SYNCHRONIZATION, VARIABILITY, AND NONLINEARITY
ANALYSIS: APPLICATIONS TO PHYSIOLOGICAL TIME SERIES

by

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Synchronization, Variability, and Nonlinearity Analysis:
Applications to Physiological Time Series

Abstract

by

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In this thesis, we study synchronization, variability, nonlinearity analysis and their applications in physiological time series. For synchronization analysis, we explore both intensity and directionality of interaction. We propose a computational method to specify frequency ratio $n : m$, detect the moment when the frequency ratio changes, and also propose a novel method to measure the intensity of synchronization in $n : m$ coupled system. Our method involves circular Poincaré analysis of stroboscope and circular change point detection techniques. It is used to quantify interaction between respiration and ventilator recorded from lung injured rats. For directionality of coupling, we study Fourier series estimation approach and information-theoretic approach. We learn that Fourier series estimation approach is not practical because it is unknown how to automatically select an appropriate data segment for the estimation process. On the other hand, we show that the information theory approach simplifies the process of selecting a data segment to compute directionality of coupling. Therefore, it is appropriate for the physiological time series. The last topic in synchronization analysis is the study of neurodevelopment in neonates by evaluating synchronization in the EEG recorded from different regions of the brain. The result suggests that synchronization can be used to distinguish infants with different gestational ages. Specifically, based on intensity of synchronization in EEG, the late
preterm group is more similar to the fullterm group than the mid preterm group. For the variability analysis, we propose a novel method to quantify heart rate variability (HRV) in ventilated rats after lung injury. We discover that periodicity of R-R interval is a key to distinguish difference of HRV in two ventilation groups. For nonlinearity analysis, we attempt to distinguish a nonlinear dynamical system from nonlinear transformation of a linear system. We investigate a nonlinear detection technique based on IAAFT surrogate and realize that its performance depends on both degree of nonlinearity of the transformation functions and nonlinear measures. Finally, we propose a novel technique to be used together with Barahona prediction method to fully distinguish various nonlinear schemes. Our method is based on residual analysis of a Volterra-Wiener-Korenberg model.
Chapter 1

Introduction

Physiological time series data encompass signals that are measured from living systems. Examples of physiological time series include cardiac rhythms (electrocardiogram or ECG), brain waves (electroencephalography or EEG), body temperature, oxygen saturation, respiration, eye movements (electro-oculogram or EOG), muscle activity (electromyogram or EMG), etc. Digital signal processing techniques have been used for the analysis of physiological time series data to improve our understanding of the living systems that generate the time series data as well as the interactions between various systems in both health and disease. There are numerous examples of physiological time series analysis that have attracted the attention of clinicians, research scientists, and engineers. Some examples include the detection and prediction of epileptic seizures and sleep apnea, variability analysis of heart rate, and the study of the cardiorespiratory interaction related to some clinical pathology.

Applying digital signal processing in the application of physiological time series is a challenging task. Each physiological data usually requires special methods or procedures in order to answer specific research and clinical questions. Hence, the study of physiological time series data naturally involves multidisciplinary team research, where engineers, scientists and clinicians are working collaboratively to acquire the necessary data, develops methods for data analysis, and interpret the results of the data analysis.
In this thesis, we explore three aspects of dynamical systems that are relevant to the study of physiological time series: synchronization, variability, and nonlinearity. The main topic of investigation involves the study of synchronization between multiple physiological systems from measured times series data and includes quantifying both the intensity and directionality of the synchronization. The analysis of variability is then applied to the study of heart rate variability in a rat after lung injury is induced. We are also interested in distinguishing different types of variability, e.g. variability that is the result of purely stochastic fluctuations or on the contrary, the direct result of nonlinear dynamic interactions in the system. The thesis is organized as follows.

Chapter 2 focuses on the detection of high-order synchronization in periodic oscillators by an external force. The basic concepts of synchronization are discussed and then a novel method to detect \( n : m \) phase synchronization when the frequency ratio \( n : m \) varies is proposed. The idea behind our algorithm involves using a stroboscope of Poincaré plot and change point detection in circular data. We apply this method to study interaction between respiration and ventilation. We also show an example of frequency locking phenomena between heart rate and respiration, as well as between heart rate and ventilation in a rat model.

In physiological applications, both the intensity and direction of interaction are important. Chapter 3, we attempt to find a proper method to quantify directionality of coupling in physiological time series. We compare two approaches for measuring the directionality of coupling. These methods are based on Fourier series estimation and information theory. The mathematical background of each method and the test results with a simulated coupling system are given. Then we select the approach that provides the most consistent and meaningful results to determine the directionality of cardiorespiratory coupling in the same model that was used in Chapter 2.

We present another application of synchronization analysis based on the phase synchronization in chaotic oscillator in Chapter 4. This application is the study of neurodevelopment in neonates by examining the synchronization in EEG measured from different regions of the brain. The objectives is to distinguish mid preterm...
infants from full term infants using measured EEG during sleep and also to further classify late preterm infants into either the mid preterm or the full term group using the intensity of the synchronization.

Heart rate variability analysis (HRV) is a study of the variability of the intervals between consecutive heart beats (R-R intervals) detected from an ECG. HRV can be used to assess the status of a variety of clinical diseases. In chapter 5, we compare HRV of lung injured rats in two mechanical ventilation groups. A key to distinguish HRV in the two groups is the periodicity of their RR interval. We propose a novel method to measure periodicity by examining power spectrum and autocorrelation plot. This method is compared to other more traditional measures of HRV to determine it’s potential use in clinical decision-making.

From the early days of developing methods that can detect complexity in time series data, an important question has been the detection of nonlinearity in time series data. Have an understanding of the nonlinear structure of a system is essential in the modeling process and for interpreting the results of time series analysis. In physiological applications, for example, we would like to know whether the system that generates a time series is linear or nonlinear so that we can choose a proper technique to analyze the signal. Therefore, in the final chapter of this thesis, we study how to classify different nonlinear structures from times series data. The objective is to distinguish time series generated from a nonlinear stochastic system from those generated from a linear stochastic system with different (memoryless) nonlinear transformations on the inputs and outputs. We investigate a few nonlinear detection approaches such as time reversibility, surrogate data, and prediction methods. We test these methods with synthetic time series and explore their limitations and pitfalls. Finally we present a computational procedure for classifying different nonlinear structures, and demonstrate its performance on synthetic data.
Chapter 2

High order synchronization in periodic oscillators

Synchronization is an adjustment of rhythms of oscillating objects due to their weak interaction or coupling. Synchronization phenomenon is abundant in science, nature, engineering and social systems. Examples of synchronous systems are clocks, singing crickets, cardiac pacemakers, firing neurons and applauding audiences. These phenomena are universal and can be understood within a common framework based on modern nonlinear dynamics. Synchronization of nonlinear periodic systems was first discovered by Huygens in 1673, who noticed that two pendulum clocks that hang on the same wall can synchronize [1].

Generally physiologic systems interact rather function independently, thus synchronization in physiologic systems may reflect coordination between systems. Therefore, developing a deeper understanding of the different types of interaction that can occur and how the strength of these interactions change related to different physiological events, including transitions from health to disease, is beneficial. Examples of systems that are known to operate in variations states of synchronize are cardiac pacemakers, firing neurons, the cardiorespiratory system, and the respiratory system driven by a mechanical ventilator.

When the synchronization occur at different frequencies or $n : m$ synchronization
where \( n : m \) is the ratio of the frequencies of two oscillators, it is necessary to know the frequency ratio \( n : m \) to compute the intensity of synchronization. In addition, in real application, the frequency ratio tends to vary, for example from \( n : m \) to \((n + 1) : m\), due to the variability in the systems. Therefore, detection of changes of frequency ratio is also required. The objective of this chapter is to be able to computationally determine frequency ratio \( n \) and \( m \) and to automatically detect the moment when the ratio changes.

We organize this chapter as follows. First, we summarize the basic concepts of the mechanism of synchronization process. Then, a visualization method is presented following with our computational method. Next, we propose a proper method for quantifying synchronization index in this type of coupling systems. Finally, we apply this method to an experimental animal model to investigate the relationship between patterns of respiration and ventilation. We also show an example of frequency locking phenomena between heart rate and respiration, as well as between heart rate and ventilation patterns.

2.1 Basic concepts of synchronization

The concepts of synchronization are presented by Pikovsky et al. [1] in the book entitled *Synchronization: A universal concept in nonlinear sciences*. In this section, we summarize some of the important concepts related to our work.

2.1.1 Definitions

Oscillators can be synchronized by an external force if there is weak interaction or coupling between the two systems. To study the characteristic of the synchronization, we use a self-sustained oscillator as the model of the oscillating object. The self-sustained oscillator is a dynamic system that dynamically transfers internal energy (e.g., between kinetic and potential energy) to produces rhythmic motion that can be characterized by period and frequency. An external force is another oscillator or
a sequence of pulses of which the motion is controlled by an external energy source. An example of synchronization for this type of system is the modern watch whose rhythm is determined by a precise quartz oscillator.

Synchronization can be described by the phase or frequency of the oscillators. When an external force is applied to the oscillator, the frequency of the oscillator is adjusted and finally becomes equal or entrained with the frequency of the external force; i.e., $\omega_e = \omega_o$ where $\omega_e$ and $\omega_o$ are the angular frequency of the external force and the oscillator respectively. This state is called frequency locking. Synchronization can also be described by the phase relationship between the oscillations. Phase is a (relative) quantity that can be used to determine the relationship between different periodic oscillations at the same frequency. Phase is angular measure between zero (0) and $2\pi$, and two oscillators are said to be synchronized when the phase difference between the two is bounded; i.e., $|\phi_e - \phi_o| < \text{constant}$ where $\phi_e$ and $\phi_o$ denote the phase of an external force and the oscillator respectively. This state is called phase locking.

**Synchronization region and transition**

The mechanism of synchronization of a periodic oscillator and an external force can be easily described using the synchronization region that shows the relationship of three variables as illustrated in figure 2.1. The variables that are essential to the synchronization process are the strength and frequency of the external force and the fundamental frequency of the oscillator ($\varepsilon$, $\omega_e$, and $\omega_o$, respectively). In the figure on the left, the shaded area is the region where the oscillator is synchronized with an external force. If the strength of an external force $\varepsilon$ is weak, the frequency mismatch between the external force and the oscillator ($\omega_e - \omega_o$) must be small in order that the synchronization is maintained. However, if the strength of an external force is stronger, the frequency mismatch can be larger.

The synchronization region can also be used to describe transition between different states of synchronization. Let $\Delta \phi = \phi_e - \phi_o$ be the phase difference between an
external force and the oscillator. At point 1 where $\omega_e = \omega_o$, $\Delta \phi = 0$ and remains constant as long as the parameters are unchanged as shown in the diagram on the right. At point 2, the systems are still synchronized but $\omega_e > \omega_o$ resulting in a constant but positive phase difference (note that $\Delta \phi < 0$ if $\omega_e < \omega_o$). At the point 3 that is at the border of the synchronization region, the dynamics of the phase difference are intermittent. When the frequency mismatch further increases, the phase difference becomes more and more uniform as occurs at curves 4 and 5.

**High order synchronization**

Synchronization can occur when the frequency of an external force and the oscillator are not equal as shown in figure 2.2. If we fix the amplitude of an external force at a specific level denoted by the dashed line and increase its frequency, synchronization can occur when the frequency ratio of an external force and the oscillator is, for example, one half or one or one and a third or one and a half or two. This is called $n : m$ synchronization where $n$ and $m$ are integers and the regions are called *Arnold tongues*. For example, $2 : 1$ synchronization means one cycle of an external force is
equal to two cycles of the oscillator. Therefore, the condition of frequency locking for $n : m$ synchronization should be changed to $n\omega = m\omega_o$ and the condition of phase locking should be changed to $|n\phi - m\phi_o| < \text{constant}$.

![Diagram of Arnold tongues](image)

Figure 2.2: Arnold tongues or regions of $n : m$ synchronization. This figure is the reprinted version of figure 3.19 (a) in Ref. [1]. Copyright ©A. Pikovsky, M. Rosenblum and J. Kurths 2001. Reprinted with the permission of Cambridge University Press.

**Synchronization in the presence of noise**

Real systems are generally perturbed by noise that can affect synchronization. If the noise is weak and bounded, the phase differences tend to fluctuate but the systems remain synchronized because the state of the system is still in the synchronization region. However, if the noise is unbounded, for example, Gaussian noise, or strong bounded, the system state can escape the synchronization region for a short period of time before returning to the synchronization region again. This phenomenon will cause a phase slip which is a rapid change of the phase difference by $2\pi$. Figure 2.3 shows the effects of the noise on the phase difference.
2.1.2 Measuring degree of synchronization

There are two steps to measure the degree of synchronization. The first step is to extract the phase from the original time series. The second step is to compute the synchronization index, usually defined in the interval [0, 1] using the phase information obtained from the first step.

Phase extraction

As mention earlier, the phase contains information about the state of the oscillator. Phase ranges from zero to $2\pi$ when the oscillator travels from the original point to a full cycle. Computing phase from the pulse trend time series is straightforward using the marked event approach. Let $t_k$ be the sequence times where the oscillator completes a full cycle or any event that occurs once per cycle, for example, the R peak in an ECG signal; the phase is then defined as

$$\phi_{rk} = 2\pi(k - 1)$$  \hspace{1cm} (2.1)

where $k$ is the number of the events or the pulses. Note that the phase is defined only at the time of marked events. The value of the phase increases linearly and is
2π away at the subsequent point. In general, we have to resample the phase using a linear interpolation method if we need the sampling rate of the phase and the original time series to be the same.

Phase can be wrapped in $[0, 2\pi]$ or $[-\pi, \pi]$ interval because phase at $2k\pi = 2\pi$, where $k$ is an integer. In this case, the phase can be computed as

$$
\phi_n = 2\pi \frac{n - n_1}{n_2 - n_1} \tag{2.2}
$$

where $n_1$ and $n_2$ are the time of the marked events before and after $n$. Defining phase this way is convenient because it is easier to have the same sampling rate with the original time series. It is also easy to visualize the sequence of the phase because it is bounded. Figure 2.4(a) shows an example of the phase extracted from ECG signal of a rat.

![Figure 2.4](image)

Figure 2.4: (a) Marked event phase extracted from rat ECG signal. (b) Hilbert phase of a noisy Van der Pol oscillator. The original signals are below and the phases are above.

Another well-known phase extraction approach that is used for narrow band time series is the Hilbert phase transform. The Hilbert transform is based on the analytic signal [2] that is defined as $h_n^x = x_n + jx_n'$, where $x_n$ is the original time series and $x_n'$ is the discrete Hilbert transform [3], defined as

$$
x_n' = \text{DTFT}^{-1} \left[ \text{DTFT} \left[ \frac{1}{\pi x_n} \right] \cdot \text{DTFT} \left[ x_n \right] \right]. \tag{2.3}
$$
The DTFT is the Discrete-Time Fourier Transform, and DTFT\(^{-1}\) is the inverse Discrete-Time Fourier Transform. Finally, the instantaneous phase of the time series \(x\) is arctan \(\left( \frac{x_n'}{x_n} \right)\). Unlike marked event phase, the Hilbert phase does not need to be piecewise linear as shown in figure 2.4(b) on the preceding page. In this example, phase is extracted from the noisy Van der Pol oscillator time series.

\[
\dot{x} = y \\
\dot{y} = 0.02(1 - x^2)y - x + \eta
\]

where \(\eta\) is Gaussian noise with \(\mu = 0\) and \(\sigma = 2\).

**Computing synchronization index**

A couple of methods for computing the phase synchronization index have been widely used. The first method, introduced by Palus [4], measures the dependence between phases using mutual information. Let \(\theta^x\) and \(\theta^y \in [-\pi, \pi]\) be the phase of systems \(x\) and \(y\). Let’s \(p(\theta^x)\) and \(p(\theta^y)\) be the probability density functions of the phases \(\theta^x\) and \(\theta^y\) respectively, and let \(p(\theta^x, \theta^y)\) be their joint probability density function. The mutual information is defined as

\[
MI = -\sum_{i=1}^{M} \sum_{j=1}^{M} p_{i,j}^{\theta^x \theta^y} \log_2 \frac{p_{i,j}^{\theta^x \theta^y}}{p_i^{\theta^x} p_j^{\theta^y}}
\]  

(2.5)

where \(M\) categories were used to partition the data. Here the partition is based on the marginal equiquantization method (each bin has similar probability rather than similar distance as suggested by [4]). If \(\theta^x\) and \(\theta^y\) are independent then \(p^{\theta^x} p^{\theta^y} = p^{\theta^x \theta^y}\) so \(MI = 0\). If they are identical then \(p^{\theta^x} = p^{\theta^y} = p^{\theta^x \theta^y}\) so \(MI > 0\). Mutual information can be normalized to have \([0, 1]\) interval using a method proposed by Su et al. [5].

Because the synchronization index could be a positive number even the two systems are not synchronized, Palus [4] proposed a surrogate test\(^1\) to prevent the spurious

\(^1\)For further information about surrogate method, please refer to chapter 6 on page 66.
detection. The hypothesis is that the surrogate transformation will destroy coupling between two time series. Therefore, the mutual information of the phase of original time series must be higher than that of the surrogate data in order to confirm the presence of synchronization. The method of comparing mutual information of the original and the surrogate time series has been described in Ref. [6].

Based on suggestion of Palus [4], Fourier Transform (FT) surrogate is appropriate for periodic oscillator. FT surrogate preserves the power spectrum of the original time series; therefore, the surrogate time series oscillates at the same frequency as the original time series but the coupling between them has been destroyed. However, generating phase surrogate for the marked event time series such as a sequence of pulses or ECG time series is different. In this case, they suggest performing the shuffle surrogate of the interval data (ex. R-R interval) and then generating new sequence of pulses from the surrogate interval. Then the surrogate phase is generated from the new sequence of pulses. However, if the new interval has high variability, we believe iterated amplitude adjusted Fourier transform (IAAFT) surrogate is better than shuffle surrogate because IAAFT surrogate retains both power spectral density and probability distribution function\(^2\). Therefore, in case of physiological time series such as R-R interval, the IAAFT surrogate would be more similar to physiological time series than the shuffle surrogate.

The second method of computing synchronization index is to measure the variance of the phase difference defined as \(\theta_{xy} = n\theta^x - m\theta^y\). Generally, phase difference is defined in \([-\pi, \pi]\) interval to gain the information of phase lead or lag. Because phase is defined in \(2\pi\) interval, the statistic of circular data introduced by Fisher [7] must be used instead of the general statistical method.

Consider figure 2.5 on the following page which illustrates phase differences on the unit circle. For simplicity, we show only 2 points of phase differences, \(\theta_{xy}^1\) and \(\theta_{xy}^2\). If we project both vectors onto the x and y axes, then we have \(\cos(\theta_{xy}^1)\) on the x axis and \(\sin(\theta_{xy}^1)\) on the y axis (see figure 2.5(a)). Next we compute the mean of

\(^2\)If the interval data has less variability, computation of IAAFT surrogate may not convert.
the projected vectors on both the x and y axes given by
\[ R_x = \sum_{n=1}^{N} \cos(\theta_{n}^{xy}) / N \] and
\[ R_y = \sum_{n=1}^{N} \sin(\theta_{n}^{xy}) / N \] respectively (see figure 2.5(b)). Then, the circular mean of
the phase difference is
\[ \overline{\theta^{xy}} = \arctan \left( \frac{R_y}{R_x} \right) , \] (2.6)
and the circular variance of the phase difference is defined as
\[ CV = 1 - \sqrt{R_x^2 + R_y^2} \] (2.7)
(see figure 2.5(c)). Finally, the index of phase synchronization is defined as \( 1 - CV \), i.e.,
\[ PS = \sqrt{\left( \frac{1}{N} \sum_{n} \sin(\theta_{n}^{xy}) \right)^2 + \left( \frac{1}{N} \sum_{n} \cos(\theta_{n}^{xy}) \right)^2} \] (2.8)

It can be observed that if two systems are synchronized, \( \theta_{n}^{xy} \approx \phi \) for all \( n \), then
the circular variance is very small hence \( PS \approx 1 \). On the other hand, if the systems
are not synchronized, the phase difference uniformly increases in the \([-\pi, \pi]\) interval,
therefore, the circular variance is almost one so that \( PS \approx 0 \). It is essential to
emphasize that the circular variance of uncoupled systems does not need to be 1,
i.e., \( PS > 0 \). Therefore, the surrogate method must also be used as in the mutual
information approach.

![Figure 2.5: The steps of computing basic circular statistic.](image)
2.1.3 Example: Forced Van der Pol oscillator

Let us show an example of synchronization of a noisy Van der Pol oscillator and a sinusoidal signal. The forced Van der Pol is defined as

\[
\begin{align*}
\frac{dx}{dt} &= y(t) \\
\frac{dy}{dt} &= 0.02 \left(1 - x(t)^2\right) y(t) - w^2 x(t) + \varepsilon \sin(v t) + \eta(\mu, \sigma),
\end{align*}
\]

(2.9)

where \(v\) and \(\varepsilon\) are the frequency and amplitude of the sinusoidal signal. \(w\) is the frequency of the Van der Pol oscillator. \(\eta(\mu, \sigma)\) is Gaussian white noise with mean \(\mu = 0\) and standard deviation \(\sigma = 0.1\).

In the first example we show the phase difference when the synchronization state changes from inside to outside of the synchronization region by changing the frequency of the sinusoidal signal but keeping its amplitude unchanged. We set \(\varepsilon = 0.1\), \(w = 3/2\).

Initially, we set \(v = 1\) to be in the synchronization region and obtain 3 : 2 synchronization scheme. The phase difference is shown in figure 2.6(a) on the next page. We present the phase difference \((\theta_{xy} = 3 \times \theta_x - 2 \times \theta_y)\) in three formats in figure 2.6. On the left, we plot the phase difference against time; on the right we plot it on the unit circle so that time information is not included. We also plot the circular histogram inside the unit circle to show the distribution of the phase differences that fluctuate around \(\pi/2\). When we increase the frequency of the sinusoidal signal to \(v = 1.005\), the synchronization state moves to the border of the region. This results in quasi-periodic motion with increasing phase difference as shown in figure 2.6(b) on the following page. The phase difference spreads over the unit circle. However, the distribution is not uniform. The peak of the distribution can be observed at angle 0. If we further increase the frequency of the sinusoidal signal to \(v = 1.1\), the phase difference linearly increases and its distribution is uniform on the unit circle as shown in figure 2.6(c).

Next, we show an example of the effect of the amplitude of the external force \(\varepsilon\) on the synchronization index. In this example, we fix the frequency of the Van
Figure 2.6: Phase differences of forced Van der Pol in time (left) and circular format (right). (a) inside, (b) at the border, (c) outside of synchronization region.
der Pol oscillator at $w = 1$ and frequency of sinusoidal signal at $v = 1.05$ (1 : 1 scheme) and then increase $\varepsilon$ from 0 to 0.4 with the step size of 0.025 so that the state of synchronization is getting into the synchronization from the bottom as shown in figure 2.7 on the left. However, instead of presenting the plots of the phase difference, we calculate the synchronization indices at each value of $\varepsilon$ as shown in figure 2.7. The blue boxes are box plots of the synchronization indices of the surrogate data. The symbols $\times$ and $\circ$ denote the synchronization indices of the original time series that are less than and greater than the indices of the surrogate data respectively.

The results of synchronization indices computed from both the mutual information method and the variance of the phase difference are similar. At $\varepsilon < 0.1$, the synchronization indices of the original data are positive but not greater than the indices of the surrogate data. Therefore, the synchronization is not established. For $0.1 < \varepsilon < 0.2$, the synchronization indices of the original data increase rapidly and are greater than the indices of the surrogate data. This indicates that the system is entering into the synchronization region. For $\varepsilon > 0.2$, the system is already in the synchronization region, the synchronization indices slowly increases to be 1 for the variance of phase difference method and about 0.8 for the mutual information method (the mutual information method has better degree of monotonicity). Note that the synchronization indices of the surrogate data stay at the same level.
2.2 Determining $n$ and $m$

When the synchronization occur at different frequency ratio or $n : m$ synchronization, it is necessary to know the frequency ratio $n : m$ to compute the intensity of synchronization using both variance of the phase difference and mutual information. In the variance of the phase difference method, the number $n$ and $m$ are used to compute phase difference $\theta_{xy} = n\theta_x - m\theta_y$. For the mutual information method, although it is unnecessary to specify the number $n$ and $m$, it is essential to ensure that they are constant because mutual information is based on the relationship of probability distribution of the phase which varies when there are more than one pair of frequency ratio. The information of frequency ratio is also required in the surrogate method because a data segment that is used for generating surrogate must have single entrainment pattern. To clarify this, let’s consider an example of a noisy periodic signal $x$ in which the frequency abruptly jumps from $f_1$ to $f_2$ at $t = \tau$. When we compute surrogate $x_s$, it will have mixing frequency component between $f_1$ and $f_2$. Therefore, $x_s$ at time $t < \tau$ is not the right surrogate of $x$ at time $t < \tau$ because $x_s$ at time $t < \tau$ contains frequency component $f_2$ which does not present in the original data during this time. Therefore, the moment when the frequency ratio $n : m$ changes must be known so that the data can be segmented before computing the surrogate.

2.2.1 Constant $n$ and $m$

A simple method that can be used to determine the ratio $n : m$ is the trial and error method. The number $n$ and $m$ are determined by plotting $\theta_{xy}$ with different pairs of $n$ and $m$ and select the one that is corresponding to the plateau of the $\theta_{xy}$, that is where the slope of $\theta_{xy}$ is minimal.

Another method is a phase stroboscope proposed by Schäfer et al. [8]. Stroboscope is a plot of the phase of the oscillator at the time when the phase of the external force gains some fixed value (ex. when the phase of the external force equals zero or the beginning of the cycle) or vice versa. For simplicity, let us call this time as $t_x$ and
let us call the phase of the driven system at $t_x$ as $\phi^y(t_x)$. If the two systems are coupled (phase locked), $\phi^y(t_x)$ would form visible horizontal lines and the number of horizontal lines is equal to the number $m$ regardless of the number $n$ (or vice versa if we investigate $\phi^x(t_y)$). If it is frequency locked, $\phi^y(t_x)$ still forms the visible lines but does not need to be parallel to the horizontal axis. In other words, the slope of the line does not need to be zero.

As an example, let’s consider the stroboscope of forced Van der Pol defined in equation (2.9) in figure 2.8. We set $w = 3/2$ and $v = 1$ so that it is 3 : 2 synchronization. It can be seen that the number of horizontal lines is two which is equal to $m$. If we plot the phase of external force at the time when the phase of oscillator is zero, the number of lines will be three which equals the number of $n$ (not shown here).

### 2.2.2 Varying $n$ and $m$

Stroboscope is also useful for detecting changes of frequency ratio because the number of visible horizontal lines of the stroboscope changes when the number of $m$ changes. An example is the forced Van der Pol defined in equation (2.9) in which the frequency of the sinusoidal signal is varied as in equation (2.10). Note that the natural frequency is selected to be $w = 2/3$ for this example. The stroboscope of this forced Van der Pol oscillator is shown in figure 2.8. The green dots form two flat horizontal lines which are equal to the number of $m$.

**Figure 2.8:** Stroboscope of forced Van der Pol oscillator. The green dots form two flat horizontal lines which are equal to the number of $m$. 

As an example, let’s consider the stroboscope of forced Van der Pol defined in equation (2.9) in figure 2.8. We set $w = 3/2$ and $v = 1$ so that it is 3 : 2 synchronization. It can be seen that the number of horizontal lines is two which is equal to $m$. If we plot the phase of external force at the time when the phase of oscillator is zero, the number of lines will be three which equals the number of $n$ (not shown here).
Pol is presented in figure 2.9.

\[ v = \frac{2}{3}, \quad 0 \leq t < 5 \quad (1 : 1) \]
\[ v = 1, \quad 5 \leq t < 10 \quad (2 : 3) \]
\[ v = \frac{4}{3}, \quad 10 \leq t < 15 \quad (1 : 2) \]
\[ v = 2, \quad 15 \leq t < 20 \quad (1 : 3) \]
\[ v = 2.1, \quad 20 \leq t < 25 \quad \text{(uncoupled)} \]

Figure 2.9: Stroboscope of dynamic \( n : m \) forced Van der Pol.

### 2.3 Computational method of determining \( n \) and \( m \)

Although the stroboscope method is able to detect changes in \( n : m \) synchronization, the number \( n \) and \( m \) are obtained only by visual inspection method which is not appropriate for analyzing a large data set. Therefore, we propose an automated method to determine numbers \( n \) and \( m \) as well as to detect moments when they change. We also propose a novel method to quantify strength of synchronization that is not affected by varying frequency ratio. Following is the details of our method.
2.3.1 Constant $n$ and $m$

To determine $n$ and $m$ computationally, we have to consider the stroboscope in a different aspect. We noticed that when $x$ and $y$ are synchronized, $\phi^y(t^x)$ repeats at every $k \cdot m$ point where $k$ is an integer. Consequently, the Poincaré plot\(^3\) of $u = \phi^y(t^x_i)$ and $v = \phi^y(t^x_{i+\tau})$ when $\tau = m$ will be on the line of identity. For example, consider the stroboscope of the $3 : 2$ synchronized forced Van der Pol in figure 2.8 on page 18. Its Poincaré plots with delays $\tau = 1$, $2$, and $3$ are shown in figure 2.10. The points $(u, v)$ are on the line of identity only when the delay $\tau$ is $2$.

To enable the computational method, we need to change the line of identity so that it is parallel to the horizontal axis. However, notice that the domain of both $u$ and $v$ are defined on a torus instead of general 2-dimensional plane of a real number as a conventional Poincaré plot (the domain of both $u$ and $v$ are $[-\pi \, \pi]$). To explain in more detail, let’s consider the torus illustrated in figure 2.11(a) on the next page. If we cut a ring from the torus, we will have a cylinder with length and circumference equal to $2\pi$. Then, if we unfold the cylinder, we will have a plane with the width and

\(^3\)The conventional Poincaré plot is a scatter plot on a two dimensional $x - y$ plane between $x(t)$ and $y(t) = x(t + \tau)$ where $\tau$ is the time delay. Two common features of the Poincaré plot are SD1 and SD2 that are correlated with the short-term and long-term variability of the time series respectively. The process begins with changing coordinates so that $x$ axis changes to the line of identity which is at $45^\circ$ from the original $x$ axis. Therefore, any point $[x \, y]$ in the new coordinate frame is $x' = [x] \cdot \left[ \frac{1}{\sqrt{2}} \frac{1}{\sqrt{2}} \right]^T$ and $y' = [x] \cdot \left[ -\frac{1}{\sqrt{2}} \frac{1}{\sqrt{2}} \right]^T$. Then SD1 is the standard deviation of $y'$ and SD2 is the standard deviation of $x'$. 

![Figure 2.10: Poincaré plot of forced Van der Pol at different time delay.](image-url)
length equal to $2\pi$ shown in figure 2.11(c) which is similar to the plane in figure 2.10 on the previous page.

Because the domain of $u$ and $v$ is defined as $[-\pi, \pi]$, we cannot change coordinates using the same procedure as in the conventional Poincaré analysis. Instead, we have to twist the torus (or cylinder) so that the line of identity is parallel to the original $u$ axis and perpendicular to the $v$ axis. This is done by having $u' = [u \ v] \cdot [1 \ 0]^T$ and $v' = [u \ v] \cdot [-1 \ 1]^T$. Remember that by doing this, the line $v' = 0$ is the line of identity. In fact, we use only $v'$ as the feature to detect the appropriate value of $m$. $v'$ at each specific time of $x$ can be simplified as

$$v'(t_i^x) = \phi^y(t_i^x) - \phi^y(t_{i-\tau}^x). \quad (2.11)$$

The Poincaré plot of the previous example after changing of coordinates is shown in figure 2.12.

Figure 2.12: Poincaré plot of forced Van der Pol after changing of coordinates.
The computational method for determining optimal value $m^*$ begins with computing the initial $\hat{m} = \tau$ such that the circular mean of $|v'(\tau)|$ is minimized. After we have found $\hat{m}$, we searched for optimal $n^*$ by comparing the derivative of the phase $\hat{m} \cdot \theta^y$ and $\frac{n}{g} \cdot \theta^x$, for $n = 1, 2, 3, ...$ where $g$ denotes greatest common divisor of $n$ and $\hat{m}$. We use Wilcoxon rank sum test to determine the equality of the derivative of the phase. We record $p_n$ which is the p-value of each test. Finally, the optimal value $m^* = \frac{\hat{m}}{g}$ and $n^* = \frac{n}{g}$ where $n$ corresponds to the largest $p_n$.

Note that we divide $n$ and $\hat{m}$ by $g$ in order to take care of the issue when $\hat{m} \neq m^*$. For example, let $\hat{m} = 3$. If $n = 3$, then $g = 3$ so we finally compare the derivative of the phase $1 \cdot \theta^y$ and $1 \cdot \theta^x$. Hence, $p_3 = p_1$ and $n^* : m^*$ will be $1 : 1$ instead of $3 : 3$.

### 2.3.2 Varying $n$ and $m$

If coupling scheme or $n : m$ ratio varies, we need to detect the moment when the numbers change before determining their values. We have shown in section 2.2.2 that stroboscope can be used to track changing of $m$ by examining changing of the number of horizontal lines. Actually, this property also presents in the Poincaré plot of the stroboscope as changing in circular mean of $v'$. To give an example, let us again consider forced Van der Pol model when the frequency of the sinusoidal signal is varied as in figure 2.9 on page 19. Plots of $v'_r(t^x_i)$ with $\tau = 1, 2, \text{and } 3$ are presented in figure 2.13 on the next page. From the plot, the mean value of $v'_r(t^x_i)$ changes when $m$ changes.

For example, at $\tau = 3$, the mean value of $v'_r(t^x_i)$ changes at $t = 10, 15, 20$. Combining with the changing point of the plot when $\tau = 1$ and $2$, the mean value of $v'_r(t^x_i)$ changes at $t = 5, 10, 15, 20$ which are the moment when we change the frequency of the sinusoidal signal. Note that we have to examine all $v'_r(t^x_i)$ because the position of $\phi^y(t^x)$ repeats at every $k \cdot m$ point where $k$ is a positive integer number. i.e., when $\tau = m$, $v'_r(t^x_i) \approx v'_{k \cdot \tau}(t^x_i)$ for $k > 1$. As a result, we may not see any change point if we examine $v'_r(t^x_i)$ when $m$ changes from $m = \tau$ to $m = k \cdot \tau$.

To detect changes of circular mean of $v'$, We modified change point detection
Figure 2.13: Plots of $v'(\tau)$ with $\tau = 1, 2, \text{ and } 3$.

algorithm proposed by Piryatinska et al. [9] so that it is suitable for circular data. Specifically, we change the family of statistics defined in equation (4.1.1) in Ref. [9] to

$$Y_N(n, \delta) = \left[ 4 \left( 1 - \frac{n}{N} \right) \frac{n}{N} \right]^\delta \left( \frac{A + B}{2} \right)$$

(2.12)

where

$$A = \left| \frac{1}{n} \sum_{k=1}^{n} \sin(v'_k) - \frac{1}{N-n} \sum_{k=n+1}^{N} \sin(v'_k) \right|$$

(2.13)

$$B = \left| \frac{1}{n} \sum_{k=1}^{n} \cos(v'_k) - \frac{1}{N-n} \sum_{k=n+1}^{N} \cos(v'_k) \right| .$$

Note that $k$ and $n$ in this equation denote the time index of $v'_\tau(t^*_i)$. The term $(A + B)/2$ can be thought of as the mean absolute value of the mean phase difference between the first $n$ and last $N - n$ of the time series on vertical and horizontal axes of the unit circle. In addition, we multiply the weighted term by 4 to make this

\footnote{Change point detection algorithm is a routine to detect statistically significant change in the mean of a time series. Please refer to the full description of the routine in Ref. [9].}
term have the maximum value equal to 1 if δ = 1 so that \( Y_N(n, \delta) \) will also have the maximum value equal to 1. Consequently, we do not need to compute the threshold \( C \) for \( Y_N(n, \delta) \) but just select \( C \in [0, 1] \) which is very convenient. In our study, we set \( \delta = 0.5 \) for stage 1 and \( \delta = 0.1 \) for stages 2 and 3 and then set \( C = 0.1 \) for all stages.

As an example, figure 2.14 illustrates the result of change point detection algorithm of the \( v'_\tau(t^x_i) \) presented previously in figure 2.13 on the preceding page. The symbol * denotes the time when the circular mean of \( v'_\tau(t^x_i) \) changes. The symbol • at the top of the figure denotes the combination of all change points detected from \( v'_\tau(t^x_i) \) at all \( \tau \). The circular mean between each change point is not statistically different from zero.

Figure 2.14: Change points of \( v'_\tau(t^x_i) \).

Figure 2.15: Initial result of \( n : m \) detection of forced Van der Pol.
After all change points are detected, we can use the method presented in section 2.3.1 to determine frequency ratio $n^*$ and $m^*$ during the time of each change point. The result of $n^* : m^*$ from the forced Van der Pol in figure 2.14 is shown in figure 2.15 on the previous page. The $n : m$ results are plots above the change points marked by • symbol.

It can be observed from the example of $n : m$ detection result in figure 2.15 that short segments of $n^* : m^*$ are detected at the transition point ($t \approx 0$ and $t \approx 5$). Generally, systems cannot establish the synchronization in a very short period of time. In fact, in this example, the ratios $1 : 3$ detected at $t \approx 0$ and $t \approx 5$ are wrong. We eliminate these ambiguous ratios by replacing with either $n : m$ ratio found before or after this point. For the two candidates, we performed the same procedure as when we searched for $n^*$ after we found $m'$. We selected the new $n^* : m^*$ that corresponds to the largest p-value. Figure 2.16 shows the final result of $n : m$ detection of the forced Van der Pol oscillator.

![Figure 2.16: Final result of $n : m$ detection of forced Van der Pol.](image)

2.4 Quantifying intensity of synchronization in varying $n : m$ synchronization

With the information of $n$ and $m$, we are now be able to compute synchronization index based on both variance of the phase difference method and mutual information. However, if coupling scheme changes very often and the surrogate test is required,
both methods may not be appropriate because we could have very short data segment with a single entrainment pattern. On the other hand, if the surrogate test is not required, the variance of the phase difference method is possible. However, at a moment when the frequency ratio changes, phase difference could abruptly changes too as an example illustrated in figure 2.17. This results in spuriously higher variance when equation (2.7) is used.

![Figure 2.17: Phase difference $\theta^x_y = n^x\theta^x - m^y\theta^y$ of forced Van der Pol.](image)

We propose a new method to compute synchronization index that is not effected by varying frequency ratio. Our method is to measure the short-term variability of $\phi^y(t_{i+}\tau^*)$, i.e., the circular variance of $v'(\tau^*)$ where $\tau^*$ corresponds to $m^*$. If the circular variance of $v'(\tau^*)$ is small, we learn that the two systems have frequency locking. In addition, if the circular variance of $v'(\tau^*)$ is small and the circular mean is also statistically not different from zero, then the two systems are coupled. Figure 2.18 illustrates the example of $v'(\tau^*)$ of the forced Van der Pol. When the systems are coupled ($0 \leq t < 20$), then the circular mean of $v'(\tau^*)$ is not statistically different from zero and the circular variance is very small. However, when the system are uncouple ($t > 20$), the circular mean of $v'(\tau^*)$ is statistically different from zero but the circular variance is still small implying that the two systems have frequency locking but are not phase coupled. This conclusion cannot be obtained if we use the variance of the phase difference method to compute the synchronization index. We use one sample test for the mean angle to test the hypothesis that the circular mean of $v'(\tau^*)$ is equal to zero [10]. Note that this method cannot be used with the surrogate test because the data contain multiple entrainment patterns.

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Another index that takes the advantage of knowing number \(n\) and \(m\) is the regularity of the frequency ratio \((n/m)\) which can be measured by sample entropy. This technique measures how the parameters of the systems change over time i.e., how the systems change coupling scheme. However, measuring this index has not been included in this study.

## 2.5 Physiological examples

This section presents an example of synchronization analysis of mechanical ventilation and spontaneous respiration from a study of effects of ventilatory methods after lung injury in rats. The ventilatory methods that were compared are biologically variable ventilation (BVV) and continuous mechanical ventilation (CMV). We recorded diaphragmatic electromyogram (DiaEMG), electrocardiogram (ECG) and ventilator piston trigger signals in spontaneously breathing, anesthetized, intubated adult male Sprague-Dawley rats \((n=15)\). Following a 1h baseline recording, ALI was induced with 2ml/kg of 0.1N HCl via endotracheal tube, and either BVV \((n=7)\) or CMV \((n=8)\) was continued for 4h. Then the rats were recovered for another 1h. Figure 2.19 on the next page shows examples of raw signals recorded from representative rats in the BVV and CMV groups during ventilatory period.
2.5.1 Synchronization in respiration and ventilator

We measured the synchronization between the onset of the respiration and the ventilator piston trigger signals. The onset of respiration was detected from the DiaEMG signal. The phase was extracted using the marked event method because the raw signals are sequences of pulses. The synchronization index was computed in 1min sliding windows with no overlap. The upper window in figure 2.20 on the following page shows instantaneous frequency of the ventilator trigger (InstVR) and respiration (InstBR) of the representative CMV (shown in figure 2.19). Although the frequency of the ventilator is relatively constant, the frequency of the respiration jumps up and down between two values resulting in alternating synchronization schemes between 1 : 3 and 1 : 2. The figure also shows that the $n : m$ detection algorithm correctly detects the moment where the synchronization scheme changes. The middle window is the plot of $\nu'(\tau^*)$ and the bottom window is the synchronization index computed in 1min time windows. In this example, despite the random frequency jumps, the ventilator and respiration remain highly synchronized.
Figure 2.20: Example of Synchronization between inspiration and ventilation signal in a CMV animal.

Another example is the synchronization between the respiration and ventilation signals in a BVV rat shown in figure 2.21. The frequency of the ventilator varied in a biologic fashion around 55 breaths per minute. The frequency of the respiratory pattern also changed corresponding to the frequency of the ventilator. The synchronization was a 1 : 2 scheme over this recording.

The final result of this study is shown in figure 2.22 as box plots of synchronization indices for the BVV and CMV groups. We divided the data into 4 periods of ventilation, each lasting about 1h. The synchronization index of the CMV group was greater than that for the BVV group in each period of ventilation. This is because the instantaneous frequency of the continuous mechanical ventilator was constant so that it was easier for the respiratory system to follow the ventilator. However, the mean synchronization index in the BVV group was approximately 0.7 which is highly significant. This result implies that the respiratory system attempts to synchronize with the ventilator even when the frequency of the ventilator varies.
Figure 2.21: Example of Synchronization between inspiration and ventilation signal in a BVV animal.

Figure 2.22: Synchronization indices of BVV and CMV groups.

2.5.2 Frequency modulation of heart rate due to respiration and ventilation

In this example we study the interaction between heart rate, respiration and the ventilator in the same data set as the previous example. The cardiorespiratory interaction is an attractive area in physiological time series analysis [11–14]. However, the cardiorespiratory system is best modeled as the interaction between two periodic oscillators which is different from synchronization of a periodic oscillator by an external force. In this case, it is difficult to distinguish between coupling and independent oscillators with a constant frequency ratio.
In this data set, rather than phase synchronization, we observed frequency locking between heart rate and respiration during ventilation in the CMV group (figure 2.23). In the plot of $v'(\tau^*)$ the two signals have frequency locking rather than coupling because the variance of $v'(\tau^*)$ is very small but the mean is not equal to zero. Because phase locking is not present, this interaction is not considered synchronization.

However, the interaction is similar to respiratory sinus arrhythmia (RSA) which is the modulation of heart rate due to breathing i.e., heart rate increases during inhalation and decreases during exhalation. Further, we discovered that heart rate can also be modulated by the ventilator and the modulation by the ventilator is even stronger than the modulation due to respiration in the CMV group.

To study the frequency modulation of the heart rate due to respiration and ventilation, we detected the R-peaks of the EKG signal and computed the R-R interval defined as the interval between successive R-peaks. Then in 2.5min segments, we compute the Lomb periodogram of the R-R interval time series and the histogram of the instantaneous frequency of respiration and ventilation. An example is shown in figure 2.24. In this example, the periodogram of the CMV rat has its peak at the ventilation frequency rather than the respiration frequency. On the other hand, ventilation has less effect on the frequency of heart rate in the BVV group.
To compare the degree of frequency modulation of R-R interval by respiration and ventilation, we convert the periodogram of R-R interval time series to a histogram and then we compute the cross correlation between histogram of R-R intervals and the histogram of respiration and ventilation. The result is presented as box plots in figure 2.25. It can be seen that the cross correlation between heart rate and ventilation frequency in the CMV group is much higher than that of BVV group. The cross correlation between heart rate and respiration frequency of the BVV and CMV
groups are not statistically different. Most importantly, the cross correlation between heart rate and ventilation frequency is statistically higher than cross correlation between heart rate and respiration frequency. This result implies that the frequency modulation of the heart rate is due to ventilation rather than respiration.

2.6 Conclusion

In this chapter, we summarized basic concept in synchronization of a periodic oscillator due to an external force. We developed an computational method to specify the frequency ratio \( n : m \) and also to detect the moment when the frequency ratio changes. Our method is based on circular Poincaré plot and circular change point detection. We also proposed a novel method to quantify intensity of synchronization of data which contain multiple coupling schemes. Our method worked effectively in quantifying synchronization between ventilator and respiration in the study of mechanical ventilation in lung injured rats.
Chapter 3

Directionality of coupling

So far we have discussed measuring the intensity of the interaction between coupled systems and applied our analytic approach to physiological signals. However, in physiological applications, both the intensity and the direction of interaction are relevant for understanding the control of a system. Coupled systems are composed of driver and driven (response) systems. If the systems have only one driver and response system, we call this unidirectional coupling. An example of unidirectional coupling is the coupling between ventilation and respiration where the respiratory pattern cannot influence ventilation. On the other hand, if the coupled systems both drive each other with equal or different intensity, we refer to this type of interaction as bidirectional coupling. An example is cardiorespiratory interaction.

The objective of this chapter is to find an appropriate method for quantifying directionality of coupling in physiological time series. We studied two approaches that were proposed in literature. The first approach is based on Fourier series estimation of the phase difference and the second approach is based on information theory. Both methods were designed for measuring directionality of coupling in noisy weak coupled oscillators\(^1\). We test these algorithms with simulated data from coupled Van der Pol oscillators.

\(^1\)Coupling direction cannot be computed if the systems are strongly coupled or synchronized because the dynamics of the two systems tend to be the same. Therefore, it is impossible to distinguish which one is the driver system and which one is the driven (response) system.
oscillators, defined as

\[ \dot{x} = 0.02 (1 - x^2) x - \omega_x^2 x + \varepsilon_{yx} (y - x) + \eta(\mu, \sigma) \]

\[ \dot{y} = 0.02 (1 - y^2) y - \omega_y^2 y + \varepsilon_{xy} (x - y) + \eta(\mu, \sigma) \]

(3.1)

where \( \omega_x \) and \( \omega_y \) are the frequencies of systems \( x \) and \( y \) respectively. We integrate the derivative functions with time step of 0.01. \( \varepsilon_{yx} \) and \( \varepsilon_{xy} \) are the parameters that control the coupling strength of system \( y \) to system \( x \) and \( x \) to \( y \) respectively. \( \eta(\mu, \sigma) \) is the Gaussian noise with mean \( \mu = 0 \) and standard deviation \( \sigma \).

In the following sections, we summarize the mathematical background of each technique and test them with simulated coupled system data. Then the advantages, limitations and pitfalls of both algorithms will be discussed. Finally, we select the preferred approach to determine directionality of coupling in experimental physiological time series data.

### 3.1 Fourier series estimation approach

The detection of directionality of coupling using the Fourier series estimation approach has been proposed by Rosenblum and Pikovsky [15]. In this section, we summarize the method and the interested reader should consult the original paper for additional details.

#### 3.1.1 Background

Briefly, the idea of the Fourier series estimation approach is that the derivative of the phase of each oscillator is a function of the phase of both oscillators, i.e.,

\[ \Delta_{\tau} \phi_x(k) = \mathcal{F}_x[\phi_x(k), \phi_y(k)] + \xi_x(k), \]

\[ \Delta_{\tau} \phi_y(k) = \mathcal{F}_y[\phi_y(k), \phi_x(k)] + \xi_y(k) \]

(3.2)

where \( \phi(k) \) is the phase defined in the interval \([0, 2\pi]\), \( \Delta_{\tau} \phi(k) = [\phi(k + \tau) - \phi(k)] / \tau \) is the derivative of the phase, \( \tau \) is the time increment and \( \xi(k) \) is random noise. The
function $F_x$ and $F_y$ are defined on a torus and can be estimated by a finite Fourier series representation given in equation (3.3) using a least squares method. Then the cross dependencies (coupling) are determined by the coefficients $c_{yx,xy}$ defined as in equation (3.4). Finally the directionality index can be computed using equation (3.5).

$$F_{x,y} = \sum_{m,l} A_{m,l} e^{im\phi_x + il\phi_y} \quad (3.3)$$

$$c_{yx,xy}^2 = \int_0^{2\pi} \left( \frac{\partial F_{x,y}}{\partial \phi_{y,x}} \right)^2 d\phi_x d\phi_y, \quad (3.4)$$

$$d = \frac{c_{xy} - c_{yx}}{c_{xy} + c_{yx}}. \quad (3.5)$$

The index is defined in the interval $[-1, 1]$ where a positive index corresponds to the direction $x \rightarrow y$, negative index corresponds to the direction $y \rightarrow x$ and 0 corresponds to symmetric bidirectional coupling\(^2\).

To give an example, we measured direction of coupling of noise free coupled Van der Pol oscillators given in equation (3.1). We set $\omega_x = 4/3 + 0.03$ and $\omega_y = 2/3$ so that the synchronization state was at the border of the $1 : 2$ synchronization region. Then we set $\varepsilon_{yx} = 0.01$ and $\varepsilon_{xy} = 0.08$ hence this was the bi-directional coupling of which the coupling from $x \rightarrow y$ was stronger than the opposite direction. The directionality index of this model was $\frac{\varepsilon_{xy} - \varepsilon_{yx}}{\varepsilon_{xy} + \varepsilon_{yx}} = 0.7778$. Figure 3.1 on the following page shows plots of $\Delta \phi_x(\phi_x, \phi_y)$ and the estimator $F_x(\phi_x, \phi_y)$ on the left and $\Delta \phi_y(\phi_x, \phi_y)$ and $F_y(\phi_x, \phi_y)$ on the right. Note that phase was extracted by the marked event phase method. From the figure, points $(\phi_x, \phi_y)$ cover the entire torus surface. In addition, $(\phi_x, \phi_y)$ characterizes $\Delta \phi_y$ better than $\Delta \phi_x$ implying that the directionality of coupling from $x \rightarrow y$ is more obvious than the opposite direction. Finally, the directionality index computed by this method is 0.7586 which is approximately the directionality index of the model.

\(^2\)The Matlab toolbox for the estimation of the Fourier series and the computation of the directionality index is provided by the author on the website http://www.stat.physik.uni-potsdam.de/~mros/damoco.html
Figure 3.1: Plots of derivative of the phase and the Fourier series estimator of system $x$ and $y$.

3.1.2 Limitation

A limitation of the Fourier series estimation approach is that to estimate the derivative of the phase using Fourier series, the scatter plot of $(\phi_x, \phi_y)$ must fill the surface of the torus. This condition can be achieved if the synchronization state is at the border of the synchronization region (point 3 in figure 2.1 on page 7) so that the dynamics of the phase difference is quasi-periodic. Another possibility is that the dynamic noise is strong enough so that the synchronization state moves continuously from the inside to the border of the synchronization region. In synthetic data, it is easy to generate a segment of time series having this property. However, it could be extremely difficult to find an appropriate segment in physiological time series data because we do not know how to check whether the state of synchronization is at the border of the synchronization region.

Another limitation is the abrupt changes that can occur in the coupling scheme from one $(n : m)$ to another (for example, $(n + 1 : m)$) which is observed in physiological time series. If a segment of time series data contains more than one coupling scheme, then the relationship between the derivative of the phase and the phase of both oscillators cannot be described by only one function as shown in the following example.
(a) Arnold tongues showing frequency jumping from one border to another.

(b) Derivative of the phase composes of more than one function.

Figure 3.2: Frequency jumping and the derivative of the phase.
Let us consider the situation where the state of synchronization jumps from the border of one synchronization region to the border of another the synchronization region in coupled Van der Pol oscillators with $\varepsilon_{xy} = 0.08$ and $\varepsilon_{yx} = 0$. In this example, we varied the frequency of the oscillator with time, i.e., we start with $\omega_x = 4/3 + 0.03$ and $\omega_y = 2/3$ which is on the right side of the $1 : 2$ region and then we abruptly change $\omega_x$ to be $2-0.02$ to the left side of $1 : 3$ region (see figure 3.2(a)). The derivative of the phase $\Delta \phi_y(\phi_x, \phi_y)$ illustrated in figure 3.2(b) shows that $\Delta \phi_y$ is composed of two functions because the coupling scheme changes from one $n : m$ ratio to another. Consequently, it is impossible to estimate this segment of data using only one estimation function. Therefore, we need to segment the data at the time when the coupling scheme jumps and use the segment of data in which the coupling scheme is constant.

In summary, computation of coupling direction based on Fourier series estimation approach works effectively in synthetic time series in which we can specify the location of the state of synchronization. In this case, the segment of data that is used to compute directionality of coupling cannot contain any changes in the coupling scheme. This method is not practical in physiological time series data because we do not know how to select a segment of data that is appropriate for the estimation process.

### 3.2 Information-theoretic approach

The coupling direction algorithm based on information theory has been presented by Paluš and Stefanovska [16]. Similar to the Fourier series estimation approach, this method uses the relationship of the phase and its derivative. However, the relationship is in the form of information sharing rather than a functional relationship. Moreover, Paluš and Stefanovska proposed the method of surrogate data testing to avoid spurious detection of coupling direction. We found that using the surrogate data test, we do not need to select appropriate segments of data as in Fourier series estimation method.
3.2.1 Background

Mutual information can be used to measure the (statistical) dependency of two variables \(x\) and \(y\) by computing \(I(x(t); y(t + \tau))\) which is the information that variable \(x\) shares with the future value of the variable \(y\). However, the information of \(y(t + \tau)\) could be contained in the current value of \(y(t)\) itself. Therefore, we condition on the variable \(y(t)\) to eliminate the information that \(y(t)\) and \(y(t + \tau)\) share and retain only the net information that \(x(t)\) and \(y(t + \tau)\) share. This measurement is called *conditional mutual information* defined as \(I(x(t); y(t + \tau)|y(t))\). Conditional mutual information \(I(x(t); y(t + \tau)|y(t))\) measures the information about \(y(t + \tau)\) that is contained in \(x(t)\) when \(y(t)\) is known. Thus, it measures how well system \(x\) can predict the future of system \(y\) when the present value of system \(y\) is known. The computation of conditional mutual information is relatively similar to the computation of regular mutual information. Let \(H\) be the joint entropy, \(I(x; y|z)\) can be computed as

\[
I(x; y|z) = H(x, z) + H(y, z) - H(x, y, z) - H(z). \tag{3.6}
\]

To measure the coupling strength in the \(x \to y\) direction, the same variables as in the Fourier series estimation method are used, i.e., let \(\phi\) be the phase defined in the \([0, 2\pi]\) interval, compute

\[
I_{xy} = I(\phi_x(t); \Delta r \phi_y|\phi_y(t)) \\
I_{yx} = I(\phi_y(t); \Delta r \phi_x|\phi_x(t)) \tag{3.7}
\]

and defined the direction index as

\[
d = \frac{I_{xy} - I_{yx}}{I_{xy} + I_{yx}}. \tag{3.8}
\]

Similar to the computation of the synchronization index presented previously in section 2.1.2 on page 11, surrogate data were used to validate the computation of the conditional mutual information. The hypothesis is that the coupling direction in the surrogate data will be destroyed. The method of generating the surrogate data is still
the same i.e., we use FT surrogate for the original waveform of the data and we prefer the IAAFT surrogate method if the original data is of the pulse sequence type and the interval data has high variability so that the computation of IAAFT surrogate is correct. Because surrogate data is used, the segment of data must not contain dynamic changes in frequency. Note that the marked event phase computed from the sequence of pulses (such as R-R intervals) must be resampled so that the sampling rate of the phase is high enough to be able to compute $\Delta \phi$. Paluš and Stefanovska computed $d^s = \frac{I^s_{xy} - I^s_{yx}}{I^s_{xy} + I^s_{yx}}$ where $I^s_{xy}$ is the conditional mutual information obtained from the surrogate data and concluded that the direction index $d$ is meaningful only if $d$ is outside the region $\mu \pm 2\sigma$ of $d^s$. However, the definition of $d^s$ is incorrect because $I^s_{xy}$ and $I^s_{yx}$ should not have any relationship.

After the information theoretic approach was proposed, Paluš and Vejmelka [17] discussed several techniques that can be used to prevent spurious detection of the coupling direction. It was observed that some parameters of the data that affect the detection result are length, frequency, complexity, and noise. One parameter that was not studied is the sampling rate of $\phi$ which affects the variable $\Delta_r \phi$. The sampling rate must be high enough so that $\Delta_r \phi^s$ of the surrogate data will not have a different distribution from the original data.

Moreover, they clarified that the conditional mutual information $I_{xy}$ is meaningful only if $I_{xy} > I^s_{xy}$ because the conditional mutual information of the surrogate data (in which the direction of coupling has been destroyed) should be lower than that of the original data. Modifying their idea, we define the directionality index as:

- **UniDxy** Uni-directional from $x$ to $y$ if $I_{xy} > I^s_{xy}$ but $I_{yx} \leq I^s_{yx}$.

- **UniDyx** Uni-directional from $y$ to $x$ if $I_{yx} > I^s_{yx}$ but $I_{xy} \leq I^s_{xy}$.

- **BiD** Bi-directional if $I_{xy} > I^s_{xy}$ and $I_{yx} > I^s_{yx}$. In this case, the directionality index is as defined in equation (3.8).

- **NoD** No direction of coupling detected if $I_{xy} \leq I^s_{xy}$ and $I_{yx} \leq I^s_{yx}$. 

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3.2.2 Example: Coupled Van der Pol oscillators

We used noisy coupled Van der Pol oscillators to illustrate the computation of the directionality of coupling using information theory approach. We employed the marked event phase extraction method (the marked event is the local maximum) and resampled the phase with a sampling frequency of 100 Hz. We set $\tau = 10s$ and set the number of bins for the entropy computation to be 16. In the first example, we set $\omega_x = 4/3 + 0.03$, $\omega_y = 2/3$, $\eta = 0.01$.

For UniDxy, we set $[\varepsilon_{xy} \varepsilon_{yx}] = [0.03 0]$ and computed conditional mutual information of the original and 19 IAAFT surrogate data realizations and the results are given in figure 3.3(a). For UniDyx, we set $[\varepsilon_{xy} \varepsilon_{yx}] = [0.05 0]$; figure 3.3(b). For BiD, we set $[\varepsilon_{xy} \varepsilon_{yx}] = [0.03 0.05]$; figure 3.3(c). The directionality index of this case was -0.46 which was negative due to the fact that $\varepsilon_{yx} > \varepsilon_{xy}$. Finally, for the case of NoD, we set $[\varepsilon_{xy} \varepsilon_{yx}] = [0 0]$ the result is given in figure 3.3(d).

To further clarify the meaning of NoD, we measured the directionality index of tightly coupled Van der Pol oscillators by setting $[\varepsilon_{xy} \varepsilon_{yx}] = [0.03 0.05]$ and $\omega_x = 2/3$ to be inside the synchronization region with a coupling scheme of 1 : 1. The result is shown in figure 3.3(e). Although this was bidirectional coupling, the result of this method was NoD because the systems were tightly coupled; therefore, it was difficult to specify the direction. The difference between the current and the previous example can be seen in the plot of mutual information of the original and surrogate data. In the previous example (figure 3.3(d)), the mutual information of the original data was less than that of the surrogate which implies that the systems were uncoupled or very weakly coupled. However, in the final example (figure 3.3(e)), the mutual information of the original data was greater than that of the surrogate data implying that the system were coupled. In summary, NoD can imply that the systems are uncoupled or too tightly coupled so that it is impossible to find a coupling direction and mutual information can be used to distinguish these two cases.

In comparison of the Fourier series estimation and conditional mutual information
approaches, the limitation of both methods is that the segment of data that needs to be used for computing directionality must have only one coupling scheme. In other words, it should not contain dynamically changing frequency. However, the Fourier series estimation approach further requires that the phase of the segment of data must fill the surface of torus so that the estimation process is effective. On the other hand, surrogate data testing in conditional mutual information method allows us to use any segment of data to compute directionality of coupling. If the segment of data is not appropriate (it is generated from an uncoupled system or too tightly coupled system), the result would be \textbf{NoD}. Consequently, the information approach is more appropriate than the Fourier series estimation approach for computing directionality of coupling in physiological time series. In the following section, we will use this method to determine the coupling direction in cardiorespiratory systems.

### 3.3 Application to lung injury study data

In this section we specify the coupling direction among variables such as heart rate, the ventilator, and respiration in the lung injury data set described earlier in section 2.5. First, we compute the coupling direction in multiple 2.5min epochs of cardiorespiratory systems. We use the method of detecting changes in coupling scheme...
presented in the previous chapter so that the coupling scheme in each 2.5min epoch was constant. We divided epochs into Uncoupled and Coupled groups based on mutual information. Specifically, in Uncoupled group, mutual information of the phase of the original data was statistically less than that of the surrogate data. In Coupled group, mutual information of the phase of the original data was statistically greater than that of the surrogate data. Then we classified the result into four categories which were NoD, UniDr-hr, UniDhr-r, and BiD. The results are shown in figure 3.4.

From the result of the Uncoupled group, it was difficult to determine the direction during baseline in which the majority of the epochs were in the NoD category. However, the coupling direction from respiration to heart rate (hr) was clearer in the ventilation and recovery periods. During the ventilation period in the CMV group, unidirectional coupling from heart rate to respiration was observed for about 10% of the epochs which was not observed in the BVV group. Note that we did not consider the result of the Coupled group because if the systems are highly coupled, we cannot say anything about direction.
Figure 3.5: Coupling direction between ventilation (v) and respiration (r). UniDv-r denotes unidirectional coupling from ventilation to respiration and Unir-v denotes unidirectional coupling from respiration to ventilation.

To further prove the efficacy of this method, we applied it to determine the direction of coupling between ventilation and respiration. Actually, this coupling is known to be unidirectional from ventilation to respiration. Moreover, because ventilation and respiration were highly synchronized (from Chapter 2), it was impossible to compute direction in this kind of system. The results shown in figure 3.5 confirm this because almost 100% of the epochs were in the Coupled group and were in the NoD category.

Finally, we applied this technique to determine the coupling direction between ventilation and heart rate. Again, we know that ventilation and heart rate should be uncoupled because the interaction between them is in the form of frequency modulation rather than synchronization. The results shown in figure 3.6 also confirm this because almost 100% of epochs were in the Uncoupled group and were classified as NoD.
3.4 Conclusion

In this chapter, we investigated various methods for quantifying the directionality of coupling to determine their applicability to the analysis of physiological time series data. Two coupling direction methods were studied, one based on Fourier series estimation and the other on information theory. We found that the Fourier series estimation method is not appropriate when the coupling scheme is dynamically changing. Moreover, this method is not practical in physiological time series because we do not know how to automatically select an appropriate segment of data for the estimation process. On the other hand, we found that the surrogate data test in the information theory approach simplifies the process of selecting a segment of data to compute the directionality of coupling. The only requirement is that the segment of data must have a constant coupling scheme. This limitation can be addressed by using the method of detecting changes of coupling scheme presented in the previous chapter. Therefore, the information theory method is practical for physiological time series applications. We applied this method to study the directionality of cardiorespiratory...
coupling in experimental lung injury data in rats and found the coupling direction from respiration to heart rate during ventilation.
Chapter 4

Synchronization in a chaotic oscillator: application in neurodevelopment

In chapter 2, we examined the interaction among heart rate, respiration and ventilation based on a model of synchronization in periodic oscillators. In this chapter, we present another application of synchronization analysis in physiological time series; the study of neurodevelopment in newborns as indicated by synchronization in the electroencephalogram (EEG) recorded from different regions of the brain. The hypothesis is that the difference in brain maturation is related to the degree of synchronization of the EEG. The infants were divided into mid preterm, late preterm and fullterm groups based on their gestational age. The ultimate goal of this research is to verify if infants in the late preterm require more attention. If the late preterm infants are more similar to the mid preterm infants than the fullterm infants, then the late preterm infants may need special care, similar to infants in the mid preterm group. To test this hypothesis, first, we wanted to distinguish the mid preterm from the fullterm infants and then to classify the late preterm infants into either the mid preterm or fullterm groups. In section 4.1, we provide basic information and terminology about EEG and brain maturation in newborns as well as a literature review about EEG analysis related to brain maturation.
Unlike previous examples, synchronization analysis of the EEG is based on synchronization of chaotic oscillators in which several cases of synchronization can occur. Two coupled chaotic oscillators are said to be in generalized synchronization when a functional relationship connects their dynamical variables [18]. Complete synchronization can be attained if identical systems are sufficiently coupled so that their states coincide after transients dissipate [19]. Phase synchronization is the situation where two coupled chaotic oscillators maintain their phases in step with each other while their amplitudes remain uncorrelated [20]. In addition to the methods of quantifying the degree of synchronization that we presented in chapter 2, other methods have been published for chaotic synchronization such as recurrence analysis [21], non-linear interdependency [22], a method based on the correlation dimension [23], and event synchronization [24]. However, we will use phase synchronization based on the Hilbert phase transform, mutual information, and cross correlation of the original waveform because of their simplicity (note that we compute mutual information of the phase instead of the original waveform in chapter 2). For those who are interested in the techniques for quantifying synchronization in chaotic oscillators, we summarized the mathematical background and also tested their performance in appendix A. Finally, the details of the proposed methodology for EEG data is given in section 4.2.

4.1 EEG and brain maturation

EEG is obtained by attaching multiple electrodes to the scalp and recording the electrical activity of compound action potentials and the synaptic activity of a large number of neurons underlying the electrodes [25]. In neonates (infants less than 4 weeks old), a 10-20 electrode placement scheme is standard and includes frontal-temporal, frontal-central, temporal-occipital, and central-occipital electrodes as illustrated in figure 4.1 on the following page. An electrode is identified by one or two letters and a number. The letter refers to the area of the scalp where the electrode is placed, for example, F-Frontal lobe, C-Central lobe, T-Temporal lobe, O-Occipital lobe, and
Figure 4.1: The 10-20 EEG electrode placement system widely used in neonatal EEG.

Z refers to an electrode placed on the mid line. The even numbers denote the right hemisphere of the head; the odd numbers denote the left hemisphere of the head.

The age of infants can be defined in two ways, namely the gestational age and the post conceptional age. Gestational age (GA) is the estimated number of weeks of gestation or the time after the last menstrual cycle to the date of birth. Post conceptional age (PCA) is defined as the estimated gestational age plus the weeks of life. Infants born at a gestational age of less than 38 weeks are considered preterm babies; those born at a gestational age of 38-42 weeks are fullterm [26].

Two major sleep states are recognized in newborns: active and quiet sleep. In active sleep, the breathing is irregular together with the emergence of rapid eye movement (REM), small body movements and twitches. Quiet sleep is characterized by an absence of lateral eye movements with regular breathing. Quiet sleep is analogous to NREM sleep, and active sleep is analogous to REM sleep in adults. Sleep periods in which these observations do not fit the criteria for active or quiet sleep are termed indeterminate sleep. Active sleep and quiet sleep occur in alternating cycles of about twenty minutes. Indeterminate sleep occurs most often at sleep onset [27]. In general, active sleep is the predominant sleep state in the newborn and consists of greater than 70% of definable sleep time in the smallest premature infants and approximately 50% in fullterm infants [28].
Neurologists observed that neonatal EEG patterns change as a function of post conceptional age. Some EEG features that are helpful in determining whether the EEG is appropriate for the infant’s post conceptional age include the appearance and disappearance of specific waveforms and patterns, the discontinuity of background activity, and the percentages of inter hemispheric synchrony. For more information, see Ref. [28–31].

Previously, most of the knowledge of EEG maturation was based on visual analysis which is a time consuming task and requires a trained expert on neonatal EEG. Also, experts may disagree because the definitions of the maturational aspects of the EEG and methods of analyzing the EEG are not uniform. Therefore, quantitative analysis of EEG has been developed for better predictions of brain maturation.

The adjustment of the EEG power spectrum in newborns has been analyzed by many authors [32–37]. Generally, the power spectrum of the EEG is divided into four frequency bands: Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), and Beta (13-22 Hz) (the frequency range in each band may be defined discordantly). Scher et al. [33] used regression analyses to choose the least number of measures that best reflected maturation trends of EEG-Sleep in healthy preterm neonates. Those measures include sleep architecture (length of each sleep state), continuity (arousal number and duration), EEG spectrum (δ, θ, α, and β frequency bandwidths), phasic events (body movements and REMs), and autonomic measures (cardiac, respiration, and rectal temperature). They reported that the variability in spectral energy in the α band measured during quiet sleep and the total spectral EEG (0.5-22 Hz) energy during active sleep were the dominate factors in determining brain maturation in the preterm, i.e., they significantly decreased with increasing post conceptional age.

Recently, nonlinear time series analytic approaches have been applied to EEG data. Scher et al. [38] illustrated the application of dimensional analysis to assess neonatal sleep states at increasing gestational ages up to fullterm age. It was determined that the dimension increased for both active and quiet sleep as the preterm infant matured toward fullterm. Janjarasjitt et al. [39] investigated the relationship
between the complexity of sleep EEG time series and neurodevelopment for premature or fullterm neonates using correlation dimension (D2) where dimensional complexity was measured using Theiler’s modification of the Grassberger-Procaccia algorithm. They confirmed the result that the dimensional complexity of the neonatal EEG increases with neurodevelopment and brain maturation. Complexity analysis has also been studied by Zhang et al. [40] using Sample entropy (SampEn). They found that SampEn increases during both active and quiet sleep before 42wks PCA but does not change in quiet sleep and even decreases in active sleep after newborns reach 42wks.

In this research, we will use synchronization analysis to study brain maturation in neonates. We expect a difference in the strength of synchronization between mid preterm and fullterm neonates. Moreover, we expect that the difference between the late preterm to the fullterm is less than that between the late preterm and the mid preterm cohorts.

### 4.2 Methodology

#### 4.2.1 The data

Overnight EEG recording from 22 babies in the Normative Matched Cleveland Cohort were used in our analysis. These neonates were classified as normal according to their Brazy scores which were less than or equal to 3 and were they were divided into mid preterm (n=5), late preterm (n=7), and fullterm (n=10) groups.

The EEG signals were measured using unipolar acquisition scheme, and the data was converted to bipolar montage prior to analysis. For example, Fp1-T3 = (Fp1-Ref) - (T3-Ref). We measured coupling strength between inter hemispheric as well as intra hemispheric EEG channels using these 12 electrode pairs: Fp1-T3 : Fp2-T4, Fp1-C3 : Fp2-C4, Fp1-O1 : Fp2-O2, T3-O1 : T4-O2, T3-C3 : T4-C4, C3-O1 : C4-O2, Fp1-Fp2 : T3-T4, Fp1-Fp2 : C3-C4, Fp1-Fp2 : O1-O2, T3-T4 : C3-C4, T3-T4 : O1-O2, and C3-C4 : O1-O2. Figures 4.2 on the next page show the configuration of all electrode pairs.
Figure 4.2: Twelve electrode pairs that were used to compute synchronization index.

Prior to analysis the signals were filtered into the 4 frequency bands using zero-phase, band-pass filters. These filters had cut off frequencies as follows: Total (0.5-(Fs/2-1) Hz), Delta (0.5-4 Hz), Theta (4-8 Hz), and the higher frequency band (8-Fs/2-1) (Fs stands for sampling frequency). The 60 Hz artifact was also removed.

Only EEG epochs from well defined active and quiet sleep states were used for analysis. Once identified, these epochs were used to segment the signal into 30s epochs. The number of neonates and epochs in each group are summarized in table 4.1 on the following page.

For each epoch, the degree of synchronization was computed using cross correlation, Hilbert phase synchronization and mutual information. The details of the Hilbert method and mutual information are presented in section 2.1.2 on page 11. Note that in this study, the mutual information was computed from the original waveform instead of the phase of the waveform. Mutual information measures statistical dependency (e.g. from nonlinear correlation) between two time series. Cross correlation (CC) is a statistical measure that quantifies the degree of linear dependence between two time series [41]. The cross correlation at time delay $d \in [-D, D]$ is defined as

$$C_{xy}(d) = \begin{cases} \frac{1}{N-d} \sum_{n=1}^{N-d} \hat{x}_{n+d} \hat{y}_n, & d \geq 0 \\ C_{xy}(-d), & d < 0 \end{cases}$$

(4.1)
where \( \hat{x} \) denotes a normalization of the variable \( x \), i.e., \( \hat{x} = (x - \mu_x)/\sigma_x \), \( \mu_x \) and \( \sigma_x \) denotes mean and standard deviation of \( x \), similarly for \( \hat{y} \). When \( d = 0 \), cross correlation is precisely the correlation coefficient which has a maximum value equal to \( \pm 1 \) if \( x \) and \( y \) are linearly dependent, and minimum value equal to 0.

\[
CC = \max_d |C^{xy}(d)| 
\] (4.2)

The total of 288 synchronization indices were computed from 4 frequency bands \( \times 3 \) techniques \( \times 2 \) sleep states \( \times 12 \) electrode.

Table 4.1: Number of EEG recordings, active, and quiet sleep epochs in each group.

<table>
<thead>
<tr>
<th>Group</th>
<th>GA (weeks)</th>
<th>Babies</th>
<th>A/S epochs</th>
<th>Q/S epochs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid preterm</td>
<td>28-34</td>
<td>5</td>
<td>90</td>
<td>170</td>
</tr>
<tr>
<td>Late preterm</td>
<td>34-37</td>
<td>7</td>
<td>126</td>
<td>238</td>
</tr>
<tr>
<td>Fullterm</td>
<td>37-42</td>
<td>10</td>
<td>180</td>
<td>340</td>
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4.2.2 Test design

We divided the statistical analysis into two steps. In step one, we tested the hypothesis that the mean of each synchronization index of mid preterm was equal to that of the fullterm group. We used the repeated measures ANOVA method to test the difference in the means of all synchronization indices. All indices were transformed using log transformation to normalize the distribution. We rejected the null hypothesis at a p-value less than or equal to 0.05.

In step two, we used the synchronization indices that were able to distinguish mid preterm and fullterm groups to classify the neonates from the late preterm group. We computed the mean Mahalanobis distance between the synchronization index of each neonate in the late preterm to the mid point (centropid) of preterm and fullterm groups. Then we assigned the late preterm neonate to the group which was closer. Finally, we computed the percentage of the late preterm neonates who were assigned to the mid preterm and fullterm groups.
The mean Mahalanobis distance is given by

$$d_m = \frac{1}{N} \sum_{i=1}^{N} \frac{(y_i - \mu_x)^2}{\sigma_x^2}$$

(4.3)

where $y_i$ is a synchronization index at epoch $i$ of a recording in the late preterm group, $\mu_x$ and $\sigma_x^2$ is the mean and variance of the mid preterm (or fullterm) group, $N$ is the total number of epochs of $y$.

### 4.3 Results

Table 4.2 on the following page summarizes the results of the first step. The symbol $\times$ denotes active sleep and $\circ$ denotes quiet sleep and both symbols indicate that the difference in synchronization indices was statistically significant to reject the null hypothesis, indicating that the EEG synchrony from mid preterm and fullterm are statistically significantly different. A synchronization index that does not have any mark means that index failed to reject the null hypothesis. For example, the cross correlation computed from the EEG pair C3-O1 : C4-O2 in the total frequency band during both active and quiet sleep was able to distinguish the mid preterm and fullterm neonates.

The results show that the frequency bands and the synchronization techniques had less effect on the test whereas the electrode pair and sleep state have a more important role. The difference in EEG synchronization of the mid preterm and fullterm infants was observed consistently in two electrode pairs which were C3-O1 : C4-O2 and T3-T4 : C3-C4. The synchronization indices computed during active sleep were mostly in the later pair while that during quiet sleep were presented in both pairs.

The indices that resulted in rejecting the null hypothesis were used in the second step to classify the late preterm group into one of the two previous groups. The results showed that using all of these indices, the majority of late preterm neonates were closer to the fullterm group than the mid preterm group.
Table 4.2: The significance of statistical testing of the hypothesis that mid preterm is equal to the full term babies. See text for the description of the symbols.

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<tbody>
<tr>
<td>Total</td>
<td>CC</td>
<td>HB</td>
<td>MI</td>
<td>×</td>
<td>×</td>
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### 4.4 Conclusion

Based on synchronization indices from different techniques, frequency bands, sleep states, and electrode pairs, we conclude that the mid preterm and fullterm neonates are separable. Moreover, the majority of late preterm neonates in this study were closer to the fullterm group than to the mid preterm group.
Chapter 5

Heart rate variability in ventilated rats after lung injury

Heart rate variability analysis (HRV) is the study of the variability in beat-to-beat (R-R) intervals measured from the ECG signal. It has been used to assess the status of clinical diseases [42] and can be measured in different ways. Standard HRV involves time domain analysis, frequency domain analysis, and Poincaré analysis. Time domain analysis consists of mean, standard deviation, and coefficient of variance (mean/standard deviation) of the instantaneous heart rate, inverse of the R-R interval. Frequency domain (power spectral) analysis involves calculating the power in the low and high frequency bands of the ECG and the ratio between them. Because the R-R time series is not uniformly sampled, standard methods for Fourier analysis are not directly applicable. The Lomb-Scargle method [43] is appropriate for computing the periodogram (power spectral density plot) of the R-R interval time series. Poincaré analysis is based on a scatter plot of the current and the next R-R interval [44]. To quantify the plot, we measure SD1 (short-term variability), SD2 (long-term variability) and the ratio between the two. This analytic approach and interpretation are standard but has many limitations [45]. In addition to the standard HRV analysis methods, nonlinear HRV analysis methods such as detrended fluctuation analysis which is a technique for detecting long-range correlation in a time series [46] and
TPVA analysis that quantifies nonlinear information in Poincaré plot [45] have been used as well.

**5.1 Periodicity in R-R interval time series**

In this chapter, we investigate HRV in ventilated rats after lung injury in which we hypothesize that the BVV group, which is healthier, would have greater HRV than the CMV group. Initially, we use the standard methods to measure HRV in 2.5min epochs of the ECG. The results in figure 5.1 show that HRV computed by these standard methods were not different in the BVV and the CMV groups.

![Figure 5.1: Standard HRV of the BVV and CMV groups.](image)

Next we examine the power spectrum of representative rats from the BVV and CMV groups in figure 5.2, and we observe that they are different. Based on the periodogram, the R-R intervals of the BVV rat had an irregular frequency component or wide bandwidth. On the other hand, the power spectrum of R-R intervals of the CMV rat had a narrow bandwidth with a dominant peak only at a single frequency component. This difference was also observed in the autocorrelation plot. The autocorrelation of the BVV rat was flat while the autocorrelation of the CMV rat approached that of a periodic signal. In summary, we observed that the R-R intervals of the CMV rat are more periodic than that of the BVV rat.

In the next section, we describe a methodology for measuring the periodicity in R-R intervals and also test the method with synthetic data. Then, we show the results of the method applied to the physiological time series data.
5.2 Methodology development

We propose two approaches to quantify regularity of the frequency or the periodicity of the R-R interval time series. The first approach uses the periodogram and the second approach uses the autocorrelation function.

5.2.1 Power spectral density approach

For the power spectral density approach, we compute the power spectral density by the Lomb-Scargle method and set the low frequency components \( f < 0.3 \text{ Hz} \) of the power spectrum to zero to exclude low frequency modulation of the ECG R-R interval time series. Then, we compute the summation of the power (total power) and divide each frequency component by the total power so that the power spectrum is in the form of relative power.

We then use two methods to quantify the bandwidth. The first is the peak of the relative power (maximum of the periodogram or \textbf{maxPER}). The peak of the relative power of a narrowband signal should be higher than that of a wideband signal.
Although this method is simple; it only depends on only one frequency component so that it might be sensitive to noise or any other frequency components that are not related to the influence of respiration or ventilation on the ECG signal. To account for the entire spectrum, we use the Relative Shannon Entropy (tRSE) which is a measure of the degree to which the histogram is similar to the uniform distribution. This measures how the relative power spectral density is distributed over the entire frequency range. We divide the frequency range into 20 bins, and for each bin $i$ we compute the sum of the relative power $P(i)$. Next, we compute tRSE as

$$tRSE = 1 + \sum_{i=1}^{M} \frac{P(i) \ln P(i)}{\ln M}$$  

If the relative power $P$ is similar to the uniform distribution over the frequency range, $P(i) \approx 1/M, \; i = 1, ..., M$ so tRSE $\approx 1 + \frac{\ln 1/M}{\ln M} \approx 0$. In contrast, if the relative power is concentrated in a particular frequency band then $P_i \approx 1$ for the frequency band $i$ and approximately zero elsewhere. Therefore, tRSE $\approx 1 + \frac{\ln 1}{\ln M} \approx 1$.

In summary, increasing tRSE from zero to one implies that the bandwidth of the R-R interval time series becomes narrower or the R-R interval time series is closer to a periodic signal.

### 5.2.2 Autocorrelation approach

Another way to quantify the regularity of the frequency of the R-R interval time series is to use the autocorrelation function that measures similarity of a time series with itself at increasing time-delays. Given a wide-sense stationary time series, its autocorrelation function is periodic if the time series is periodic. If the time series has a wide frequency range, its autocorrelation function would decrease faster and become more irregular when the time-delay increases.

Because the R-R interval time series is usually non-stationary, before computing autocorrelation function, it must be detrended by dividing the time series into multiple linear segments using the change points detection algorithm proposed in [47]. Then,
each segment is estimated using a linear least squares fit to the data. Finally, the linear trend is subtracted from each segment. We define autocorrelation function as

\[
R_{xx}(d) = \frac{1}{N-d} \sum_{n=1}^{N-d} \hat{x}_n \hat{x}_{n+d}
\]  

(5.2)

where \( x \) is the R-R interval time series, \( d \) is the delay, \( \hat{x} = (x - \mu_x)/\sigma_x \), \( \mu_x \) and \( \sigma_x \) denote the mean and standard deviation of \( x \), \( R_{xx}(d) \in [-1 1] \). It is essential to emphasize that the delay \( d \) represents number of heart beat rather than time because the R-R interval time series is not uniformly sampled.

Multiple options can be used to discriminate the autocorrelation of the R-R interval time series. We measured the degree of correlation by calculating the maximum (\( \text{maxACF} \)) and mean (\( \text{meanACF} \)) of the absolute value of the autocorrelation for \( d = 25 - 50 \). The range \( d \) could be selected differently depending on the frequency of the signal. In addition, we measured the predictability (complexity) of the autocorrelation by computing Sample Entropy (\( \text{SampEn} \)) [48]. We did not use standard parameters from literature, but rather used the false nearest neighbor technique to determine \( m \) and used the first minimum of the mutual information of the data to select the delay \( \tau \) [49, 50]. Finally, we set the tolerance \( r = 0.4 \times \text{SD} \) where SD was the standard deviation of autocorrelation.

### 5.2.3 Test of methods with simulated data

In this section, we applied the proposed methods to synthetic data to illustrate their capability in distinguishing the regularity of frequency or bandwidth. We used the Van der Pol oscillator

\[
\frac{d^2x}{dt^2} = (\mu - x^2) \frac{dx}{dt} - (\omega + U(-C, C))x(t)
\]  

(5.3)

where \( \mu = 1 \) and \( \omega = 40 \) that controls the frequency. \( U(-C, C) \) denotes uniform random noise applied directly to \( \omega \) to modify the bandwidth of the oscillator. We
solved the equation (5.3) using the 4th order Runge-Kutta method with step size of 0.2 and the length of data is 943 points. The data was generated for 21 values of $C$, from 0 to 50 with a step size of 2.5. It is important to emphasize that we did not try to simulate the R-R interval time series but to just simulate an oscillator that we could control its bandwidth. Figure 5.3 shows examples of data generated for $x$, its relative power spectrum, and its autocorrelation at 3 selected levels of $C$. When $C$ is increased, the bandwidth of the generated signal is wider and the autocorrelation function decay faster.

Figure 5.3: Simulated Van der Pol at different values of $C$.

For each value $C_i$, $i = 1, \ldots, 21$, we generated 20 data sets $x_{(i,j)}$, $j = 1, \ldots, 20$ using different realizations of the uniform random noise $U(-C_i, C_i)$. For each data set $x_{(i,j)}$, we measured variability using the techniques described in section 5.2. To compare all indices in terms of their ability of detecting change in variability when bandwidth changes, we computed the degree of monotonicity using the algorithm modified from the one proposed in [51]. Let $S \in \mathbb{R}^{21 \times 20}$ of which each element $S_{(i,j)}$ is the result of
a variability measure of data set \( x_{(i,j)} \). If \( S \) depends monotonically on the variable \( C \), we would expect \( S_i < S_k \) for all \( C_i < C_k \), where \( S_i \) is the mean value of the vector \( S_i \) (\( i \)-th of \( S \)). To determine whether \( S_i < S_k \), we used the rank sum test with significance level \( \alpha = 0.05 \). Let the result of the hypothesis testing \( h_{(i,k)} \) be 0 if the null hypothesis \( S_i = S_k \) cannot be rejected, \( h_{(i,k)} \) is 1 if the null hypothesis is rejected in favor of \( S_i < S_k \) and \( h_{(i,k)} \) is -1 if the null hypothesis is rejected in favor of \( S_i > S_k \). Then, the degree of monotonicity is defined as

\[
M = \frac{2}{r(r-1)} \sum_{i=1}^{r-1} \sum_{k=i+1}^{r} h_{(i,k)}
\]

where \( r = 21 \) is the number of elements of the variable \( C \).

The result of variability measures and degree of monotonicity of the Van der Pol oscillator are presented in figure 5.4 on the next page. Note that in the figure, all indices except SampEn are subtracted from 1 to plot them using the same axes with SampEn. From the plot, tRSE was the most sensitive in detecting changes in the bandwidth. It decreased almost linearly when \( C \) increased. The value of the remaining indices depended on the range of \( C \). maxPER, maxACF, and meanACF behaved similarly. They decreased slowly at lower \( C \), then more rapidly and finally leveled off becoming asymptotic to the \( C \) axis. This behavior may be described by a Gaussian model. SampEn had a threshold then linear trend. It was non-varying at lower values of \( C \) and then increased linearly but with quite large variance at the upper half value of \( C \). These results suggest that tRSE performs over a wide range of bandwidth while maxPER, maxACF, and mean ACF are best at narrow bandwidth; SampEn at wide bandwidth.

### 5.3 Results

We divided the R-R interval time series into multiple epochs with the length of 2.5min and then computed the HRV indices for each epoch. The result of the periodicity
Figure 5.4: Variability indices and the degree of monotonicity.

Figure 5.5: Heart rate variability before, during, and after ventilation in lung-injured rats.
analysis of the R-R interval times series for ventilated rats after lung injury is presented in figure 5.5 on the preceding page. Both techniques and various measures had consistent results. For the power spectral approach, tRSE and maxPER increased in the CMV group during ventilation as compared to BVV. MaxACF and meanACF in BVV and CMV groups were equivalent at baseline but significantly higher in the CMV group as compared to the BVV during the ventilation period, then were equal again during the recovery period. In addition, maxACF and meanACF of the BVV group at baseline and during ventilation could be different. These results suggest that the periodicity of R-R interval during CMV increased whereas irregularity of the R-R interval during BVV also increased.

5.4 Conclusion

In conclusion, we found that periodicity is a key to distinguishing HRV in the BVV and CMV groups. We applied some techniques to quantify the periodicity using the periodogram and autocorrelation function. We found that CMV introduced periodicity to the R-R intervals as quantified by increasing tRSE while BVV enhances stochastic structure in power spectral density of the R-R intervals because maxACF decreases. Therefore, our methods confirm that the lung injured rats that were supported by BVV had more heart rate variability than the rats that were supported by CMV.
Chapter 6

Classification of nonlinear structures in dynamical systems

Variability analysis is important in many applications, especially in physiological systems where it plays an important role in distinguishing health and disease. However, there are different forms of variability, e.g. stochastic and nonlinear deterministic, and our long term goal is to develop analysis methods that can not only quantify variability, but also classify its source. One step in that direction is being able to determine the structure of the system being studied from observation of time series data. In physiological applications, this would provide important information that can help guide our analysis approach. However, determining the structure of a dynamical system (e.g. linear or nonlinear) using only output time series data is a challenging problem. Examples of time series data generated from four different systems are shown in figure 6.1. By visual inspection, the time series look different but are impossible to classify. In fact, the bottom time series is the only one generated by a nonlinear system. The top time series is generated from a linear system driven by Gaussian white noise and the second time series from the top is actually the cube of the top time series. Finally, the third time series from top is the linear system driven by non-Gaussian white noise. For the first 3 systems, the nonlinearity arises from nonlinear transformations of the inputs and outputs; not from nonlinear dynamics.
The problem of nonlinear detection has been studied widely, primarily in the context of understanding if computations on the system outputs (e.g. correlation dimension) are the result of linear, nonlinear or chaotic dynamics.

In this chapter, we are interested in classifying four nonlinear system structures as illustrated in figure 6.2. In the figure, $G$ denotes Gaussian random input signal, $L$ denotes linear system, $n$ denotes static (memoryless) nonlinear transformation (function), $N$ denotes nonlinear system, and $Y$ denotes the output of the system. Examples of output time series of each type of system is illustrated in figure 6.1. The abbreviations and details for each system are given below.

- **GL** Linear system driven by Gaussian white noise input.
- **GLn** Linear system driven by Gaussian white noise input, observed through a static nonlinear output function.
- **GnL** Linear system driven by non-Gaussian white noise input. The non-Gaussian input signal, for example, could be generated by passing a Gaussian white noise signal through a memoryless non-linear map.
- **GN** Nonlinear system driven by Gaussian white noise input.

Generally, classification of **GL** and **GN** is not difficult. However, nonlinear transformations of outputs and inputs such as in **GLn** and **GnL** systems can make the
time series look nonlinear and confuses most of the classification algorithms. Among several approaches of nonlinear detection proposed in literature [52–58], the first method that we highlight is the work of Weiss [59] published in 1975. Weiss proved that linear stochastic processes are time reversible\(^1\) and that time reversibility is preserved under memoryless transformations. In other words, if the time series is \(\text{GLn}\) then it is reversible. He suggested a simple test for time reversibility that involved estimating the third moment of the first differences i.e., \(\text{REV}=\langle (x_n - x_{n-\tau})^3 \rangle\), which should be zero if the data are reversible. In 1995, Diks et al. [60] used this theorem to develop a statistical testing method to test the hypothesis that a time series is \(\text{GLn}\). However, rejection of the hypothesis may not imply that the time series is generated by a nonlinear dynamic system. In fact, the time series could be \(\text{GnL}\). Specifically, a linear system with an input signal that has a asymmetric distribution is not reversible. Therefore, if the hypothesis testing based only time reversibility is rejected, the only conclusion that can be made is that the data is not \(\text{GLn}\).

Another nonlinear detection approach is the surrogate data method introduced by Theiler et al. [6]. This method has been used widely in various applications [61–66]. The procedure of the surrogate data method begins with generating surrogate data sets that are consistent with a null hypothesis. The nonlinear statistic for the original

\(^{1}\)A time series is reversible if it is invariant with respect to time reversal.
and the surrogate data sets are then compared. If the value computed from the
original data is statistically different from the values computed from the surrogates,
then the null hypothesis is rejected.

The method of generating surrogate depends on the null hypothesis. Theiler et al.
[6] proposed a method to generate the surrogate data according to the null hypothesis
that the data is generated from a GL system. In this case, the data has Gaussian
distribution and its autocorrelation is fully characterized by the linear system. There-
fore, the surrogate data set can be generated such that its amplitude distribution is
Gaussian and its autocorrelation is identical to the original data. This surrogate
method is called Fourier Transform (FT) surrogate where the Fourier transform of
original data is computed and then the phase is randomized (the Fourier amplitude
is preserved). The surrogate is the inverse Fourier transform which has Gaussian
distribution and the same power spectrum with the original data.

In case of GLn, the surrogate should have the same autocorrelation and ampli-
tude distribution as the original data. However, due to a nonlinear transformation,
the amplitude distribution function is no longer Gaussian. For the case that the mea-
urement or transformation function is invertible, i.e., a monotonic function, Theiler
et al. [6] proposed the Amplitude Adjusted Fourier Transform (AAFT) method to
generate surrogates. Briefly, the AAFT surrogate is a shuffled version of the original
data in which the rank information of the surrogate is equal to the rank of the gen-
erated Gaussian input with the same linear autocorrelation as the original data. As
a result, the amplitude distribution of the surrogate and original data are identical.
However, the autocorrelation is the same only if the data is of infinite length.

To solve the problem of the autocorrelation in AAFT, the Iterated Amplitude
Adjusted Fourier Transform (IAAFT) surrogate method was introduced by Schreiber
and Schmitz [67]. IAAFT surrogate data is also generated by shuffling the original
time series but with a constraint that the autocorrelation is preserved. It is
claimed that failure to reject the null hypothesis of IAAFT surrogate test implies
that the system is either GL or GLn when n is monotonic. However, Schreiber and
Schmitz [67] tested IAAFT surrogate method with only one nonlinear static monotonic function \( f(x) = x\sqrt{|x|} \) and a nonlinear discriminating statistic (Prediction error). Hence, it is possible that the IAAFT surrogate method may not be valid for all monotonic functions and nonlinear discriminating statistics. To investigate this claim, we study the IAAFT surrogate method in section 6.1. Surprisingly, evidence shows that the IAAFT surrogate method depends on the degree of nonlinearity of the nonlinear transformation and nonlinear statistic that is used to measure nonlinearity. Specifically, the IAAFT surrogate method may reject the linear hypothesis of \( GLn \) if the nonlinear transformation function is strongly nonlinear. In addition, even if the function is not strongly nonlinear, the IAAFT surrogate method may reject the linear hypothesis when it is used in conjunction with certain nonlinear statistics such as correlation dimension or sample entropy.

Even if the IAAFT surrogate method works as claimed, rejection of the null hypothesis does not always imply nonlinear dynamics. The system could be \( GnL \), which is similar to the time reversibility technique, or the transformation is non-monotonic. In fact with our results, rejection of the null hypothesis could imply that the system is \( GLn \). Therefore, the only information we obtain from IAAFT surrogate test is that if the time series is \( GL \), then IAAFT surrogate test will reject the null hypothesis.

A technique that addresses this limitation was proposed by Barahona and Poon [68]. The technique is based on a comparison of the prediction power of linear and nonlinear models of the Volterra-Wiener-Korenberg form. We will refer to this as the *Barahona prediction* method. The procedure begins with predicting the given time series using discrete Volterra-Wiener-Korenberg series which is composed of a family of polynomial (linear and nonlinear) autoregressive models with degree 1, 2, 3, \ldots, \( d \) and memory 1, 2, 3, \ldots, \( k \), then searching for the best linear model (\( d = 1 \)) and the best nonlinear model (\( d > 1 \)) according to the Akaike Information Criterion. Finally, if the variance of the residuals computed from the best nonlinear model is statistically less than the variance of the residuals computed from the best linear model, it can be concluded that the nonlinear model has more prediction power than the linear model.
hence nonlinearity is detected. We present the performance of this method in section 6.2, and these results confirm that this method is able to distinguish GN from GL, GLn and GnL.

Based on the results of the Barahona method, two more tests are required in order to separate GL, GLn and GnL. Therefore, we proposed the Gaussian and correlation test of residual in section 6.3. Finally, conclusions are given in section 6.4.

6.1 Investigating nonlinearity using IAAFT surrogate method

Although IAAFT surrogate method was designed to test the null hypothesis that the system is GL or GLn when n is monotonic, Schreiber and Schmitz used only one nonlinear output function in a GLn model to verify the technique. In this section we investigate the performance of the IAAFT surrogate method for different types of nonlinear output functions with different degrees of nonlinearity. Our hypothesis is that the test result does not depend on the monotonicity but does depend on the degree of nonlinearity of the function.

Before testing our main hypothesis, we verified the performance of the IAAFT surrogate method by investigating the method when the input system is GL and GN. We generate the synthetic data corresponding to the scheme illustrated in figure 6.2 on page 68 to be the input of the test. The linear process GL was selected as a first order autoregressive model defined in equation (6.1).

\[ x_n = 0.85x_{n-1} + \eta_n \]  

(6.1)

where \( \eta_n \) represents Gaussian white noise with zero mean and unity variance.

For the nonlinear system (GN), we used a nonlinear autoregressive model given in equation (6.2). This model is similar to the previous one but it has a nonlinear
form.

\[ x_n = 0.65x_{n-2} \]
\[ -1.2x_{n-1}^2 + 1.1x_{n-2}^2 \]
\[ +1.1x_{n-1}x_{n-2} - 1.1x_{n-1}x_{n-3} \]
\[ -1.1x_{n-2}x_{n-3} + 1.1x_{n-2}x_{n-4} \]
\[ +1.1x_{n-3}x_{n-4} + \eta_n \]  

(6.2)

We expect the test to accept the linear hypothesis when the test system is \( \text{GL} \) and reject the linear hypothesis when the test system is \( \text{GN} \).

For the \( \text{GLn} \) case, we observed \( f(x_n) = x_n\sqrt{|x_n|}, x_n|x_n|, \) and \( x_n^3 \) namely \( \text{GLn1}, \text{GLn2}, \) and \( \text{GLn3} \) respectively. We also have models that include non-monotonic functions \( f(x_n) = |x_n|^3, x_n^2, \) and \( |x_n| \) namely \( \text{GLn4}, \text{GLn5}, \) and \( \text{GLn6} \) respectively. Figure 6.3 shows plots of the input and output of these nonlinear functions.

![Figure 6.3: Degree of nonlinearity of (a) monotonic and (b) non-monotonic functions.](image)

In addition, we investigate the performance of the test when the system is \( \text{GnL} \). We study the case when the input of the test linear system is non-Gaussian with both symmetric and asymmetric distribution. We use two nonlinear functions \( f(\eta_n) = \eta_n|\eta_n| \) and \( f(\eta_n) = |\eta_n| \) namely \( \text{GnL1} \) and \( \text{GnL2} \) to transform the Gaussian input respectively. The distribution of the transformed Gaussian input signal is shown in figure 6.4.

The influence of the nonlinear discriminating statistic on the results is also investigated. In principle, any nonlinear measure that characterizes time series by
A real number can be used as a discriminating statistic in the surrogate data method \cite{ref1, ref2}. In this test, we use nonlinear measures whose performance has been previously investigated by Schreiber and Schmitz \cite{ref3} (Schreiber and Schmitz investigated the performance of nonlinear statistics when certain parameters were changed). The nonlinear measures studied were Correlation Dimension (D2), Prediction Error (PE), higher order autocorrelation (C3), and time reversibility (REV). In addition, we include Sample Entropy (SampEn), and time-delayed Mutual Information (MI) in our analysis. The following details the IAAFT surrogate algorithm, parameter selection of nonlinear measures, and statistical hypothesis testing as well as the results of the investigation.

### 6.1.1 Algorithms for generating IAAFT surrogate data

The IAAFT algorithm was described in Ref. \cite{ref4} and can be summarized as follows.

**Step 1.** Given the original data \( x^0 = x^0_1, x^0_2, \ldots, x^0_N \), compute \( X^0 = X^0_1, X^0_2, \ldots, X^0_N \) where \( X^0 \) is the Fourier transform of \( x^0 \). Record the Fourier amplitudes \( |X^0_n|, \quad n = 1, 2, 3, \ldots, N \). Also record the rank information of \( x^0 \). Here, for example, \( \text{rank}(x^0_n) = k \) if \( x^0_n \) is the \( k^{th} \) smallest value in \( x^0 \).

**Step 2.** Randomly shuffle \( x^0 \) and name the shuffled version as \( x^i \).

**Step 3.** Compute the Fourier Transform of \( x^i \), and call it \( X^i \), then compute the Fourier amplitudes \( |X^i_n|, \quad n = 1, 2, 3, \ldots, N \).
Step 4. Adjust the Fourier Transform amplitudes $|X_n^i|$ back to $|X_n^0|$ using the formula $\hat{X}_n^i = X_n^i \cdot \frac{|X_n^0|}{|X_n^{i-1}|}$, $n = 1, 2, 3, \ldots, N$. Then compute the inverse Fourier Transform of $\hat{X}_n^i$ and call it $\hat{x}_n^i$.

Step 5. Re-order $x^0$ to have the same rank information as $\hat{x}_n^i$ and call it $x_n^i$ again. Here, if $\text{rank}(\hat{x}_n^i) = k$, after re-ordering we have $\text{rank}(x_n^i) = k$ as well.

Step 6. Steps 3 to 5 are repeated until the error of the Fourier amplitude $|X_n^i|$ of the previous and the current iteration changes very little. Finally, the surrogate data is $x^i$ of which the amplitude distribution is identical to $x^0$ and the autocorrelation is almost the same. In this study, we use the tolerance function shown in equation (6.3) as a criteria to terminate the iteration. We stop the computation if $\varepsilon < 1e^{-6}$.

$$\varepsilon = \frac{\sum_n (|X_n^i| - |X_n^{i-1}|)^2}{\sum_n (|X_n^0|)^2} \cdot 100$$  \hspace{1cm} (6.3)

6.1.2 Parameter selection for nonlinear measures

Correlation dimension (D2) measures self-similarity in a time series [71]. In the computation of correlation dimension, the embedding dimension $m$ and time-delay $\tau$ for the delay reconstruction must be appropriately specified. Generally, the false nearest neighbors technique has been used to determine the embedding dimension $m$ [49]. For the time-delay $\tau$, either the first zero crossing of autocorrelation function or first minimum of the time-delayed mutual information of the data can be used [50]. However, because this study is a comparative analysis, the true dimension value was not essential. Therefore, we selected dimension $m = 3$ and $\tau = 1$ as suggested by Theiler et al. [6] and Schreiber and Schmitz [67].

Sample entropy (SampEn) quantifies predictability in a time series [48]. Sample entropy requires selecting the pattern length matching parameter $m$, the time-delay $\tau$, and $r$ which is the scale or tolerance parameter that is typically chosen as $0.2 \times SD$, where $SD$ is the standard deviation of the data. For computational simplicity, we used a pattern length $m = 3$ and a time-delay $\tau$ as in the correlation dimension technique.
Although unity time-delay $\tau$ may affect the measure due to high autocorrelation [72], we would expect that the effect is the same for the original and IAAFT surrogates because they have almost identical autocorrelation functions.

Mutual information (MI), derived from information theory [73], measures the statistical dependence of two time series. We measured mutual information of the data and its unity time-delayed version. In the computation of mutual information, we divided the data into 20 bins and normalized mutual information to the $[0,1]$ interval using the method proposed in Ref. [5].

Nonlinear prediction error (PE) is another nonlinear statistic that is based on time-delay reconstruction. The basic idea is to try to predict the future values by averaging all neighboring delay vectors closer than $\epsilon$ in the embedded space. Details about the root mean square (RMS) error of a simple nonlinear predictor can be found in Ref. [69, chap. 4]. We computed the one step ahead predictor and selected dimension $m=3$, time-delay $\tau=1$, and neighborhood size $\epsilon=1/4$ of the root mean square of the data as suggested by Schreiber and Schmitz [70].

Finally, higher order autocorrelation (C3) and time reversibility (REV) are parameter free methods. Higher order autocorrelation is a generalized version of linear autocorrelation by adding more than one lag, i.e., $C3=\langle x_n x_{n-\tau} x_{n-2\tau} \rangle$ where $\langle \cdot \rangle$ denotes the mean value. Again, time reversibility is given by $REV=\langle (x_n - x_{n-\tau})^3 \rangle$.

### 6.1.3 Statistical hypothesis testing

Statistical hypothesis testing is used to test the null hypothesis that the nonlinear statistic value computed from the surrogates is not statistically different from that computed from the original data. Theiler et al. [6] suggested the non-parametric rank-order test for the case that only one realization of the original data is available. For one-sided test, $1/\alpha -1$ surrogate data must be generated, where $\alpha$ is the selected significance level of the test. For two-sided test, $2/\alpha -1$ surrogate data are required. However, when multiple realizations of the original data are available, Theiler et al. [6] suggested that it is possible to compare two distributions direct-
ly using non-parametric test such as Mann-Whitney Rank-Sum test that compares the full distributions instead of just the mean. We used the later method in this investigation.

### 6.1.4 Test design and results

We generated 100 realizations of 2048 samples of Gaussian white noise. Each realization was used as an input signal for different processes as described at the beginning of the chapter to create the original data. For each of the corresponding original data sets, we created a surrogate data set using the IAAFT method described in section 6.1.1, then we computed the nonlinear measures as described in section 6.1.2 for both original and surrogate data sets. Finally, we compared the two distributions (original and surrogate data sets, each with 100 realizations) using the Mann-Whitney Rank-Sum test. We rejected the linear hypothesis at p-value less than or equal to 0.01.

<table>
<thead>
<tr>
<th>Systems</th>
<th>D2</th>
<th>SampEn</th>
<th>MI</th>
<th>PE</th>
<th>C3</th>
<th>REV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GL</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GN</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>GLn1</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GLn2</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GLn3</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GLn4</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GLn5</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>GLn6</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>GnL1</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>GnL2</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>R</td>
</tr>
</tbody>
</table>

The result of Mann-Whitney Rank-Sum test is summarized as rejected (R) or accepted (A) in table 6.1. The value of nonlinear measures of the original and surrogate sets is presented as box plots. Figure 6.5 is the result of the GL and GN cases, figure 6.6 is the GLn case, and figure 6.7 is the GnL case.

In the GL system, all nonlinear measures of the original and surrogate data sets
were not statistically different. Conversely, for GN system, all nonlinear measures of surrogate data sets were significantly different from the original data sets. (see figure 6.5 and the first two rows in Table 6.1 on the previous page). This result confirms that the IAAFT method correctly accepts the linear hypothesis when the data were generated by a linear system and rejects the linear hypothesis when the data were generated by a nonlinear system.

In GLn systems, REV accepts the linear hypothesis in all cases as expected (time reversibility is preserved under nonlinear memoryless transformations). In contrast, D2, SampEn, and MI reject the linear hypothesis following various transformation
functions except $\text{GLn1}$ in which the transformation function $f(x_n) = x_n\sqrt{|x_n|}$ is weakly nonlinear as shown in figure 6.3(a). The separation between these nonlinear measures computed from the original and surrogate data sets is more apparent when the nonlinearity of transformation becomes stronger as shown in figure 6.6.

The result based on PE and C3 depended on the degree of nonlinearity of the function. Although they accept the linear hypothesis when the function is monotonic, they reject the linear hypothesis when the function is non-monotonic and strongly nonlinear ($\text{GLn5}$ and $\text{GLn6}$). This finding raises the question: what is the detection result if the memoryless nonlinear function is monotonic but strongly nonlinear. To confirm that PE and C3 can be used in the case of monotonic functions, further study is required to make sure that PE and C3 accept the linear hypothesis of $\text{GLn}$ system when the nonlinear function is memoryless.

Acceptance or rejection of the linear hypothesis in $\text{GnL}$ systems depends on the nonlinear measures. Based on our investigation, D2, SampEn, MI, and PE reject the linear hypothesis in both systems but C3 accepts the linear hypothesis in both systems. REV accepts $\text{GnL1}$ which is reversible (has symmetric input distribution) but rejects $\text{GnL2}$ which is not reversible (has asymmetric input distribution). The test result of REV confirms that rejecting the linear hypothesis based on time reversibility may not imply nonlinearity.
6.1.5 Discussion and conclusion

The detection of nonlinear systems of the type $\text{GLn}$ depends on the specific nonlinear measures and output function. Time reversibility accepts the linear hypothesis regardless of the function. However, it also accepts the linear hypothesis if the system is $\text{GnL}$. Prediction error and higher order autocorrelation might incorrectly reject the linear hypothesis at some point depending on the strength of the monotonic nonlinear input function. Complexity measures such as correlation dimension, sample entropy, and mutual information always rejects the linear hypothesis if the nonlinear function is not too weak. Finally, for the $\text{GnL}$ system, the IAAFT surrogate test could reject or accept the linear hypothesis depending on the nonlinear function and nonlinear discriminating statistics.

6.2 Barahona prediction method

Barahona prediction method detects nonlinearity by trying to estimate a Volterra-Wiener-Korenberg model from the time series data given in linear and nonlinear form. If the nonlinear form fits the time series better, then the time series is assumed to be from a nonlinear system. Otherwise, it is a linear process. This method was designed for distinguishing nonlinear deterministic dynamics from stochastic linear dynamics. In this section, we applied the Barahona prediction method to distinguish $\text{GN}$, a nonlinear stochastic process, from $\text{GL}$, $\text{GLn}$, and $\text{GnL}$.

We used the same synthetic model for the $\text{GL}$ and $\text{GN}$ systems as in section 6.1.1. The nonlinear function for $\text{GLn1}$ and $\text{GLn2}$ systems were $f(x_n) = x_n^3$ and $f(x_n) = x_n^2$ respectively. We selected both monotonic and non-monotonic functions to explore and possible differences in the results. Finally, we used $f(\eta_n) = \eta_n^2$ to transform the Gaussian input in the $\text{GnL}$ model. The following are the details of this method as well as the test results and a discussion about the technical issues of the method.
6.2.1 Solving the Volterra-Wiener-Korenberg model

The computational procedure of the Barahona prediction method was given in Ref. [68]. Here we present this procedure with detail as follows.

Consider the time series \( x = x_1, x_2, x_3, \ldots, x_N \) that can be predicted by the discrete Volterra-Wiener-Korenberg model with degree \( d \) and memory \( k \)

\[
\hat{x}_n = a_0 + a_1 x_{n-1} + a_2 x_{n-2} + \ldots + a_k x_{n-k} + a_{k+1} x_{n-1}^2 + a_{k+2} x_{n-1} x_{n-2} + \ldots + a_{M-1} x_{n-k}^d = \sum_{m=0}^{M-1} a_m z_m(n)
\]

(6.4)

where \( \hat{x}_n, n = k + 1, \ldots, N \) is the prediction, and \( z_m(n) \) is composed of all distinct products of \( (x_{n-1}, x_{n-2}, \ldots, x_{n-k}) \) up to degree \( d \). For example, for \( d = k = 2 \), \( z_2(n) = x_{n-1}, x_{n-2}, x_{n-1}^2, x_{n-1} x_{n-2} \) and \( x_{n-2}^2 \). \( M = (d + k)!/(d!k!) \) is the total number of unknown coefficients \( a_m \). Equation (6.4) can be written as a linear system equation \( \hat{x} = Z a \) where \( \hat{x} \in \mathbb{R}^{N-k}, Z \in \mathbb{R}^{(N-k) \times M}, \) and \( a \in \mathbb{R}^M \). The coefficients \( a \) can be computed by minimizing the square of residuals

\[
\varepsilon = x - \hat{x} = x - Z a
\]

(6.5)

where \( x = x_{k+1}, \ldots, x_N \). This is a least squares optimization problem and the optimal solution \( a \) is the vector that solves the linear equation

\[
Z^T Z a = Z^T x
\]

(6.6)

Equation (6.6) can be solved using any linear solver. In this thesis, we solve this equation using an orthogonal-triangular decomposition of the symmetric matrix \( Z^T Z \).

6.2.2 Searching for the best linear and nonlinear model

After the coefficients \( a \) of the model have been determined, the predicted time series \( \hat{x} \) and the residual \( \varepsilon \) can be computed using equation (6.4) and (6.5) respectively (we
selected \( \hat{x}_n = x_n \) for \( n = 1, 2, 3, \ldots, k \). Then, the best linear model can be obtained by choosing the dimension \( d^* = 1 \) and searching for the optimal memory length \( k^* \) that minimizes the Akaike information criterion (AIC) [74]

\[
AIC(d, k) = \frac{1}{2} \log \left( \frac{\sum_{n=1}^{N} \varepsilon_n^2(d, k)}{\sum_{n=1}^{N} (x_n - \bar{x})^2} \right) + \frac{1}{N} \frac{(d + k)!}{d! k!} \tag{6.7}
\]

where \( \bar{x} = 1/N \sum_{n=1}^{N} x_n \). For the best nonlinear model, we search for both variables \((d^*, k^*)\) with \( d^* > 1 \) that also minimizes the AIC. Note that this is an optimization problem with one integer variable when searching for the best linear model and two integer variables when searching for the best nonlinear model. Therefore, it could be difficult solving this problem using the proposed optimization method. Accordingly, an easier way to solve this problem is to calculate AIC for all values \((d, k)\) in a particular range and then select \((d^*, k^*)\) that corresponds to the minimum AIC value.

### 6.2.3 Comparing the best linear and nonlinear model

We tested the null hypothesis that the prediction power of the best nonlinear model is not better than that of the linear model by comparing the variance of the residuals computed from both models. To determine what test statistic should be used, we first test the null hypothesis that the two distributions are Gaussian using \( \chi^2 \) test with significance level \( \alpha = 0.01 \). If the residuals are Gaussian then the F-test can be used to test the equality of variance of the two normal distributions. Alternatively, we use the non-parametric Ansari-Bradley test for non-Gaussian residuals. For the one-sided test, the null hypothesis is rejected in favor of the alternative hypothesis that the variance of residuals of the best nonlinear model is less than the variance of residuals of the best linear model, i.e., nonlinearity is present, at significance level \( \alpha = 0.01 \).
6.2.4 Test design and results

We generated 2048 data points for each of the 5 synthetic models defined in section 6.2 and performed nonlinear estimation using the method described in section 6.2.1-6.2.3. We searched for the optimal model using $d = 1 - 3$ and $k = 1 - 4$. Figure 6.8 illustrates the cost function as a function of the degree of nonlinearity $d$ and memory $k$ (equation (6.7)). The x-axis represents $k$ and each line of the plot represents $d$ as the following: — for $d = 1$ (linear model), · · · for $d = 2$ (second-order nonlinear model), and - - - for $d = 3$ (third-order nonlinear model). The * illustrates the optimal value of $d$ and $k$ of the linear model (—) or the nonlinear model (other line). Comparisons of the linear and nonlinear residuals are given in figure 6.9. Table 6.2 summarizes the results and p-values of the residual variance test.

The linear hypothesis could be rejected (at p-value = 2.5e-6) only for GN model of which the variance of the residuals of the nonlinear model were significantly less than that of the linear model (figure 6.8(e)). The variances of the residuals of the linear and nonlinear models of the other systems were not statistically different; hence, the linear hypothesis could not be rejected.

Table 6.2: Results of residual variance test. A/R-Accept/Reject linear hypothesis with (p-value).

<table>
<thead>
<tr>
<th>Systems</th>
<th>GL</th>
<th>GLn1</th>
<th>GLn2</th>
<th>GnL</th>
<th>GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>A (0.53)</td>
<td>A (0.33)</td>
<td>A (0.31)</td>
<td>A (0.13)</td>
<td>R (2.5e-6)</td>
</tr>
</tbody>
</table>
6.2.5 Discussion and conclusion

It is necessary to mention that the method that we presented was slightly modified from the original work of Barahona and Poon [68]. First, we use Ansari-Bradley instead of Mann-Whitney statistic as suggested in Ref. [68] for variance test in the case of non-Gaussian distributions because Mann-Whitney tests for equality in the median is not appropriate in this situation. Another difference is that Barahona and Poon confirm the test using surrogate data. They proposed that nonlinearity is detected when the best nonlinear model from the original data is more predictive than both the best linear model from the original data and the best linear and nonlinear models from the surrogate data. However, they also claimed that the surrogate data are always best approximated by a linear model and the prediction power of the best linear model from the original and surrogate data are generally equal. We interpret this statement as equivalent to the surrogate data are superfluous in this procedure. Therefore, we did not perform the nonlinear test on the surrogate data set.

We found that we need to be careful about the length of the time series and the number of parameters in the Volterra-Wiener model determined by the degree $d$ and memory $k$. The wider the range of $d$ and $k$ that we want to use to search for the best linear and nonlinear models, the greater number of parameters that must be estimated, hence, the longer the time series has to be. For example, if we want to search for the best model using $d$ and $k = 1-5$, then at the maximum value of both variables, the total number of parameters to estimate is $M = (5 + 5)!/(5!5!) = 252.$
Therefore, the time series with a length of 1000 may be too short. We have found that if we use time series that are too short for the number of parameters to be estimated, then it was likely that nonlinearity would be detected in a linear system.

In conclusion, although the Barahona prediction method has been introduced to detect nonlinearity in deterministic and chaotic dynamics, we have shown that it can be applied to detect nonlinear stochastic dynamics as well. However, large values of degree $d$ and memory $k$ should not be used if the length of data is short.

### 6.3 Residual analysis of Volterra-Wiener model

In this section, we propose a method to distinguish $\text{GL}$, $\text{GLn}$, and $\text{GnL}$. Our method is called residual analysis which is based on the hypothesis that when applying Barahona’s method to different systems, the properties of the residuals might be different. In fact, the Volterra-Wiener model is simply a nonlinear AR model. Hence, if we estimate $\text{GL}$ or $\text{GN}$ systems, and the coefficients of the models are correctly estimated, the residuals of the model should be a Gaussian white noise sequence. Similarly, the residuals of the $\text{GnL}$ system should be non-Gaussian but could be uncorrelated because the input of this system is a nonlinear memoryless transformation of a Gaussian random signal. Actually, the distribution of the residuals can be observed in figure 6.9(a), 6.9(e), and 6.9(d) on the preceding page.

Consider an example of a $\text{GLn}$ system that is given by the AR model $x_n = \alpha x_{n-1} + \eta_n$ where $\eta_n$ is a Gaussian white noise signal with zero mean and unity variance, and perform a nonlinear memoryless transformation (square) on the signal to yield

$$x_n^2 = \alpha^2 x_{n-1}^2 + 2\alpha x_{n-1} \eta_n + \eta_n^2 \quad (6.8)$$

Replace $x_n^2$ by $y_n$ and $x_{n-1}^2$ by $y_{n-1}$. Also let $\alpha^2 = \beta$ and $2\alpha = \gamma$, we have

$$y_n = \beta y_{n-1} + \gamma \sqrt{y_{n-1}} \eta_n + \eta_n^2 \quad (6.9)$$

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Equation (6.9) is obviously a nonlinear model with non-Gaussian input and the nonlinear term contains cross-correlation of the delayed output and input. Our hypothesis is that when we perform the Barahona method, the linear model will be a better fit to the data because the nonlinear model will not be able to fit the function \( \gamma \sqrt{y_{n-1}} \eta_n \) in the model if the degree and memory are not sufficiently large (if possible). In addition, \( \eta_n^2 \) will be the input. Finally, when examining the residual term \( \gamma \sqrt{y_{n-1}} \eta_n + \eta_n^2 \), it should be non-Gaussian and correlated. The non-Gaussian distribution of the residuals is presented in figure 6.9(c) on page 83. The following is the computational method that we use to test our hypothesis.

### 6.3.1 Test design and result

The procedure is based on section 6.2, where the test of Gaussian residuals is given in section 6.2.3. The only thing that needs to be done is to test if the residuals of the best (linear or nonlinear) model is temporally correlated. To perform this test, we use the shuffle surrogate method summarized in Ref. [6]. The null hypothesis for this test is that the observed data is temporally uncorrelated. The surrogate data sets are generated by shuffling the time-order of the original time series. The amplitude distribution of the surrogate and original data will be the same but any temporal correlations within the original time series will be destroyed. Then we use nonlinear prediction error as the nonlinear discriminating statistic. Because we have only one realization of the residuals, a non-parametric rank-order test is used to compare the surrogate and the original data. A significance level \( \alpha = 0.05 \) is chosen and 19 surrogate data sets are generated. The distributions of the residuals have already been shown in figure 6.9. The nonlinear prediction error of the original and surrogate sets are presented in figure 6.10 and the statistical testing results are summarized in table 6.3.

All results confirmed our hypothesis. The residuals of GL and GN were all Gaussian and uncorrelated. The residuals of GLn were non-Gaussian and correlated, which is different from GnL of where the residuals were uncorrelated but
non-Gaussian.

Table 6.3: Results of Gaussian and temporal correlation test. Y/N=Yes/No

<table>
<thead>
<tr>
<th>Systems</th>
<th>GL</th>
<th>GLn1</th>
<th>GLn2</th>
<th>GnL</th>
<th>GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaussian?</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Uncorrelated?</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

6.3.2 Discussion and conclusion

We proposed residual analysis of the Barahona method to explore insightful information about nonlinear schemes. Specifically, GLn can be separated from GnL. However, we presented only an auto-regressive model (AR) as the synthetic linear system. In fact, we also performed this analysis with a moving average (MA) model and an auto-regressive moving average (ARMA) model and the results were similar.

In addition, we also performed the analysis on deterministic and chaotic dynamics of which there is no Gaussian input. An example is the Henon map defined in equation (6.10) which is a polynomial model. When we estimated this system by Volterra-Wiener model, the best model was nonlinear and the residuals were zero.

\[ x_{n+1} = 1 - ax_n^2 + bx_{n-1} \quad (6.10) \]

Another example is the Ikeda model defined in equation (6.11) in which the non-linearity is not represented by a polynomial. Using the Barahona method, the best model was nonlinear which was detected at not too high degree and memory. However, the residuals were not zero mean and had large amplitude because the model may
require larger memory or higher degree to better fit the time series data. The residual analysis showed that the residuals were non-Gaussian and correlated. Therefore, this finding might also be used to further separate GN from nonlinear deterministic and chaotic time series.

\[
x_{n+1} = 1 + u(x_n \cos t_n - y_n \sin t_n) \\
y_{n+1} = u(x_n \sin t_n + y_n \cos t_n) \\
t_n = 0.4 - \frac{6}{1 + x_n^2 + y_n^2}
\] (6.11)

Table 6.4: Results of Gaussian and temporal correlation test as well as nonlinear test using Barahona method. L/NL=Linear/Nonlinear, Y/N=Yes/No

<table>
<thead>
<tr>
<th>Systems</th>
<th>GL</th>
<th>GLn1</th>
<th>GLn2</th>
<th>GnL</th>
<th>GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barahona test</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>NL</td>
</tr>
<tr>
<td>Gaussian?</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Temporally uncorrelated?</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

6.4 Conclusion

The objective of this chapter is to classify nonlinear structures presented in figure 6.2 on page 68. We have shown that the although the IAAFT surrogate method may not be appropriate for this task, the Barahona method can be used to separate GN from the others, and residual analysis can be used to distinguish GL, GLn and GnL. When we use the Barahona method together with residual analysis, these four systems are separable because the combination of the test results of each system is different as summarized in table 6.4.
Appendix A

Synchronization measures in chaotic oscillator

This appendix presents various synchronization measurement techniques for a chaotic oscillator proposed in literature. Synchronization measurement techniques that we explored are linear cross correlation, mutual information, phase synchronization based on Hilbert and Wavelet transformation, event synchronization, and generalized synchronization based on nonlinear inter-dependency and recurrence analysis. Actually some of them were presented in previous chapters already. Section A.1 summarizes mathematical background of the selected techniques. Section A.2 presents performance of these techniques to detect synchronization in a synthetic data.

A.1 Mathematical background

A.1.1 Phase synchronization

In addition to Hilbert transform, phase of a time series can also be extracted using wavelet phase transform. This method is based on complex Morlet wavelet transform [75] defined by a positive bandwidth $f_b$, a wavelet center frequency $f_c$, on a
$K$-points regular grid in the interval $[lb, ub]$. 

$$\varphi_k = \frac{1}{f_b \sqrt{2\pi}} e^{\frac{-k^2}{2f_b^2}} e^{2\pi f_c k}, \quad k = 1, \ldots, K \quad (A.1)$$

Convolution of the time series with the Morlet wavelet is a complex time series of wavelet coefficients

$$w^x_m = x_n \otimes \varphi_k, \quad m = 1, \ldots, N + K - 1 \quad (A.2)$$

and phase of $x$ is the angle of the wavelet coefficient $w^x_m$. After the phase of $x$ and $y$ is computed, the method for computing synchronization index is similar to the Hilbert phase technique presented in section 2.1.2.

### A.1.2 Generalized synchronization

Several statistical measures have been introduced for the detection of Generalized synchronization (GS) such as recurrence analysis [21], the method of mutual false nearest neighbors [18, 76], synchronization likelihood [77] and mutual predictability to detect dynamical interdependence [22]. In this section, we explored two methods which are based on the analysis of recurrence and nonlinear interdependence. Both methods have the same basic idea, that is, any two states of $x$ that are close to each other corresponds to two states of $y$ that are also close to each other. Both algorithms are based on nonlinear time series analysis where the nonlinear system is described by a phase space representation using a time-delay embedding technique. Here $x_n$ and $y_n$, $n = 1, \ldots, \hat{N}$, with $\hat{N} = N - (m - 1)\tau$ the state vector with time-delay $\tau$ and embedding dimension $m$ obtained from false nearest neighbor method [78].

#### Recurrences

Recurrence of a trajectory of a dynamical system is a return of the trajectory in state space to a neighborhood of a point where it has been before [3]. Analysis of recurrence
involves computing Euclidean distances between all points in the state space. The recurrence at point \( x_i, i = 1, ..., \hat{N} \) is defined as

\[
 r^x_{i,j} = \Theta (\epsilon - \| x_i - x_j \|_2^2) = 1
\]  

(A.3)

where \( \epsilon \) is a predefined threshold, \( \Theta(x) \) is the Heaviside function, i.e., \( \Theta(x) = 0 \) if \( x \leq 0 \) and \( \Theta(x) = 1 \) if \( x > 0 \). Hence, \( r_{ij} = 1 \) means \( x_i \) and \( x_j \) are neighbors, \( r_{ij} = 0 \) implies that \( x_i \) and \( x_j \) are far away from each other. Note that the total number of possible pairs is \( N_{ij} = \frac{\hat{N}(\hat{N}-1)}{2} \).

The criteria for the detection of generalized synchronization by means of recurrence was proposed by Romano et al. [21]. In this work, an index that quantifies the degree of similarity between the respective recurrences of both systems was defined. This index is based on the average probability of joint recurrence over time, and is given by

\[
 RR^{xy} = \frac{1}{N_{ij}^2} \sum_{i=1}^{\hat{N}-1} \sum_{j=i+1}^{\hat{N}} r^x_{i,j} \cdot r^y_{i,j} 
\]  

(A.4)

If both systems \( x \) and \( y \) are independent, then the average probability of a joint recurrence is expected to be approximately zero. In contrast, if they are in generalized synchronization, their respective recurrences must occur simultaneously, and hence \( RR^{xy} = RR^x = RR^y \), where \( RR^x \) (\( RR^y \)) denotes the average probability of recurrence over time in the state space of \( x \) (\( y \)), defined as

\[
 RR^x = \frac{1}{N_{ij}} \sum_{i=1}^{\hat{N}-1} \sum_{j=i+1}^{\hat{N}} r^x_{i,j} 
\]  

(A.5)

We modified the synchronization index defined in [21]) to be

\[
 GS_R = \frac{1}{2} \left( \frac{RR^{xy}}{RR^x} + \frac{RR^{xy}}{RR^y} \right) 
\]  

(A.6)

By this construction, low \( GS_R \) indicate independence between \( x \) and \( y \) and high \( GS_R \) indicate higher levels of (generalized) synchronization.
Nonlinear interdependency

An algorithm for detecting generalized synchronization by means of nonlinear interdependency was proposed by Arnhold et al. [22]. This synchronization index was based on the mean Euclidean distance of nearest neighbors of points $x_n$ and $y_n$. The algorithm is summarized as follows:

Let us call $i_{n,k}$ and $j_{n,k}$ the time indices of the $k$-th neighbor of $x_n$ and $y_n$, respectively. For each $x_n$ the squared mean Euclidean distance from $x_n$ to $x_{i_{n,k}}$ where $i_{n,k}$ is the time indices of the $k$-th neighbor of $x_n$ is defined as

$$r^x_n = \frac{1}{K} \sum_{k=1}^{K} (x_n - x_{i_{n,k}})^2$$  \hspace{1cm} (A.7)

Similarly, the squared mean Euclidean distance from $x_n$ to $x_{j_{n,k}}$ where $j_{n,k}$ is the time indices of the $k$-th neighbor of $y_n$ is

$$r^{xy}_n = \frac{1}{K} \sum_{k=1}^{K} (x_n - x_{j_{n,k}})^2$$  \hspace{1cm} (A.8)

If the systems are strongly synchronized, then $r^x_n \approx r^{xy}_n$, while $r^x_n \ll r^{xy}_n$ is always true for independent systems. Accordingly, the nonlinear interdependency is defined as

$$s^{xy} = \frac{1}{N} \sum_{n=1}^{N} \frac{r^x_n}{r^{xy}_n}$$  \hspace{1cm} (A.9)

Similar to analysis of recurrence, the synchronization index is defined as

$$GS_S = \frac{s^{xy} + s^{yx}}{2}$$ \hspace{1cm} (A.10)

where $s^{yx}$ is obtained by changing $x$ to $y$ in equation (A.7) - (A.8).

A.1.3 Correlation dimension

The measure of synchronization based on quantifying the correlation dimension of a coupled systems was proposed by Janjarasjitt and Loparo [23]. The index was defined
as the ratio of the sum of the correlation dimensions of the subsystems to the correlation dimension of the coupled dynamical systems determined from a concatenated embedding vector obtained from the two subsystems, i.e.,

$$CD = \frac{v^x + v^y}{v^\phi}$$ (A.11)

where $\phi_i = [x_i | y_i]$. The correlation sum for a collection of points $x_i$ is the fraction of all possible pairs of points which are closer than a given distance $\epsilon$.

$$C_x(\epsilon) = \frac{2}{N(N-1)} \sum_{i=1}^{\hat{N}-1} \sum_{j=i+1}^{\hat{N}} \Theta(\epsilon - \|x_i - x_j\|_2^2)$$ (A.12)

In the limit with an infinite amount of data ($\hat{N} \to \infty$) and for small $\epsilon$, $C$ is expected to scale like a power law, $C(\epsilon) \propto \epsilon^v$, and we can define the correlation dimension $v^x$ of time series $x$ by

$$d(\hat{N}, \epsilon) = \frac{\partial \ln C_x(\hat{N}, \epsilon)}{\partial \ln \epsilon},$$

$$v^x = \lim_{\epsilon \to 0} \lim_{\hat{N} \to \infty} d(\hat{N}, \epsilon)$$ (A.13)

It is obvious that the two limits defined in this formula can lead to difficulties in the analysis of practical time series because $\hat{N}$ is limited by the sample size of the data, and the range of meaningful choices for $\epsilon$ is limited by the inevitable lack of near neighbors at small length scales. We use Grassberger-Proccacia estimator in which $v^x$ is the slope of the plot of $\log C(\epsilon)$ versus $\log \epsilon$. The slope is estimated based on the least-squares linear regression [78].

A.1.4 Event synchronization

Introduced by Smirnov and Bezruchko [24] and discussed by Kreuz et al. [51], event synchronization (ES) is based on the relative timing of certain events extracted from the time series. This algorithm quantifies the level of synchronization by measuring
numbers of simultaneous appearances of events. In this study, events were defined as local maximum and minimum. $x_n$ is a local maximum if $x_n > x_{n \pm 1}$, and $x_n$ is a local minimum if $x_n < x_{n \pm 1}$. The local maximum and minimum were determined simultaneously by detecting the change of sign at every point of the time series.

$$s_n^x = \text{sign}(x_n - x_{n-1}) + \text{sign}(x_n - x_{n+1})$$ (A.14)

Where sign(.) is the signum function, i.e., $\text{sign}(x) = 1$ if $x > 0$, -1 if $x < 0$, and 0 if $x = 0$. From the condition of maximum and minimum, $s_n^x = 2$ if and only if $x_n$ is a local maximum, and $s_n^x = -2$ if and only if $x_n$ is a local minimum.

Let $e_{n,k}^x = 1$ if event $k = 1, ..., K$ occurs at point $n$ of the time series $x$, $e_{n,k}^x = 0$ otherwise. Therefore, the occurrences of the local maximum and minimum at point $n$ are

$$e_{n,\text{max}}^x = \text{sign}(s_n^x - 2) + 1$$ (A.15)

$$e_{n,\text{min}}^x = 1 - \text{sign}(s_n^x + 2)$$ (A.16)

To quantify the relative timing of all $K$ events, the number of times that event $k$ appears in time series $y$ after it appears in time series $x$ within a time lag $l$ is counted by

$$c_{xy}^l = \frac{1}{\sqrt{N_{e_x}N_{e_y}}} \sum_{k=1}^{K} \sum_{n=1}^{N-1} \sum_{m=n}^{n+l} e_{n,k}^x e_{m,k}^y$$ (A.17)

where $N_{e_x}$ denotes number of occurrence of all events found in time series $x$, i.e.,

$$N_{e_x} = \sum_{k=1}^{K} \sum_{n=1}^{N-1} e_{n,k}^x$$ (A.18)

Similarly, $c_{yx}^l$ and $N_{e_y}$ are defined accordingly. Finally, the synchronization index based on this technique is

$$ES = \frac{c_{xy}^l + c_{yx}^l}{2}$$ (A.19)
A.2 Performance of synchronization measures

We evaluated these synchronization techniques with coupled Rössler systems in which their coupling strength were determined by parameter $C$. The coupled Rössler system were generated by integrating equations (A.20) using a 4th order Runge-Kutta integration scheme with a step size of 0.001 and a sampling interval of 0.01.

\[
\begin{align*}
\dot{x}_1 &= -0.95x_2 - x_3 \\
\dot{x}_2 &= 0.95x_1 + 0.15x_2 \\
\dot{x}_3 &= 0.2 + x_3(x_1 - 10) \\
\dot{y}_1 &= -1.05y_2 - y_3 + C(x_1 - y_1) \\
\dot{y}_2 &= 1.05y_1 + 0.15y_2 \\
\dot{y}_3 &= 0.2 + y_3(y_1 - 10)
\end{align*}
\] (A.20)

Figure A.1 illustrates short segments of Rössler time series $x$ (solid) and $y$ (dash) corresponds to 3 values of $C$.

Figure A.1 illustrates short segments of Rössler time series $x$ and $y$ at different coupling strengths. The systems had weak synchronization at small value of $C$ and had complete synchronization at the maximum value of $C$.

We generated 4000 points of the coupled Rössler systems and used $x_1$ and $y_1$ as coupled signals. Forty one sets of data were generated for a level of $C$ that was varied from 0 to 2 in steps of 0.05. For each data set corresponding to each coupling strength, we measured synchronization index using the techniques mentioned in section A. The parameters for the measurement techniques are summarized in table A.1.
Table A.1: Parameters of synchronization measurement techniques: maximum time delay $D$, bandwidth $f_b$, center frequency $f_c$, grid $K$, lower bound $lb$, upper bound $ub$, embedding dimension $m$, time delay $t$, and threshold $\epsilon$.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$D$</th>
<th>$f_b$</th>
<th>$f_c$</th>
<th>$K$</th>
<th>$[lb \ ub]$</th>
<th>$m$</th>
<th>$t$</th>
<th>$\epsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td>0</td>
<td>2</td>
<td>$1/2\pi$</td>
<td>16</td>
<td>[-4 4]</td>
<td>3</td>
<td>1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Figure A.2: Coupling strength for eight measures of synchronization. See text for abbreviation.

Figure A.2 shows synchronization indices measured by linear cross correlation ($CC$), mutual information ($MI$), phase synchronization based on Hilbert ($PS_H$) and Wavelet ($PS_W$) transforms, event synchronization ($ES$), generalized synchronization based on nonlinear inter-dependency ($GS_S$) and recurrences ($GS_R$), and correlation dimension ($CD$). At $C = 0$ all indices are zero except correlation dimension. Event synchronization was not sensitive to $C < 0.8$. Mutual information, recurrence, and nonlinear inter-dependency gradually increased. Cross correlation increased rapidly at $0 < C < 0.25$ and remained approximately constant after $C > 0.5$.

To compare all indices in terms of their sensitivities to degrees of coupling, we measured degree of monotonicity as introduced by Kreuz et al. [51]. The results are presented in table A.2.

In conclusion, eight techniques of synchronization measurement were implemented
and evaluated with coupled Rössler systems. All techniques had satisfactory ability to distinguish intensity of synchronization. Among these techniques, \textbf{cross correlation} has the highest averaged degree of monotonicity whereas correlation dimension exhibits the lowest one. The Wavelet technique had higher degree of monotonicity than the Hilbert technique. Finally, recurrence analysis performs better than nonlinear inter-dependency.

<table>
<thead>
<tr>
<th>Measures</th>
<th>CC</th>
<th>$PS_H$</th>
<th>$PS_W$</th>
<th>MI</th>
<th>GS$_S$</th>
<th>GS$_R$</th>
<th>CD</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td>0.9951</td>
<td>0.9037</td>
<td>0.9268</td>
<td>0.9732</td>
<td>0.9780</td>
<td>0.9927</td>
<td>0.6927</td>
<td>0.7659</td>
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