Causality detection in cortical seizure dynamics using cross-dynamical delay differential analysis

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ABSTRACT
Most natural systems, including the brain, are highly nonlinear and complex, and determining information flow among the components that make up these dynamic systems is challenging. One such example is identifying abnormal causal interactions among different brain areas that give rise to epileptic activities. Here, we introduce cross-dynamical delay differential analysis, an extension of delay differential analysis, as a tool to establish causal relationships from time series signals. Our method can infer causality from short time series signals as well as in the presence of noise. Furthermore, we can determine the onset of generalized synchronization directly from time series data, without having to consult the underlying equations. We first validate our method on simulated datasets from coupled dynamical systems and apply the method to intracranial electroencephalography data obtained from epilepsy patients to better characterize large-scale information flow during epilepsy.

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Establishing and detecting information flow in a complex system with many interacting components is challenging yet crucial for many scientific fields. Currently available methods for inferring directionality and causality from observed time series signals are often limited by the number of data required and computational processing time. In this study, we present an efficient and accurate method for measuring causal interaction. We demonstrate that our method, cross-dynamical delay differential analysis (CD-DDA), can estimate the magnitude and direction of information flow in simulated datasets accurately. Furthermore, we applied our method to brain signals obtained from epilepsy patients to characterize previously unidentified seizure-related information flow.

I. INTRODUCTION
Determination of causality and direction of information flow is fundamental to various fields of science, from neuroscience to climate research. In neuroscience, for example, information flow and the nonlinear dynamical causal architecture in brain electroencephalography (EEG) data are important for understanding and predicting events (e.g., seizures). Various regions in the brain might be causally connected even if the data from those regions do not show strong correlations. This might be due to the spatiotemporal nonstationarity of the system.

As pointed out by Yule in 1926, correlation does not imply causation. Yule also made a connection between the introduction of delays and causal relations between time series. In 1969, Granger introduced a statistical measure of causality that is widely used in signal processing. This work is closely related to the work of Wiener, which was published in 1956. Since Granger causality (GC) relies on linear autoregressive models, it may not yield good results for some nonlinear systems. To circumvent the limitations of the linear Granger causality test, Brock et al. proposed a test based on correlation integrals and Baek and Brock. Hiemstra and Jones, and Bai et al. and then introduced nonlinear Granger causality. In 2000, Schreiber introduced transfer entropy for information transfer between nonlinear dynamical systems. If the systems are linear Gaussian processes, GC and transfer entropy are equivalent. Determining causality from dynamical attractors of nonlinear dynamical systems...
and the concept of generalized synchronization (GS) were introduced by Schiff et al., Arnhold et al., Hirata et al., and Sugihara et al., among others. One implementation is Sugihara’s convergent cross-mapping (CCM). CCM is based on standard uniform delay embeddings and is, therefore, limited to a subset of the dynamical systems found in nature. In 2018, a focus issue in Chaos was published that summarizes recent developments for causality detection.

Recent articles used complex network theory to characterize causality of multivariate data.

Here, we determine causality through nonlinear, nonuniform, functional embeddings as an extension of delay differential analysis (DDA) and call this method cross-dynamical DDA (CD-DDA). We first test CD-DDA on simulated data from coupled dynamical systems found in nature. In 2018, a focus issue in Chaos was published that summarizes recent developments for causality detection.

II. DETECTING CAUSALITY USING DELAY DIFFERENTIAL ANALYSIS (DDA)

DDA combines differential embeddings with linear and nonuniform functional delay embeddings to relate the current derivatives of a system to the current and past values of the system variables. Inspired by Max Planck’s “natural units,” the DDA model maps experimental data onto a set of natural embedding coordinates.

The general nonlinear DDA model is

$$\tilde{u} = \sum_{i=1}^{I} a_i \prod_{n=1}^{N} \tau_{n,i}^m + \rho_u = \mathcal{F}_u + \rho_u$$  \hspace{1cm} (1)

for \( \tau_{n,i} \in \mathbb{N}_0 \), where \( N \) is the number of delays (usually 2), \( I \) is the number of terms (typically around 3), and \( u_{n,i} = u(t - \tau_{n,i}) \), relating the signal derivative \( \tilde{u} \) to the signal nonuniformly shifted in time. We then use the coefficients \( a_i \) and the least square error \( \rho_u \) as features. Note that we explicitly added \( \rho_u \) to highlight its use in the causal DDA measure introduced below. To restrict complexity of the DDA model, most of the terms in Eq. (1) are set to zero. We, therefore, consider here DDA models with two delays \( \tau_{n,i} \), three terms, and a degree \( \sum_{i,j} m_{n,j} \leq 4 \) of nonlinearity.

To put DDA in context, a general nonlinear, real-valued function can be expressed in a Taylor series expansion of functionals of increasing complexity around some fixed point. When the function \( F(*) \) represents the behavior of a dynamical system, that is, a time series model where the input is formed from past inputs \( [u(t), u(t - \tau_{1}), \ldots] \), the expansion becomes a Volterra series. We have

\[
\tilde{u} = u_0 + \sum_{i=0}^{\infty} \sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} g_{i_1,i_2} u_{i_1} u_{i_2} + \cdots + \sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} \cdots \sum_{i_q=0}^{\infty} g_{i_1,i_2,\ldots,i_q} u_{i_1} u_{i_2} \cdots u_{i_q},
\]

with the linear and nonlinear data components modeled as separate model terms. To find a model that is a projection onto a stable manifold, we consider low-order models composed of a finite number of leading terms in Eq. (2), such as Eq. (1). This makes CD-DDA different to GC since we use (1) a derivative on the left side of the equation instead of the time series itself in GC, (2) nonuniform functional embeddings on the right side of the equation that were selected from the data instead of uniform linear embeddings of lags 1, 2, ... in GC, (3) two delays instead of a chain of around 10–15 delays in GC, and (4) three term models that are selected to fit each time series instead of around 15 general terms.

To be more explicit, let us give an example. A typical DDA model for the analysis of EEG and intracranial EEG (iEEG) data is the three term model [all \( a_i \) in Eq. (1) except three are set to zero]:

\[
u = a_1 u_1 + a_2 u_2 + a_3 u_3^2 + \rho_u, \hspace{1cm} (3)
\]

where \( u(t) \) is the time series from one EEG channel and \( u_i = u(t - \tau_i) \). The derivative on the left side is computed using a 5-point center derivative algorithm. The coefficients \( a_i \) are estimated with numerical singular value decomposition (SVD) to minimize the least square error. The DDA model that best fits the overall dynamical properties of the system [e.g., (3) for EEG data] can be found by supervised (maximizing the classification performance) or unsupervised (minimizing the least square error \( \rho \) ) structure selection from a list of candidate models (see, e.g., Refs. 18 and 17).

DDA is a nonlinear data analysis framework that (1) uses unprocessed data so as not to disturb the nonlinear properties of the data, (2) uses sparse models that match the macroscopic architecture of the underlying dynamical system, (3) disregards amplitude information to concentrate on the dynamical aspects of the data, and (4) can be extended for detection of dynamical causality in the data to understand information flow in the system. Previously, it has been demonstrated that DDA captures essential features of data to produce exceptional classification performance.

Let us consider two dynamical systems from which the time series \( u(t) \) and \( v(t) \) are measured, respectively. In order to consider whether there is a causal interaction between these two time series, we start by looking for a model

\[
u = F_u + \rho_u, \hspace{1cm} (4)
\]

minimizing the error for the time series \( u \). We also minimize the error for \( v(t) \) and get

\[\dot{v} = F_v + \rho_v, \hspace{1cm} (5)\]

If we assume, for example, a unidirectional causal influence of \( u(t) \) on \( v(t) \),

\[\dot{u} = F_u + F_v + \rho_{uv}, \hspace{1cm} (6)\]

the errors \( \rho_u \) and \( \rho_{uv} \) should be similar since the coefficients of \( F_v \) are irrelevant. In contrast, for

\[\dot{v} = F_v + F_u + \rho_{vu}, \hspace{1cm} (7)\]

the errors \( \rho_v \) and \( \rho_{vu} \) are different.
We then define \( C_{uv} \) as our CD-DDA measure of the causal influence of \( v(t) \) on \( u(t) \) and \( C_{wu} \) for a causal influence of \( u(t) \) on \( v(t) \),

\[
C_{uv} = |\rho_u - \rho_{uv}|; \quad C_{wu} = |\rho_v - \rho_{wu}|. \tag{8}
\]

We additionally use the significance \( \mu \), where \( \mu \) is the mean and \( \sigma \) is the standard deviation, of the estimated coefficients of the terms \( F_u \) in Eq. (6) and \( F_v \) in Eq. (7) to estimate the synchronization level, \( S \).

### III. APPLICATIONS TO SIMULATED DATA

To test CD-DDA, we generate simulated data from coupled Rössler\(^1\) and Lorenz\(^2\) systems. The first example was previously studied in Ref. 24 and is an autonomous, chaotic Rössler system driving a periodic Rössler system. Our second simulated example is a Rössler system driving a Lorenz system. For the coupled Rössler system, the functions \( F_u \) and \( F_v \) are the same. For the coupled Rössler and Lorenz system, we need to select individual functions \( F_u \) and \( F_v \) since these two systems are dynamically different.

We compared our measure with linear Granger causality,\(^9\) transfer entropy or conditional mutual information,\(^7\) and convergent cross-mapping\(^4\) for a chaotic Rössler system driving a periodic Rössler system and for a Rössler system driving a Lorenz system. Our measure performed as well or better than the other three measures for both of these systems, and we report these findings in Figs. 2 and 4 in the supplementary material.

#### A. Chaotic Rössler system driving a periodic Rössler system

In this example, we unidirectionally couple two Rössler systems, where the driving system \( R_1 \) is chaotic and the driven system \( R_2 \) is periodic\(^4\)

\[
\begin{align*}
R_1 & \quad \dot{x}_1 = -\omega_1 y_1 - z_1, \\
& \quad \dot{y}_1 = x_1 + a y_1, \\
& \quad \dot{z}_1 = b + z_1(x_1 - c), \\
R_2 & \quad \dot{x}_2 = -\omega_2 y_2 - z_2 + \epsilon (x_1 - x_2), \\
& \quad \dot{y}_2 = x_2 + a y_2, \\
& \quad \dot{z}_2 = b + z_2(x_2 - c),
\end{align*}
\tag{9}
\]

with \( a = 0.15 \), \( \omega_1^2 = 1.015 \), \( \omega_2^2 = 0.985 \), \( b = 0.2 \), and \( c = 10 \). We modified the system in Ref. 24 to the system above as explained in the Appendix. The coupling strength \( \epsilon \) was varied between 0 and 0.25 using 30,000 linearly spaced steps. The integration step size was set to 0.05 with a transient of \( 10^5 \) time points discarded. The remaining data were downsampled by a factor of 2 resulting in \( 10^3 \) data points for each coupling strength.

We selected the DDA models by minimizing the model error \( \rho_u \) from \( u = x_1 \) or \( u = x_2 \) and get

\[
F_u = a_1 u_1 + a_2 u_2 + a_3 u_3^3, \tag{10}
\]

with \( u_i = u(t - t_i), \) \( t_1 = 32 \delta t, \) \( t_2 = 9 \delta t, \) and \( \delta t = 0.025. \)

We calculated \( C_{uv} \) and \( C_{wu} \) for \( u = x_1 \) and \( v = x_2 \) in sliding windows (window duration 3000 \( \delta t \) or 50 pseudoperiods, window shift 1000 \( \delta t \)) and show these results in Fig. 1 (middle panel).

Each coupling strength displays \( C_{uv} \) for all time windows in the direction of \( u = x_1 \) to \( v = x_2 \) (blue dots) and \( C_{wu} \) in the direction of \( v \) to \( u \) to (red dots). \( C_{uv} \) increases with increasing coupling strength while \( C_{wu} \) remains close to zero and begins to increase around the

---

**FIG. 1.** Pearson correlation \( r \) between response system components \( x_2 \) (system \( R_2 \)) and \( x_1 \) (system \( R_1 \)) for determining the onset of synchronization (dashed line) between \( R_1 \) and \( R_2 \) (upper panel). Cross-dynamical measures for a driven periodic Rössler system by a chaotic Rössler system across coupling strength, \( \epsilon \). For each coupling strength, 97 time windows are plotted as dots. Blue dots indicate chaotic driving periodic (\( C_{uv} \)), and red dots periodic driving chaotic (\( C_{wu} \)) (middle panel). The average across time windows for each coupling strength is overlaid in cyan and orange. Pearson correlation between \( C_{uv} \) across time windows for \( \epsilon_k \) and \( \epsilon_{k+1} \) in red and for \( C_{wu} \) in blue. Both values converge to one after the onset of generalized synchronization.
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We are able to recover the correct direction of causal inference for coupling between 0.05 and 0.15 for the longer (Fig. 1, middle window lengths. We call this our measure of synchronization, $S$, of the three DDA parameters that shows the greatest difference across synchronized, then there is a map between trajectories on the driving attractor and trajectories on the response attractor.\(^2\) The auxiliary systems approach requires introducing a second response system $R$, with the variables $(x_v, y_v, z_v)$ that is identical to $R$, except for initial conditions. To determine the onset of synchronization between $R_1$ and $R_2$, we see when the two driven response systems undergo complete synchronization or when the Pearson correlation between $x_2$ and $x_3$ is 1 (Fig. 1, upper panel). We can also estimate the onset of generalized synchronization by correlating $C_w$ for $\epsilon_k$ with $\epsilon_{k-1}$ across all time windows, and doing the same for $C_x$ (Fig. 1, lower panel). After the onset of synchronization, neighboring $\epsilon$ values share the same synchronized manifold, whereas before, neighboring $\epsilon$ values follow distinct driven attractors.

In Fig. 2 (left panel), we investigate the effect of short time windows (see also Fig. S1 in the supplementary material). While the main effect of $C_w$ remains for even just five pseudoperiods, we also see $C_x$ unexpectedly increase before the onset of generalized synchronization.

In Fig. 2 (right panel), we show the onset of generalized synchronization in a purely data driven manner: first, we estimate the significances for the three additional, cross DDA parameters of $F_x$ and $F_y$ in Eqs. (6) and (7). Then, we recalculate the significance measures for two slightly different window lengths (300 ± 20 \(\delta t\)). When the two time series $u$ and $v$ are not synchronized, trajectories on the driving and driven attractors are unrelated, and different window lengths will yield similar significance measures. If the time series are synchronized, then there is a map between trajectories on the driving and driven attractors, and measures of significance will be sensitive to window length. To assess synchronization, we take the maximum of the three DDA parameters that shows the greatest difference across window lengths. We call this our measure of synchronization, $S$.

We are able to recover the correct direction of causal inference for coupling between 0.05 and 0.15 for the longer (Fig. 1, middle panel) and shorter (Fig. 2, left panel) data windows, as well as after adding 20 dB noise (see Fig. S1 in the supplementary material).

B. Rössler system driving Lorenz system

In this example, we unidirectionally drove a Lorenz system $L$ with a Rössler system $R$:\(^3\)

$$
\begin{align*}
\dot{x}_1 &= -\alpha(y_1 + z_1), \\
\dot{y}_1 &= \alpha(x_1 + ay_1), \\
\dot{z}_1 &= \alpha(b + z_1(x_1 + c)), \\
\dot{x}_2 &= \sigma(-x_2 + y_2), \\
\dot{y}_2 &= Rx_2 - y_2 - x_2z_2 + \epsilon y_1^3, \\
\dot{z}_2 &= x_2y_2 + \beta z_2,
\end{align*}
$$

where $a = b = 0.2$, $c = -5.7$, $\sigma = 10$, $R = 28$, and $\beta = -8/3$. 

 FIG. 2. Effect of short time windows: the left plot shows the CD-DDA causality measures $C_x$ and $C_w (a = x_v, v = x_j)$ for system (9) for a window length of 300 \(\delta t\), or 5 pseudoperiods. This plot can be compared to the middle panel in Fig. 1. The right plots show our synchronization measure or significances $S_w$ and $S_w$ for the maximum of the additional three DDA parameters.

 FIG. 3. Pearson correlation $r$ between response system components $y_2$ (system $L$) and $y_1$ (system $L_2$) for determining onset of synchronization between $R$ and $L$. Cross-dynamical measures for a driven chaotic Lorenz system by a chaotic Rössler system across coupling strength, $\epsilon$. For each coupling strength, $C$ for 97 time windows are plotted as dots. Blue dots indicate $u = y_1$, driving $v = y_2 (C_w)$, and red dots denote $v$ driving $u (C_u)$. The average across time windows for each coupling strength is overlaid in cyan and orange.
α adjusts the timescale of the Rössler system to match that of the Lorenz and is set to 6. We varied the coupling strength, $\epsilon$, between 0 and 6 over 1000 linearly spaced values. We implemented an integration step size of 0.01, removed a transient of length 10 pseudoperiods, and we have estimated to be $\epsilon = 2.2$ using the auxiliary systems approach. We also show in Fig. 3 lower panel the onset of synchronization by correlating $C$ across time windows between $\epsilon_{\text{on}}$ and $\epsilon_{\text{off}}$. We can also recover the correct direction of causal inference using significantly less data, that is, using 300 $\delta t$ instead of 3000 $\delta t$, shown in the left panel of Fig. 4. Furthermore, we can also estimate the onset of synchronization with $S_{\text{on}}$ and $S_{\text{off}}$ as shown in the right panel of Fig. 4. Notably, $S_{\text{on}}$ in red goes up near the estimated onset of synchronization determined in Fig. 3. Overall, $C$ determines the correct direction of causal inference for no noise and 20dB noise (see Fig. S3 in the supplementary material).

IV. DETECTING CAUSALITY IN EPILEPTIC SEIZURES

In Ref. 17, a genetic algorithm (GA) was used to select the model with minimum error from one second data segments for one hour periods centered on the seizure onset times. Around one million such
data segments (155 seizures, 730 iEEG channels from 13 patients) were analyzed in this way. The patient demographics and characteristics are described in Ref. 17. The DDA model selected in Ref. 17 for the characterization of epileptic seizures is

\[ \dot{u} = a_1 u_1 + a_2 u_2 + a_3 u_3 + \rho u = F u + \rho u, \]

with \( u_i = u(t - \tau_i) \).

Model (13) bifurcates at the seizure onset, as shown in Ref. 17: it has a low error after seizure onset, but not before. This DDA model will be used in the remainder of this section.

In Ref. 17, eight delays were chosen to characterize and segment the data using truncated higher order SVD. In this paper, we only use the delay pair \( \tau = (7, 10) \delta t \), where \( \delta t = \frac{1}{f_s} \) with the sampling rate \( f_s = 500 \text{ Hz} \) since this delay pair proved to be sufficient for the characterization of epileptic seizures.

In Fig. 5, the coefficient \( a_1 \) from Eq. (13) is shown for 113 channels. The onset channels are marked with stars on the \( y \)-axis. As discussed in Ref. 17, these plots can be used to localize the seizure onset region in the brain.

We can extend this analysis to CD-DDA to determine the information flow patterns during seizures. \( F_u \) and \( F_v \) are the same model as Eq. (13) since all data are iEEG data. \( u(t) \) and \( v(t) \) are recordings from two different channels. Each channel is paired with all other channels and the information received and sent is computed for each pair.

The same seizure in Fig. 5 is shown in Fig. 6, where we show information received from all other channels (upper panels) and information sent to all other channels (lower panels) for an example onset channel (a) and for an example nononset channel (b). Figure 7 zooms into the time around seizure onset. While both channels send information to another onset channel marked with a magenta arrow just before the seizure starts, only the onset channel subsequently receives information from the majority of channels at the time of the seizure. This patient has one evoked seizure, five fully developed spontaneous seizures (first of these seizures is shown in Figs. 5–7).
and one nonfully developed seizure. In the supplementary material, we show \( C \) for all seizures as well as for stimulations. All spontaneous seizures except the nonfully developed one show the same signature, where the onset channel receives a large response from a majority of channels once the seizure starts. The last seizure, seizure 6, is different because the response from the nononset channels is too weak to keep the seizure developing.

In Fig. 8, the CD-DDA feature \( C_{uv} \) from Fig. 6 at the peak in the upper panels (around 10 s after marked onset) is mapped onto a grid (right panel) that was derived from the channel locations in the clinical report (left panel). Details and exact channel locations can be found in Ref. 17 (Patient 1). The circles denote the clinically marked onset channels. It is obvious that the region around the onset channels is sending most of the information (see also Fig. 7, magenta arrows). To investigate that further, we plotted such a grid for each sliding data window, where the window length is a quarter of a second and the window shift is half that length. Figure 9 shows such a time line for the CD-DDA feature \( C_{uv} \) from Fig. 6 and the classical DDA feature \( a_i \) from Fig. 5. CD-DDA not only shows the start of the seizure earlier but also shows a constant information flow from the onset regions. Classical DDA, on the other hand, shows the generalization of the seizure and the involvement of the whole brain after seizure generalization.

V. CONCLUSION

We have developed a new tool for studying causality called CD-DDA and tested it on simulated data from dynamical systems and then further applied this technique to epileptic seizure data. Using CD-DDA, we can recover the direction of causal interaction between unidirectionally coupled systems with small parameter mismatch as well as nonequivalent systems, even with short time series and in the presence of noise (see supplementary material). Furthermore, CD-DDA can detect the onset of generalized synchronization (GS).

We have also shown that CD-DDA provides a useful measure of information flow in the brains of human patients experiencing seizures. By computing \( C \) for both directions for each channel, we can identify the channels that seem to be sending out information around the time of seizure onset. These channels match up well to the clinically determined onset channels. Future work will explore further applications of CD-DDA to brain data.

SUPPLEMENTARY MATERIAL

In the supplementary material, we present CD-DDA results for the simulated data from the Rössler and Lorenz systems in Sec. III for different window lengths and added white noise with a signal-to-noise ratio of SNR = 20 dB. We further show for the epilepsy patient of Sec. IV the CD-DDA outputs for 160 hours of data and plots around each of the seven seizures (from 30 s before to 2 min after seizure onset) as well as a plot for a stimulation.

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APPENDIX: EQUIVALENT RÖSSLER SYSTEMS

To remove the confusion of interpreting \( \omega \) as a time scaling factor, we changed the Rössler system in Ref. 24 from

\[
\dot{x} = -\Omega y - z, \\
\dot{y} = \Omega x + ay, \\
\dot{z} = b + z|x - c|
\]

(A1)

to

\[
\dot{x} = -\omega y - z, \\
\dot{y} = x + ay, \\
\dot{z} = b + z(x - c),
\]

(A2)

with \( \omega = \Omega^2 \). Both systems are exactly the same up to a scaling \( y \to \Omega y \) of the \( y \)-component in the second system. As shown in Ref. 16, \( \omega \) is one of the four possible bifurcation parameters of the Rössler system \(^{26}\) since it can be written as

\[
\dot{x} = -\frac{1}{2}y - \frac{1}{2}x + \frac{1}{2}z, \\
\dot{y} = bx + ay, \\
\dot{z} = c - cz + Kxz.
\]

(A3)

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