=1}^{Q} B_q(n) r(n-q) + r(n) \quad (6)$$

This approximation of the unknown nonlinear function is obtained by extending the TVAR model in (5) by a stochastic TVMA term (6) to

$$x(n) = \sum_{p=1}^{P} A_p(n) x(n-p) + \sum_{q=1}^{Q} B_q(n) r(n-q) + r(n) \quad (7)$$

with $n = 1, \ldots, N$ and $Q$ being the order of the MA part. Here, $B_q(n)$ is the time-varying $M \times M$ parameter matrix that weights past values of $r(n)$. If $v(n)$ contains a structure which could not be incorporated into the linear TVAR model, the partly nonlinear relationship is approximated by the TVMA term. Analogous to (2), we define the time-varying residual parameter matrix $B_q(n)$ as follows:

$$B_q(n) = \begin{bmatrix} b_{11}(n) & \cdots & b_{1M}(n) \\ \vdots & \ddots & \vdots \\ b_{M1}(n) & \cdots & b_{MM}(n) \end{bmatrix}. \quad (8)$$

#### B. Linear and Nonlinear Coherence Analysis

A time-varying version of the gPDC can be obtained by incorporating the TVAR model from (5) with the corresponding time-dependent parameter matrix $A_p(n)$. A time-varying gPDC (TV-gPDC) is then defined as

$$\pi_{ij}^L(n, f) = \frac{1}{\sigma_i(n)} \bar{A}_{ij}(n, f) \sqrt{\sum_{m=1}^{M} \frac{1}{\sigma^2(n)} A_{mj}(n, f) A_{mij}^*(n, f)} \quad (9)$$

To further incorporate the nonlinear connectivity, the additional time-varying residual parameter matrix $B_q(n)$ is transformed analogously to the linear term by

$$\bar{B}(n, f) = \sum_{q=1}^{Q} B_q(n) e^{-i2\pi fq}. \quad (10)$$

We thus define the nonlinear TV-gPDC as

$$\pi_{ij}^B(n, f) = \frac{1}{\sigma_i(n)} \bar{B}_{ij}(n, f) \sqrt{\sum_{m=1}^{M} \frac{1}{\sigma^2(n)} \bar{B}_{mj}(n, f) \bar{B}_{mij}^*(n, f)} \quad (11)$$

by integrating $\bar{B}(n, f)$ from (11) into the definition of the TV-gPDC.
C. Robust Estimation of TVAR and TVMA Model Parameters

The estimation of the time-varying parameter matrices \( A_p(n) \) and \( B_q(n) \) can be performed in different ways. One way is to evaluate the signals within moving short-time windows and to assume local stationarity. Another approach is to estimate the time-varying parameters with adaptive filters, such as the RLS algorithm [53], the LMS algorithm [28] or the Kalman filter [23]. One advantage of the latter approach is the absence of the local stationarity assumption.

Another advantage is the possibility to incorporate statistically robust algorithms, e.g., the robustly filtered \( \tau \)-, \( M \)- or \( S \)- estimators [34], [41] into the adaptive filter algorithms. As biomedical signals are often contaminated by artifacts or outlying values, it is advisable to estimate TVAR and TVMA model parameters robustly. However, advanced robust methods for dependent data are not always applicable because of their high computational complexity [34], [41]. Therefore, we introduce a computationally light and robust one-step reweighting algorithm in this paper.

1) Transition to the State Space Model: Since the Kalman filter estimates the state of a state space model, the TVAR and TVMA models must be defined in the state space [54]. This is achieved by using the following notation

\[
\begin{align*}
a(n) &= \text{vec} \left( [A_1(n), A_2(n), \ldots, A_P(n)]^T \right) \\
b(n) &= \text{vec} \left( [B_1(n), B_2(n), \ldots, B_Q(n)]^T \right)
\end{align*}
\]

(12) (13)

\[
\theta(n) = \begin{bmatrix} a(n) \\ b(n) \end{bmatrix}
\]

(14)

where \( a(n) \) is the \( PM \times 1 \) AR parameter vector, \( b(n) \) is the \( QM \times 1 \) MA parameter vector. \( \theta(n) \), as defined in (14), is the unknown parameter vector of dimension \((P + Q)M \times 1\).

The prediction error

\[
\hat{x}(n) = x(n) - \hat{x}(n|n-1)
\]

(15)

is defined by the residual of the estimation process from previous time-steps, where \( \hat{x}(n|n-1) \) is the \textit{a priori} estimate of \( x(n) \), given information up to the previous time step.

The TVAR and TVMA models can then be represented in the state space as follows:

\[
\begin{align*}
\hat{X}(n) &= [x^T(n-1), x^T(n-2), \ldots, x^T(n-P)] \\
\hat{R}(n) &= [\hat{x}^T(n-1), \hat{x}^T(n-2), \ldots, \hat{x}^T(n-Q)]
\end{align*}
\]

(16) (17)

\[
\begin{align*}
C(n) &= I_M \otimes \hat{X}^T(n) \\
D(n) &= I_M \otimes \hat{R}^T(n)
\end{align*}
\]

(18) (19)

\[
\Phi(n) = \begin{bmatrix} C(n) \\ D(n) \end{bmatrix}
\]

(20)

Here, \( \hat{X}(n) \) contains the \( P \) previous measurements, \( \hat{R}(n) \) represents the \( Q \) previous residuals defined in (15), \( \otimes \) represents the Kronecker product, and \( \Phi(n) \) is the \((P + Q)M^2 \times M\) matrix representing previous measurements \( C(n) \) and residuals \( D(n) \).

2) Kalman Filter Model: The system equation of the Kalman filter

\[
x(n) = F(n-1)x(n-1) + E(n-1)u(n-1) + w(n)
\]

(21)

describes the current state \( x(n) \) depending on the previous state \( x(n-1) \) related via a state transition model \( F(n-1) \), an optional control input \( u(n-1) \), a control model \( E(n-1) \), and a noise term \( w(n) \) with \( w(n) \sim \mathcal{N}(0, Q) \), where \( \mathcal{N}(0, Q) \) represents the zero mean Gaussian probability density function with covariance matrix \( Q \).

For estimating the AR and MA parameters of the TVAR and TVMA model, the control input and control model are dropped, and a multivariate random walk model is assumed. Thus, the state transition model \( F(n-1) \) is equal to the identity matrix.

The resulting system equation is given by

\[
\theta(n) = \theta(n-1) + w(n),
\]

(22)

where \( \theta(n) \) and \( \theta(n-1) \) are the current and previous state, respectively, and \( w(n) \) is the noise term with \( w(n) \sim \mathcal{N}(0, Q) \).

It is usually not possible to measure the true state \( x(n) \) itself, but an observation \( z(n) \) that is given by the measurement equation

\[
z(n) = H(n)x(n) + \xi(n),
\]

(23)

where \( H(n) \) is the measurement model, which maps the true state into the observation. The measurement noise \( \xi(n) \) is distributed as \( \mathcal{N}(0, R) \), where \( \mathcal{N}(0, R) \) represents the zero mean Gaussian probability distribution function with covariance matrix \( R \).

When estimating the TVAR and TVMA model parameters, the observation is given by \( x(n) \) and \( \theta(n) \) is the unknown parameter vector that is sought for.

Therefore, the resulting measurement equation is given by

\[
x(n) = F^T(n)\theta(n) + \xi(n).
\]

(24)

In this work, we assume that the covariance of the measurement noise \( R(n) \) is time-varying.

3) Proposed Robust Algorithm: In order to reduce the influence of outliers, we develop a one-step reweighting algorithm, which we incorporate into the Kalman filter. The procedure of the proposed robust algorithm is shown in Fig. 1. For each univariate time series and each time step \( n \), the algorithm proceeds as follows:

Let \( \hat{x}_m(n) \) be defined by

\[
\hat{x}_m(n) = [x_m(n-L/2), \ldots, x_m(n), \ldots, x_m(n-L/2)].
\]

(25)

Then, we robustly estimate the mean of \( \hat{x}_m(n) \) by

\[
\tilde{\mu}_{rob,n}(\hat{x}_m(n)) = \text{median}(\hat{x}_m(n)),
\]

(26)

where \( L \) is an even integer. The normalized median absolute deviation (MAD) is used to robustly estimate the standard deviation of the univariate prediction error \( \hat{r}_m(n) \)

\[
\hat{\sigma}_{mad,n}(\hat{r}_m(n)) = 1.4826 \cdot \text{median}(|\hat{r}_m(n) - \text{median}(\hat{r}_m(n))|)
\]

(27)

with

\[
\hat{r}_m(n) = [\hat{r}_m(n-L), \ldots, \hat{r}_m(n)].
\]

(28)
Estimate signal parameters $\hat{\mu}_{\text{rob},n}(\tilde{x}_i(n))$ and $\hat{\sigma}_{\text{mad},n}(\tilde{\epsilon}_i(n))$

Determine threshold $c_i(n) = k \cdot \hat{\sigma}_{\text{mad},n}(\tilde{\epsilon}_i(n))$

Is $|x_i(n) - \hat{x}_i(n)| < c_i(n)$?

Update $x_i^*(n) = w_{x_i}(n)x_i(n) + (1 - w_{x_i}(n))\hat{x}_i(n|n-1)$

Determine weight $w_{x_i}(n)$

The constant in (27) provides consistency with respect to a Gaussian distribution [34], [41]. Both the robust mean of the time series and the robust standard deviation of the prediction error are time-varying. Next, we determine a threshold

$$c_i(n) = k \cdot \hat{\sigma}_{\text{mad},n}(\tilde{\epsilon}_i(n)), \quad (29)$$

where the tuning constant $k$ depends on the chosen weighting function and is set to $k = 4.685$ and $k = 1.345$ for Huber’s weighting function and bisquare weighting function, respectively. Both values are chosen to obtain the $95\%$ asymptotic efficiency with respect to the Gaussian distribution [41].

Based on (29), if the current sample $x_m(n)$ does not exceed the threshold $c_i(n)$ around the robust time-varying mean (26), it is assumed to be noncorrupted, and it is passed to the Kalman filter. If

$$|x_m(n) - \hat{x}_m(n)| > c_m(n), \quad (30)$$

the sample $x_m(n)$ is assumed to be corrupted. Therefore, a weight

$$w_{x_m}(n) = W(y(n) - \hat{\mu}_{\text{rob},n}(\tilde{y}(n))) \quad (31)$$

is calculated using either Huber’s or the bisquare type weighting function.

After having determined $w(n)$, the outlier-cleaned observation at time instant $n$ is computed by

$$x^*(n) = w(n)x(n) + (1 - w(n))\hat{x}(n). \quad (32)$$

It is then concatenated with the previous univariate samples to form the outlier-cleaned current multivariate observation $x^*(n)$. With $x^*(n)$, the Kalman filter can calculate a robustified prediction error

$$\overline{r}(n) = x^*(n) - \Phi^T(n)\tilde{\theta}(n|n-1). \quad (33)$$

It is important to note that also (16), (18), and (20) need to be updated after each calculation of the cleaned time series value $x^*(n)$ if (30) is true. If (30) does not hold for any of the samples, the proposed robust algorithm reduces to the classical Kalman filter.

IV. METHOD VALIDATION

In this Section, a validation of the proposed algorithms is presented. The first simulation evaluates the TVAR parameter estimation by investigating its robustness against outliers and computational cost, whereas the second simulation is performed to evaluate the proposed nonlinear causality measure.

A. Simulation Models

In the first simulation, we consider a second order $3$-dimensional MVAR process, which consists of two damped stochastically driven oscillators $x_2$ and $x_3$ as well as of a stochastically driven relaxor $x_1$. This simulation has previously been used in [43] and [55] to evaluate time-varying directed interactions in multivariate neural data, and was chosen in order to be comparable with preceding approaches.

The model of the first simulation is given by

$$x_1(n) = 0.59x_1(n-1) - 0.20x_1(n-2) + \ldots$$

$$b(n)x_2(n-1) + c(n)x_3(n-1) + r_1(n) \quad (34)$$

$$x_2(n) = 1.58x_2(n-1) - 0.96x_2(n-2) + r_2(n) \quad (35)$$

$$x_3(n) = 0.60x_3(n-1) - 0.91x_3(n-2) + r_3(n) \quad (36)$$

with $N = 5000$ and time-varying parameters $b(n)$ and $c(n)$. Parameter $b(n)$ is a decaying oscillating function of $n$ and describes the influence of $x_2(n)$ on $x_1(n)$. The influence of $x_2(n)$ on $x_3(n)$ is modeled by parameter $c(n)$, which is a triangular function between 0 and 1. The signal model is driven by zero-mean unit variance Gaussian white noise $r_i(n)$.

In the second simulation, we consider a second order $3$-dimensional nonlinear signal with

$$x_1(n) = 0.59 + 0.5x_2^2(n-1) + \ldots$$

$$0.8\sqrt{x_3(n-1)^3 + r_1(n)} \quad (37)$$

$$x_2(n) = 1.58x_2(n-1) - 0.96x_2(n-2) + r_2(n) \quad (38)$$

$$x_3(n) = 0.6x_3(n-1) - 0.91x_3(n-2) + \ldots$$

$$x_2(n-1) + r_3(n). \quad (39)$$

Again, the signal is driven by standard normal white noise processes $r_i(n), i = 1, 2, 3$. Here, $x_1(n)$ is nonlinearly influenced by $x_2(n)$ and $x_3(n)$, whereas $x_3(n)$ is linearly
influenced by \( x_2(n) \). The causality patterns are expected to express the relations between \( x_1(n) \) and \( x_2(n) \) and \( x_3(n) \), respectively. However, the influence of \( x_2(n) \) on \( x_3(n) \) is only expected to show up in the linear causality patterns.

### B. Simulation Evaluation

1) **Parameter Estimation:** In most of the publications on causality analysis, only the resulting connectivity patterns are evaluated in simulations. However, in this work, we first evaluate the TVAR parameter estimation in terms of its accuracy w.r.t. the original parameters. For this purpose, we calculate the average of the mean square error (MSE) of the parameter matrix \( A(n) \) as a function of the update coefficient \( \lambda \)

\[
\text{MSE}(\lambda) = \frac{1}{N} \sum_{n=1}^{N} (\hat{A}(\lambda, n) - \tilde{A}(\lambda, n))^2 \tag{40}
\]

to gain a comparable quality criterion.

In order to compare the result to existing methods, the dual extended Kalman filter (DEKF) from [43] has been evaluated with the same simulation model and has also been iterated with different values of the update coefficient.

2) **Coherence Analysis:** To verify the correctness of the coherence analysis, the coherence patterns of the first simulation model are analyzed. As the first simulation model is constructed such that only \( x_1(n) \) is driven by \( x_2(n) \) and \( x_3(n) \), only two connectivity patterns should have values that differ from zero.

3) **Robustness against Outliers:** A very important problem in estimating the TVAR parameters is the sensitivity towards artifacts or outliers in the data. Since biomedical signals are frequently contaminated by artifacts or outliers [5], [28]–[35], researchers often exclude contaminated measurements which results in significant data loss. In some scenarios, artifacts may not always be entirely detectable by the observing researcher and, thus, contaminated parts could still be present in the signal. However, as robust statistics provides useful tools to compensate for those artifacts, we are able to make use of the contaminated data and receive a more accurate parameter estimate than by rejecting large amounts of data.

The outlier model consists of additive independently and randomly placed outliers over the course of the signal \( x(n) \), where each outlier has a random sign and a value in the range of i) \( \pm (3, 10) \times \sigma_{\text{mad}} \) and ii) \( \pm 10,000 \times \sigma_{\text{mad}} \). In model i), outliers exhibit values in a very close sigma range to the true data values, whereas model ii) simulates values heavily deviating from the bulk of the data to analyze the worst case performance. The outliers are only introduced to \( x_1(n) \) in the first simulation, \( x_2(n) \) and \( x_3(n) \) are kept clean.

To evaluate the results concerning robustness against outliers, we use measures of robust statistics: the maximum bias curve (MBC) and the breakdown point (BP) [34]. The MBC reflects maximally possible bias affected by a specific amount of contamination. The absolute value of the maximum possible asymptotic bias \( b_{\hat{\theta}}(F, \theta(n)) = \hat{\theta}_\infty(F_{\theta(n)}) - \theta(n) \) of an estimator \( \hat{\theta} \) is plotted with respect to the fraction of contamination \( \nu \):

\[
\text{MBC}(\nu, \theta) = \max\{|b_{\hat{\theta}}(F, \theta(n))| : F \in F_{\nu, \theta}\}. \tag{41}
\]

Here, \( F_{\nu, \theta} = \{(1 - \nu)F_\theta + \nu G\} \) is an \( \nu \)-neighborhood of distributions around the nominal distribution \( F_\theta \) with \( G \) being an arbitrary contaminating distribution.

The BP characterizes the quantitative robustness of an estimator by indicating the maximal fraction of outliers in the observations, which an estimator can handle before it breaks down [34]. The minimum value the BP can take is 0 % and the maximum value is 50 %, since a value beyond 50 % makes it impossible to distinguish between the actual and contaminating distributions. The higher the BP value, the larger is the quantitative robustness.

As the model parameters to be estimated are time-varying, we have to adapt the formulation of the MBC. The absolute value of the maximum possible bias has to be evaluated for every time step \( n \), such that:

\[
b_{\hat{\theta}}(F, \theta(n)) = \hat{\theta}_\infty(F_{\theta(n)}) - \theta(n), \tag{42}
\]

which changes the MBC to:

\[
\text{MBC}(\nu, \theta(n)) = \max\{|b_{\hat{\theta}}(F_{\theta(n)}, \nu)| : F \in F_{\nu, \theta(n)}, \forall n\}.
\tag{43}
\]

The maximum bias is evaluated considering the absolute maximum bias at every time step \( n \). Since an inherent change in the model parameters evokes a bias in the estimator, this criterion is much harder to comply with. For this reason, we extend the simulations by additional characteristics, i.e. the average, the median, and the 5th- and 95th-quantile.

4) **Computational Time:** Another property of interest is the computational time of the parameter estimation as well as of the causality measure calculation. For the parameter estimation, the main critical factors are the determined AR and MA model orders \( P \) and \( Q \), respectively, and the number of time series \( M \). The number of parameters to be estimated is \((P + Q)M^2\).

Moreover, for the causality measure calculation, the frequency resolution is an additional parameter, which needs to be considered. The orders and signal dimension are not only crucial for the parameter estimation but also for the causality measure calculations. Extensive simulations have been performed for various settings and results are shown depending on all of the above mentioned parameters.

5) **Nonlinearity:** For the nonlinearity validation, we consider the second simulation model, which incorporates linear and nonlinear causalities. \( x_1(n) \) is nonlinearly influenced by \( x_2(n) \) and \( x_3(n) \), respectively, and \( x_3(n) \) linearly influences \( x_3(n) \). The causality patterns are expected to express the relations between \( x_1(n) \) and \( x_2(n) \) and \( x_3(n) \), respectively. However, the causality of \( x_2(n) \) on \( x_3(n) \) is only expected to show up in the linear causality patterns.

For this setting, \( N = 5000 \) and 256 frequency bins are used for a normalized frequency range \([0, 0.5]\), and the proposed robust Kalman filter is evaluated for \( \lambda = 8.3 \cdot 10^{-5}, P = 2 \) and \( Q = 4 \).

### C. Simulation Results

1) **Parameter Estimation:** Fig. 2a shows the averaged MSE of the parameter matrix \( A(n) \) using the proposed Kalman
filter (KF) and the DEKF [43]. The averaged MSE of the desired time-varying parameter $b(n)$ and $c(n)$ is shown in Fig. 2b, likewise for the proposed Kalman filter and the DEKF. For the whole parameter matrix $\mathbf{A}(n)$, the optimal update coefficient $\lambda$ for the proposed robust Kalman filter algorithm is empirically determined as $\lambda_{\text{opt.KF}} = 1.5 \cdot 10^{-5}$ whereas the optimal update coefficient for the DEKF algorithm equals $\lambda_{\text{opt.DEKF}} = 1.5 \cdot 10^{-2}$. As it can be observed, the proposed algorithm obtains lower averaged MSE values at the optimal update coefficient value compared to the DEKF algorithm.

Fig. 3 shows the estimation of the TVAR parameters $b(n)$ and $c(n)$ for the optimal update coefficient value over time, for the proposed Kalman filter as well as for the DEKF. The accuracy is very similar, whereas the estimate of the proposed Kalman filter is slightly closer to the true parameter value, as it can also be seen in Fig. 2b.

2) Coherence Analysis: The result of the coherence analysis for the first simulation model is shown in Fig. 4 and successfully reflects the time-varying partial connectivity from channel 2 to channel 1 and from channel 3 to channel 1. The causality from channel $i$ to channel $j$ is indicated by a directional arrow, such as $\text{CH}_i \rightarrow \text{CH}_j$, $i,j = 1, \ldots, 3$. The frequency resolution is set to $\Delta f = 1/128$ on the normalized frequency range from 0 to 0.5.

3) Robustness: The simulations regarding the robustness of the estimators are again conducted for the proposed robust Kalman filter as well as for the DEKF. Both algorithms are evaluated using the first simulation model and outlier models i) and ii). The simulations are performed using 1000 Monte Carlo experiments for each scenario. Both estimator’s bias characteristics are depicted in Fig. 5. Figures 5a and 5b are obtained using outlier model i) and Fig. 5c and 5d show the results using outlier model ii).

For a contamination with outliers having a small variance, as shown in Fig. 5a and Fig. 5b, both the proposed robust Kalman filter and the DEKF achieve reasonable results and the proposed method outperforms the DEKF both on average and in the worst case. A huge performance gain is visible in Fig. 5c compared to Fig. 5d, i.e., when the signal is contaminated by large-valued outliers. In Fig. 5d, the DEKF immediately breaks down after contaminating the signal with only 1% of outliers. The proposed robust Kalman filter has a limited bias even up to 30 percent of gross outlier contamination.

4) Computational Time: Average computation times are obtained by using the first simulation model, varying model orders $P = 1:10, 15, 20$ and $Q = 0, 1, 5, 10$, and multivariate signals with a maximum of 10 dimensions. All results are averaged over 100 Monte Carlo runs. The computational time of the parameter estimation using the proposed robust Kalman filter is compared with the one of the DEKF. All the computational time estimations have been performed under a MATLAB R2012a environment on a PC equipped with Intel Core i5-760 processor (2.80 GHz) and 8 GB RAM.

Fig. 6 shows the computational times for the proposed Kalman filter as well as for the DEKF. It can be seen that the DEKF is only faster for very low orders up to $P = 4$, but the computational time grows faster with increasing order. At an order of 20, for example, the proposed algorithm is almost 8 times faster than the DEKF approach, if the MA order is set to zero. But even with an MA order $Q = 5$, the proposed algorithm is still more than 4 times faster compared to the DEKF approach.

In Fig. 7, the computational times depending on the signal dimensions are depicted. Fig. 7a shows the times for fixed
AR model order $P = 5$ for the proposed robust Kalman filter with MA model order $Q = 0$ and $Q = 5$ as well as, for comparison, the times for the DEKF. The AR model order is fixed to $P = 20$ in Fig. 7a.

According to Figs. 6 and 7, these plots reveal the superiority of the proposed method in terms of computational cost in the case of higher signal dimensions. After having estimated the required model parameters, the coherence calculation is performed. The computational times of the coherence calculation mainly depend on the frequency resolution and on the size of the estimated parameter matrices. The simulations are based on a fixed sample length $N = 1000$ and the frequency resolution as well as the estimated parameters are varied.

The results are illustrated in Fig. 8. Both the model orders $P$ and $Q$, varied in Fig. 8b, and the frequency resolution, shown in Fig. 8c and Fig. 8d, approximately linearly depend on the computation time, whereas in Fig. 8a the computational time grows faster for higher signal dimensions $M$. This is due to the quadratic impact of $M$ to the parameter order $(P + Q)M^2$.

5) Nonlinearity: The causality patterns of the causality analysis are shown in Fig. 9 and Fig. 10 for the linear and nonlinear causality, respectively. As expected, the linear TV-gPDC shows influence in the case of nonlinear causality from channel 2 to 1 and channel 3 to 1, and in case of linear causality from channel 2 to 3, whereas its nonlinear extension only recognizes the nonlinear relation between channel 2 to 1 and channel 3 to 1.

V. APPLICATION TO BIOMEDICAL TIME SERIES OF TRAUMATIC BRAIN INJURY PATIENTS

This Section describes the application of the proposed method to a multivariate biological time series of traumatic
Fig. 9. Linear time-varying generalized partial directed coherence of the second simulation model using the proposed robust Kalman filter. The y-axes represent the normalized frequency and the x-axes represent time direction expressed in data samples.

Fig. 10. Nonlinear time-varying generalized partial directed coherence of the second simulation model using the proposed robust Kalman filter. The y-axes represent the normalized frequency and the x-axes represent time direction expressed in data samples.

brain injury (TBI) patients.

For TBI patients, continuous monitoring of physiological signals, such as ICP, mean arterial blood pressure (MAP) or brain tissue oxygen level (PtiO2), has become a golden standard in neuro-intensive care units (ICU). As the primary insult, the initial mechanical damage, cannot be therapeutically reversed, the main target for TBI patient management is to limit or to prevent secondary insults through continuous physiological signal monitoring. Cerebrovascular autoregulation is one of the important mechanisms to sustain adequate cerebral blood flow [56], and impairment of this mechanism indicates an increased risk to secondary brain damage and mortality [57]. Cerebrovascular autoregulation is most commonly assessed based on the pressure-reactivity index (PRx), which is defined as a sliding window linear correlation between the ICP and ABP. However, as reported in [52], [59], the cerebrovascular autoregulation is governed by a nonlinear mechanism. Thus, capturing the nonlinear association between ICP and MAP can offer a more complete understanding of the autoregulation process.

In addition, TBI is characterized by an imbalance between cerebral oxygen delivery and cerebral oxygen consumption. Although this mismatch is induced by several different vascular and haemodynamic mechanisms, the final common endpoint is brain tissue hypoxia. Extent of tissue hypoxia was found to be correlated to poor outcomes [56]. Modeling the nonlinear coherence among brain tissue oxygen level (PtiO2), ICP and MAP can potentially be a qualified measure of the interaction between oxygen delivery and oxygen demand. This can finally lead to more individualized treatments to improve patients’ outcomes.

However, since the ICP, MAP and PtiO2 signals were collected in actual ICU environments and the sensors are sensitive to patient movements and bed angles, they are often contaminated by noise and artifacts [60], [61], see e.g. Fig. 12.

The medical data have been recorded at the Neuro-ICU of the National Neuroscience Institute, Singapore. 10 patients were considered for the analysis. From a total number of twelve different measured signals, three signals have been extracted for further analysis: ICP, MAP, and brain tissue oxygenation level (PtiO2). The MAP is measured as the mean arterial pressure (MAP). The pressures as well as the PtiO2 are measured in mmHg. The sampling frequency of all data is \( f_s = 0.1 \) Hz and no preprocessing has been performed except for subtracting the mean. None of the patients demographic nor personal information were used in this study. The proposed robust Kalman filter is applied to quantify the linear and nonlinear information transfer among ICP, MAP and PtiO2 for TBI patients.

The choice of the optimal model parameters for real signals is not straightforward as in the case of simulated data. Since we do not know the true underlying TVAR and TVMA model orders, we resort to model order selection [62]. In our case, we use an Akaike type criterion, whose minimum provides a model fit that trades off model error and complexity. As we deal with multivariate signals and need to optimize parameters of a time-varying system, only an average optimal choice can be found. The criterion is given by

\[
AIC(P, Q, \lambda) = \log(\det(\hat{\sigma}_r^2(\lambda))) + \frac{2(P + Q)M^2}{N},
\]

where \( \hat{\sigma}_r^2 \) is an estimate of the covariance matrix of the revised prediction error \( \hat{r}(n) \).

The optimal model orders and optimal update coefficient were estimated using (44). As an outcome, the following parameters were chosen: \( P_{\text{opt}} = 35, Q_{\text{opt}} = 2 \) and \( \lambda_{\text{opt}} = 0.04 \), see Fig. 11a and Fig. 11b.

A. Robustness against artifacts

Figure 12 illustrates that ICP and MAP signals, given as measured signals \( x_1(n) \) and \( x_2(n) \) respectively, can often be
coherence estimation and to evaluate the effectiveness of the proposed robust estimation method. In the experiment, we examined a 4 hours segment of (a) an ICP and (b) a MAP signal, where $x_1(n)$ and $x_2(n)$ are the measured signals, i.e. clean signals, on which artificial artifacts (sharp spikes) were added on a 15 minutes interval, and $x_1^\ast(n)$ and $x_2^\ast(n)$ are the robust signal estimates; (c) illustrates how introduced artifacts distorted and destroyed the patterns in the coherence spectrum; and (d) then demonstrates how the proposed method is robust against artifacts and is able to reconstruct the patterns in the coherence spectrum.

Fig. 13. A simulation experiment to investigate the impact of artifacts on coherence estimations and to evaluate the effectiveness of the proposed robust estimation method. In the experiment, we examined a 4 hours segment of (a) an ICP and (b) a MAP signal, where $x_1(n)$ and $x_2(n)$ are the measured signals, i.e. clean signals, on which artificial artifacts (sharp spikes) were added on a 15 minutes interval, and $x_1^\ast(n)$ and $x_2^\ast(n)$ are the robust signal estimates; (c) illustrates how introduced artifacts distorted and destroyed the patterns in the coherence spectrum; and (d) then demonstrates how the proposed method is robust against artifacts and is able to reconstruct the patterns in the coherence spectrum.

contaminated with artifacts and outliers. Thus, the nonrobust estimation of TVAR and TVMA model parameters result in errors, whereas the use of robust signal estimates, $x_1^\ast(n)$ and $x_2^\ast(n)$, yield robust estimates of the parameters. Moreover, the artifacts in the measured signals also cause errors in the estimation of coherence. To investigate the impact of artifacts on coherence estimation and to evaluate the effectiveness of the proposed robust estimation method, a numerical experiment was conducted.

As shown in Figure 13 (a) and (b), artificial artifacts (sharp spikes highlighted in red) were added on a 15 minutes interval to a 4 hour segment of clean ICP and MAP signals. Figure 13 (c) further illustrates that the introduced artifacts heavily distorted the estimated coherence spectrum and obscured the original patterns in the coherence spectrum. Nevertheless, as demonstrated in Figure 13 (d), the proposed robust method is able to correctly estimate and reconstruct the patterns in the coherence spectrum despite the presence of artifacts. This experiment justifies both the need and effectiveness of the proposed robust method for coherence estimation.

B. Coherence and patient outcome

Experiments were conducted to compare the time-varying generalized partial directed coherence (TV-gPDC) spectra of patients with good and poor outcome. Pairwise coherences among ICP, MAP and PiO2 patients were investigated. Outcomes of the patients were measured with the Glasgow Outcome Scale (GOS). Figures 14 and 15 showcase the TV-gPDC spectra of patient A and B, who did not survive, and Figure 16 shows the TV-gPDC spectra of patient C, who achieved good recovery outcome. We observed that: for patients A and B, there was high connectivity between ICP $\rightarrow$ MAP and MAP $\rightarrow$ PiO2 in the frequency regions around 0.01 Hz; however, this connectivity does not exit in patient C. We suspect that strong coherence observed in patient A and B may suggest ineffective autoregulations, which eventually lead to poor outcomes. Moreover, the detected oscillations around 0.01 Hz may also indicate the presence of a B-wave (around 0.5-2 cycle/minute [63]), which were found to indicate the failing intracranial compensation [64].

C. Linear and nonlinear coherence

In current practices, cerebrovascular autoregulation is commonly assessed based on the pressure-reactivity index (PRx), which is defined as a sliding window linear correlation between the ICP and MAP signals. Our proposed method has the advantage that it enables the simultaneous monitoring of the linear and nonlinear coherences between ICP and MAP. Figure 17 shows two examples that compare the linear and nonlinear MAP $\rightarrow$ ICP coherences. We observed that, over certain regions (e.g. second half of Figure 17 (a) and first half of (b)), the estimated linear and nonlinear coherences align closely. At the same time, there are regions (first half of Figure 17 (a) and second half of (b)), where almost no linear coherence existed but a significant nonlinear coherence was observed. This suggests that there are nonlinear correlations between neurophysiological signals that will not be captured by any linear coherence measure. Therefore, it may
be worthwhile to further investigate how estimation of non-linear coherences may help to better measure cerebrovascular autoregulation.

VI. DISCUSSION

This Section provides a brief discussion on a selection of parameters of the Kalman filter, as well as a description of the findings and limitations of the presented TBI study.

A. Discussion of the Method

The update coefficient $\lambda$ plays a role in how fast the Kalman filter algorithm adapts to statistical changes of the signal, as it controls the memory of the adaptive algorithm. By increasing $\lambda$, the filter will adapt quicker to the signal and the general accuracy of the estimated signal is increased. On the other hand a small value of $\lambda$ can increase robustness against long bursts of outliers. Thus, the determination of $\lambda$ is a trade-off between adaptation speed and robustness.

Another parameter to adjust the robustness of the Kalman filter is the length of the signal window $L$ to estimate a robust mean in (26) and (25) and to estimate a robust standard deviation in (27) and (28). As longer windows incorporate more samples, the estimate improves for stationary (or very slowly varying) signals. For highly non-stationary signals, this parameter should not be too large, so that it captures the quickly varying temporary characteristics. In this work, the window length is chosen to be $L = \max(P, 50)$.

B. Findings and Limitations of the TBI Case Study

We observed that the proposed method is robust against artifacts and outliers in the TBI data and is capable to correct the influence from artifacts and reconstruct patterns in the coherence spectrum. We also demonstrated that the proposed method can simultaneously capture linear and nonlinear coherences between neurophysiological time series signals, which may offer additional information to allow better understanding of patients’ cerebrovascular autoregulation status. Moreover, significant patterns were observed in the coherence spectrum that may act as new biomarkers to differentiate patients with good and poor outcomes.

A limitation of the case study is its small cohort size. Therefore, we did not aim to conclude any clinical findings through the study. The case study aimed at demonstrating the
capabilities and limitations of the proposed method as a new and effective tool to explore coherence spaces that were not studied before. Some interesting observations were discovered, which can inspire more comprehensive and systematic clinical studies for further investigations.

VII. CONCLUSION

A new robust time-varying generalized partial directed coherence (rTV-gPDC) measure was proposed. Robustness against artifacts was incorporated via a computationally simple one-step reweighting step in a Kalman filter. We further extended the rTV-gPDC to nonlinear causality patterns to reveal nonlinear relations between multivariate time series. We evaluated our method numerically both in terms of accuracy and robustness and compared it to an existing method. We applied our method to real life multivariate time series from traumatic brain injuries patients to showcase its potential clinical applications. Since restrictive assumptions on the stationarity of the signals and the linearity of their relationship were relaxed, and robustness against artifacts incorporated via a computationally simple manner, the rTV-gPDC is potentially a good candidate to analyze a broad range of signals.

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