PHASE BASED MEASURES OF COUPLING FOR EVENT DESCRIBING SIGNALS

by

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*We also certify that written approval has been obtained
for any proprietary material contained therein.
To all who have taught me how to be a decent human being.

I probably won’t be a super-villain anymore.
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The purpose of my efforts was to develop efficient yet comprehensive data analysis tools for the study of biological rhythms in the mammalian neural networks. I focused on two contexts in great detail; namely, the respiratory system and small neural networks.

In Chapter 2, I present a computational approach that can be used to study the relations between heartbeat and respiration using non-invasive recordings from these systems. We found that coupling was asymmetric with respiration affecting the heart beat more strongly than vice versa.

In Chapter 3, I present a measure that can be used to study functional connectivity from ensemble recordings. We show that our method, the Spike Triggered Average of the Postsynaptic Phase, reliably resolves pairwise interactions between neurons. Performance in terms of accuracy and running time were evaluated for multiple methods. We found that our measure matched or outperformed alternative approaches in various categories.
Chapter 1

Introduction

1.1 Motivation

Oscillations are widespread in nature and often perform functionally significant roles. In a single firefly, its bioluminescence waxes and wanes depending on the chemical properties generating the oscillating signal; whereas in a population of fireflies, the group’s bioluminescence waxes and wanes depending on the interaction or synchrony of the individual fireflies. Similar properties are observed in neurons where individual neurons may vacillate between periods of activity and quiescence, and yet, may suddenly synchronize with many other neurons surrounding in response to a perturbation. In my thesis, I focus on how to best quantify interactions between biological oscillators from indirect observations.

The study of interacting oscillations in Biology often utilizes electrical or chemical recordings with high temporal resolution. Statistical tools are then applied to determine if and how the systems interact, in addition to uncovering other features such as the time scales of the interactions. In most biological settings, interactions between oscillators can be investigated empirically with classical statistical measures such as the cross correlation coefficient or more involved techniques such as the crosscorrelogram, spectral coherence, and information theoretic measures. However, these approaches are often limited by their insensitivity to
the asymmetry of interactions. In the following chapters, I will show two ways to quantify coupling with empirical data.

1.2 Autonomic Control of Respiration

Cardio-respiratory coupling (CRC) corresponds to the reciprocal relationship between breathing and heartbeat rhythms. At its basic level, CRC is expressed as a constant ratio of heart beats to respiratory cycle which has been identified in several animal species at rest and during movement. Though debated, CRC may act to minimize the energy expenditure for gas exchange and thus plays an integral role in the control of homeokinesis by minimizing the work of gas exchanges and maximizing lung perfusion during inspiration. It is known that CRC is reciprocal and mediated by afferent pathways, central networks and mechanical properties of the physical system. Various pathologies which disrupt homeostasis have been associated with irregular coupling dynamics. Thus, tools that can assess CRC accurately may serve as biomarkers in determining the status of cardiac and respiratory pathologies and person’s health.

1.3 Emergence in Neural Networks

Emergence is defined as the properties that arise in complex systems built from a multitude of simple interactions. Consciousness is one example: individually, a neuron is capable of an all or none response; however, collectively arranged in networks, they allow for high order functions such as the formation of memories, sensory integration and abstract thinking. The term functional connectivity
has been used widely in the study of biological networks because physiologic connections, which exist on both macro and micro scales, may not coincide with anatomical ones. In the context of neural networks, synaptic connections may be too weak to affect the postsynaptic neuron or too strong so that the presynaptic and postsynaptic neuron have identical firing patterns.
Chapter 2

Resolving Coupling with Phase Models and Information Theory

2.1 Background

Rosenblum and collaborators proposed an approach to investigate coupling in real oscillators capable of resolving directionality and magnitude [1, 2]. Their strategy is to fit a generic model of coupled nonlinear oscillators to the data. In practice, the fitting is performed in the least-squares fashion; thus, a solution to the least-squares minimization problem always exists. In other words, an empirical model can be obtained from oscillators that are actually uncoupled, leading to spurious results. In this document, we propose a systematic computational approach to overcome this limitation. First, we compute the mutual information of the instantaneous phases and determine its statistical significance using randomized data. If the phases are statistically interdependent, then we compute the interaction functions of the oscillators. Lastly, we validate the empirical oscillator model by comparing the joint probability of the phases obtained from the model with the joint probability of the empirical phases.

We illustrate the application of our approach in two different contexts. First, we study a system of two coupled Stuart-Landau oscillators. This type of oscillator
is commonly used in theoretical and computational studies in physics as it repre-
sents the dynamics of a system close to a supercritical Hopf bifurcation; a frequent  
mechanism of obtaining a stable limit cycle [3]. Our approach reliably detects the 
presence or absence of coupling in this model as well as its directionality. Sec-
ond, we study cardio-respiratory coupling (CRC) in rats, where CRC is defined as 
the potentially reciprocal relationship between the rhythms of respiration and the 
heartbeat (Figure 2.1a) [4]. Theoretically, CRC minimizes the energy expenditure 
for gas exchange and plays an integral role in maintaining homeostasis [5–8]. Here, 
we show that the predominant coupling is due to an effect of respiration on the 
heartbeat. However, despite being weak, the effect of the heartbeat on respiration 
is also debated to be physiologically relevant.

Figure 2.1: Cardio-respiratory coupling schematic and inter-event in-
tervals for respiratory and heartbeat signals. (a) The blue ball represents 
respiration and the red ball represents heartbeat. The believed pathway asso-
ciated with mediating CRC for a given direction is labeled in the boxes. (b) 
Distribution of inter-event intervals for respiration and heartbeat in intact and 
vagotomized states. Vagotomy reduces the mean frequency of both oscillators.
Previous studies have quantified CRC using measures in the time and frequency domains. Recent reports have used $\chi^2$-statistics to quantify the deviance from uniformity of cross-correlograms of heartbeats relative to each breath [9, 10]. Other studies use spectral coherence at low frequencies [11, 12]. Although both approaches are valid, they are unable to resolve the relative strength of coupling in one direction versus the other. In the context of CRC, the empirical model of coupled phase oscillators proposed in [1, 2] is a natural choice [13–15] as it is sensitive to directionality of the interactions. In practice, two assumptions are made when using this approach. First, coupling between both oscillators is weak, in the sense that the dispersion around the mean frequency of the oscillator is small compared to the mean frequency, which is verified in Figure 2.1b; and second, the interactions between the oscillators can be truthfully represented by a phase oscillator model, i.e. the angular frequency is the only state variable, and the amplitude of the signal and its temporal modulation are irrelevant, which is verified in Figure 2.2.

2.2 Methods

2.2 Experimental Methods

Adult male Sprague-Dawley rats (Sprague Dawley/Harlan, 375-425g, n=15), were anesthetized with Isoflurane (0.5-1.0 %). Rats were intubated and breathed spontaneously. Electrocardiogram (ECG) was recorded from bipolar tungsten electrode
placed subcutaneously near the sternum and at the bottom right of the chest. Diaphragmatic electromyogram (EMG) was recorded differentially from bipolar electrodes placed percutaneously through the abdominal cavity into the diaphragm. Recordings were amplified (Grass P-511, West Warwick, RI, USA), filtered (.01-10 kHz), digitized (CED Power1401, Cambridge, UK) and stored on a computer via Spike2 software (Cambridge, UK).

Rats were given at least 30min after surgery to stabilize. One hour after the stabilization period, the vagi were dissected and transected. Recording continued for 1 hour after bilateral vagotomy. Stationary epochs were analyzed with vagi intact, immediately after transection of both vagus nerves and 1h after bilateral vagotomy (Figure 2.2).
2.2 Phase estimation

The recordings were first narrow-band pass filtered with the impulse response of the filter defined by a trapezoid with height 1 and vertices located around 0.5, 0.8, 1.3, 1.5 Hz for the EMG and 3.5, 4.0, 6.0, 6.5 Hz for the ECG. Then, the Hilbert transform was computed for each filtered signal to obtain a complex time series, the so-called analytical signal, whose angle represents the instantaneous “proto-phase”, for each oscillator, $\theta_1$, $\theta_2$. After a correction detailed in [16] was applied...
to $\theta_1$, $\theta_2$, to obtain the “genuine” phase $\varphi_1$, $\varphi_2$. Specifically, begin with $\theta$ and define

$$S_n = \frac{1}{N} \sum_{j=1}^{N} e^{-in\theta(t_j)},$$

where $\theta(t_j)$ indicates the values of the proto-phase at the $i$-th time sample. Then the genuine phase is given by

$$\varphi(t) = \theta(t) + \sum_{n \neq 0} \frac{S_n}{in}(e^{in\theta(t)} - 1).$$

We used $n = -10$ to 10 in our analysis as a larger range did not yield noticeably different results. An example of the phase in comparison with the raw data is shown in Figure 2.3.

---

**Figure 2.3: Phase of ECG and EMG recordings.** The phase of each recording is overlaid on the raw traces. Top is the ECG and bottom is the diaphragmatic EMG. B indicates breathing and H indicates heartbeat.
2.2 Mutual information of the phases

Mutual information is a non-directional measure of the dependency of two random variables based on their marginal and joint probability density functions. Intuitively, this measure describes how factorizable a joint distribution is. The mutual information, $I$, for two oscillators with phases is given by

$$I(\varphi_1, \varphi_2) = I(\varphi_2, \varphi_1) = \int_0^{2\pi} \int_0^{2\pi} P(\varphi_1, \varphi_2) \ln \left( \frac{P(\varphi_1, \varphi_2)}{P_1(\varphi_1)P_2(\varphi_2)} \right) d\varphi_1 d\varphi_2, \quad (2.1)$$

where $P(\varphi_1, \varphi_2)$ is the joint distribution of the phases and $P(\varphi_1)$ and $P(\varphi_2)$ is the marginal distribution. The sample estimate of $P(\varphi_1, \varphi_2)$ is computed with

$$P(\varphi_1, \varphi_2) = \frac{1}{N} \sum_{j=1}^{N} \delta(\varphi_1 - \hat{\varphi}_1(t_j)) \delta(\varphi_2 - \hat{\varphi}_2(t_j)), \quad (2.2)$$

where $\hat{\varphi}$ indicates empirical values of the $i$-th phase at each time sample, $j$ of $N$ samples ($Ndt$ is the total duration of the recording with $dt = 1$ ms in our case).

To construct a continuous distribution, the delta functions in (2) are convolved with a sharp symmetric distribution of unitary area and half-width $\sigma \ll 2\pi$. For our analysis, we use the von Mises distribution, which generalizes the Gaussian distribution to the case of wrap-around conditions. The von Mises distribution is given by

$$f(x|\mu, \kappa) = \frac{e^{\kappa \cos(x-\mu)}}{2\pi J_0(\kappa)}, \quad (2.3)$$

where $J_0$ is the modified Bessel function of the first kind and $\kappa = \frac{1}{2\pi\sigma^2}$. In the above expression, $\sigma^2$ is the analogue of the variance for the Gaussian distribution.
The bivariate form of the von Mises distribution is the product of (3); and so, the empirical probability distribution for the phases of two oscillators is given by

\[
P(\varphi_1, \varphi_2) = \frac{1}{N(2\pi J_0(\kappa))^2} \sum_{k=1}^{N} \exp(\kappa \cos(\varphi_1 - \hat{\varphi}_1(t_k))) \exp(\kappa \cos(\varphi_2 - \hat{\varphi}_2(t_k))).
\]  

(2.4)

This definition of the joint distribution of the phases is more robust than the traditional one obtained by building the two-dimensional histogram for the data. This is so because the calculation of the mutual information is sensitive to the size and edges of the histogram’s bins. The mutual information obviously depends on the choice of \( \sigma \) in (4); however, as long as \( \sigma \ll 2\pi \) it approximates the value for the “true” continuous distribution associated with its empirical estimation, \( P(\varphi_1, \varphi_2) \).

We use \( \sigma = 0.12 \) for our analysis.

Recall that \( I \) is used as the significance threshold for genuine coupling. As mentioned in the Introduction, this constraint is necessary because fitting the model to data always produces a coupling function, even in cases where the oscillators are independent. To determine whether \( I \) for a given experiment is significant, we rely on bootstrapping methods to obtain a tolerance for \( I \) due to chance interactions. Specifically, we compute \( I \) for the empirical phases and compare it to the 95% confidence interval of \( I \)’s computed from many randomizations of the empirical phases. The randomization we perform consists of independently permuting the cycles of both oscillators. It is worth noting that this randomization technique preserves the distribution, i.e. mean and variance, of the heartbeat and respiration periods.

For clarity, let \( I^* \) be the tolerance for significance (95th confidence interval).
The procedure to calculate $I^*$ is as follows. First, permute the cycles of the phases of both oscillators arbitrarily and compute $I$ for this particular randomization. Then, repeat this process many times ($n = 100$ in our case) and take the 95th percentile of all the $I$'s belonging to the randomizations. Compute the interaction functions only for experiments where the empirical $I$ is greater than $I^*$.

### 2.2 Empirical phase oscillator model

Following Rosenblum, et al. [1, 2, 17], the generic model of two coupled oscillators is given by

\[
\dot{\phi}_1 = \omega_1 + F_{2\rightarrow 1}(\phi_1, \phi_2) + \sigma_1 \eta_1(t),
\]

\[
\dot{\phi}_2 = \omega_2 + F_{1\rightarrow 2}(\phi_2, \phi_1) + \sigma_2 \eta_2(t),
\]

(2.5)

where $\dot{\phi}_1, \dot{\phi}_2$ is the time derivative of the phases; $\omega_1, \omega_2$ is the autonomous frequencies, $F_{2\rightarrow 1}(\phi_1, \phi_2), F_{1\rightarrow 2}(\phi_2, \phi_1)$ is the coupling function; $\eta_1(t), \eta_2(t)$ is uncorrelated white noise processes with unitary variance and scaled by constants $\sigma_1, \sigma_2$. The coupling functions can be expressed as a complex Fourier series given by

\[
F_{2\rightarrow 1} = \sum_{n,m} A_{n,m}^1 e^{i(n\phi_1 + m\phi_2)},
\]

\[
F_{1\rightarrow 2} = \sum_{n,m} A_{n,m}^2 e^{i(n\phi_2 + m\phi_1)},
\]

(2.6)

for which $n$ or $m \neq 0$ and where $n, m$ are indices synonymous to the $n : m$ phase locking indices of two oscillators, and $A_{n,m}^1, A_{n,m}^2$ are the coefficients of the respective Fourier series for given values of $n, m$. Also, each function possesses a direction: $2 \rightarrow 1$ denotes coupling in the direction from oscillator 2 to 1 and $1 \rightarrow 2$. 

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denotes coupling in the direction from oscillator 1 to 2. Incidentally, a similar approach can be applied to compute the phase-resetting curve of an oscillator from experimental data [18].

The left-hand side of (5) is directly computed from the data, and the right-hand side of (5) can be expressed as a complex Fourier series where \( \omega_{1,2} \) is given by (6) for which \( n \) and \( m = 0 \) and \( F_{1,2} \) is given by (6) for which \( n \) and \( m \neq 0 \). To avoid over-fitting, we first compute \( A_{n,m} \forall n, m's \) up to a given order, with the inner product of \( \dot{\varphi}_1 \) and \( e^{-i(n\dot{\varphi}_1 - m\dot{\varphi}_2)} \) given by

\[
A_{n,m} = \int_0^{2\pi} \int_0^{2\pi} \dot{\varphi}_1 \exp(-in\varphi_1 - im\varphi_2) d\varphi_1 d\varphi_2,
\]

which can be numerically approximated as \( \langle \dot{\varphi}_1(t) \exp(-in\varphi_1(t) - im\varphi_2(t)) \rangle \), by replacing the ensemble average with the temporal average. Then, we rank the 's and take coefficients with the largest power until 99% of the sum of the power for all the coefficients is reached, i.e. \( \sum_j |A_j|^2 > 0.99 \sum_{n,m} |A_{n,m}|^2 \), where \( A_j \) denotes the selected coefficients. When fitting the model to the data, we only use the fitting to the predetermined \( n, m \) indices. The amount of energy that cannot be accounted for the coefficients is then attributed to the energy of background noise, \( \sigma^2 \). In the final step, we fit (5) to the data using least squares. Furthermore, we use the parameters \( c_{2 \rightarrow 1}, c_{1 \rightarrow 2} \) given by

\[
c_{2 \rightarrow 1} = \sqrt{\frac{\sum_{n,m \neq 0} |A_{n,m}^1|^2}{2\pi}}, c_{1 \rightarrow 2} = \sqrt{\frac{\sum_{n,m \neq 0} |A_{n,m}^2|^2}{2\pi}},
\]

with units of Hz, to compare the strength of coupling and its directionality. In
particular, if $c_{2 \rightarrow 1} > c_{1 \rightarrow 2}$ the heartbeat drives respiration more strongly and vice versa if $c_{2 \rightarrow 1} < c_{1 \rightarrow 2}$.

Lastly, the amplitude of the interaction function has units of the reciprocal of time, Hz in our experiments. Thus, its reciprocal value provides a proxy for the time-scale of the coupling which is a few minutes in our experiments. Consequently, we selected 5-min long stationary epochs for analysis.

### 2.2 Validation of the empirical oscillator model

The final step of our approach involves the validation of the empirical oscillator model. To this end, we check whether the joint distribution of the empirical phases is statistically different from the joint distribution of the phases obtained from simulating the coupled-oscillator model. This final step is an additional measure for preventing spurious results. For our approach, statistical similarity of the two distributions is determined using both Pearson’s linear correlation coefficient, $R$ and Kendall’s $\tau$.

The Kendall’s $\tau$ coefficient is a non-parametric correlation statistic based on ranks, and takes values between -1 and +1, where -1 indicates the ranks are completely opposite with respect to each other, 0 indicates there is no association with the ranks, and 1 indicates the ranks are identical. Details for computing the p-value for a given $\tau$ are provided in [19]. Hypothesis testing is performed using Kendall’s $\tau$, where the null hypothesis is that the two distributions are independent and the alternate hypothesis is that they are dependent. We cannot perform hypothesis testing with $R$ since the error is not entirely Gaussian. Finally, we note that to compute Kendall’s $\tau$ and $R$ for the empirical and theoretical
probability distributions, we discretize them in intervals of $2\pi/100$ for both $\varphi_1$ and $\varphi_2$.

2.2 Pseudocode

We implement our approach with MATLAB, made publicly available on our website as the Empirical Phase Oscillator Model (EPhOM) software package. EPhOM will take pre-processed data as input and produce the coupling functions where applicable. An overview of our approach is as follows. Start by computing the empirical joint distribution of the data. Then, compute $I$ from the empirical joint distribution of the phases and compare it with $I^*$. Proceed with the analysis only if $I$ is significant, i.e., $I > I^*$. Next, fit the model of coupled oscillators to the data. Following, simulate the phase oscillator model and compute the joint distribution of these surrogate phases. Lastly, compute the Kendall’s $\tau$ for the empirical and the theoretical probability density functions. The results are only considered if $\tau$ is significant, that is, the p-value is less than 0.05.

2.3 Results

2.3 Numerical study

We simulate two complex Stuart-Landau oscillators with weak diffusive coupling and weakly driven with uncorrelated white noise:

$$\begin{cases} 
\dot{z}_1 = (1 + i\omega_1) z_1 - |z_1|^2 z_1 + \varepsilon_1 (z_2 - z_1) + \sigma_1 \eta_1(t) \\
\dot{z}_2 = (1 + i\omega_2) z_2 - |z_2|^2 z_2 + \varepsilon_2 (z_1 - z_2) + \sigma_2 \eta_2(t)
\end{cases}$$
In Cartesian coordinates, the model is given by

\begin{align*}
\dot{x}_1 &= x_1 - \omega_1 y_1 - x_1(x_1^2 - y_1^2) + \varepsilon_1(x_2 - x_1) + \sigma_1 \eta_1(t) \\
\dot{y}_1 &= y_1 + \omega_1 x_1 - y_1(x_1^2 - y_1^2) + \varepsilon_1(y_2 - y_1) \\
\dot{x}_2 &= x_2 - \omega_2 y_2 - x_2(x_2^2 - y_2^2) + \varepsilon_2(x_1 - x_2) + \sigma_2 \eta_2(t) \\
\dot{y}_2 &= y_2 + \omega_2 x_2 - y_2(x_2^2 - y_2^2) + \varepsilon_2(y_1 - y_2)
\end{align*}

And in polar coordinates it reads,

\begin{align*}
\dot{r}_1 &= r_1(1 - \varepsilon_1 - r_1^2) + \varepsilon_1 r_2 \cos(\varphi_2 - \varphi_1) + \sigma_1 \eta_1(t) \cos(\varphi_1) \\
\dot{\varphi}_1 &= \omega_1 + \varepsilon_1 \frac{r_2}{r_1} \sin(\varphi_2 - \varphi_1) - \sigma_1 \eta_1(t) \sin(\varphi_1) \\
\dot{r}_2 &= r_2(1 - \varepsilon_2 - r_2^2) + \varepsilon_2 r_1 \cos(\varphi_1 - \varphi_2) + \sigma_2 \eta_2(t) \cos(\varphi_2) \\
\dot{\varphi}_2 &= \omega_2 + \varepsilon_2 \frac{r_1}{r_2} \sin(\varphi_1 - \varphi_2) - \sigma_1 \eta_1(t) \sin(\varphi_2)
\end{align*}

Under the weak-coupling assumption, are roughly constant, and can be approximated as 1. In this case, the model of coupled Stuart-Landau oscillators takes the form of two weakly coupled phase oscillators, as in (5) with

\begin{equation}
F_{2 \rightarrow 1}(\theta_2, \theta_1) = \sin(\theta_2 - \theta_1),
\end{equation}

\begin{equation}
F_{1 \rightarrow 2}(\theta_1, \theta_2) = \sin(\theta_1 - \theta_2).
\end{equation}

We applied our approach to four different test cases: asymmetric coupling where oscillator 2 drives oscillator 1 more strongly than vice versa, asymmetric coupling where oscillator 1 drives oscillator 2 more strongly than vice versa, symmetric coupling, and no coupling. For all the test cases, \(\omega_1 = 3, \omega_2 = 3\pi\) and \(\sigma_1 = \sigma_2 = 0.05\). For the asymmetric cases, \(\varepsilon_1 = 0.5, \varepsilon_2 = 0.15\) and \(\varepsilon_1 =\)
0.15, \varepsilon_2 = 0.5, for the symmetric case, \varepsilon_1 = 0.5, \varepsilon_2 = 0.5, and for the uncoupled case, \varepsilon_1 = 0, \varepsilon_2 = 0. Our approach accurately resolves the presence or absence of coupling, its directionality, and its magnitude (Figures 2.4 and 2.5).

Figure 2.4: Mutual information values of simulated coupled Stuart-Landau oscillators. (a) Symmetric coupling. (b) Asymmetric coupling where oscillator 2 drives oscillator 1 more strongly than vice versa. (c) Asymmetric coupling where oscillator 1 drives oscillator 2 more strongly than vice versa. (d) No coupling.
Figure 2.5: Theoretical and empirical coupling functions of simulated coupled Stuart-Landau oscillators. In (a), (b), (c), (d) top is a schematic showing how the oscillators are coupled. Middle is the theoretical coupling function and bottom is the empirical coupling function obtained using our approach. (a) Symmetric coupling. (b) Asymmetric coupling where oscillator 2 drives oscillator 1 more strongly than vice versa. (c) Asymmetric coupling where oscillator 1 drives oscillator 2 more strongly than vice versa. (d) No coupling.
2.3 Cardio-respiratory coupling in anesthetized rats

We applied our analytical approach to a physiologic data set composed of 15 experiments. The values of mutual information ranged from highly significant to insignificant (Figure 2.6); data from 12 of 15 passed the mutual information test and 3 (see Figure 2.6, 13 through 15) were excluded because the data did not possess a significant value of the mutual information (Figure 2.6).

![Figure 2.6: Mutual information values of CRC data. The empirical and randomized values of the mutual information are presented for the 15 experiments composing our dataset.](image)

The coupled phase oscillator model was obtained for 12 experiments, and importantly, the residuals of these models, $\eta(t)$, were not correlated. The Pearson’s
linear correlation coefficients for $\eta_B(t)$ and $\eta_H(t)$ were $< 6\%$ for all the experiments analyzed. This indicates that the coupling between both oscillators is deterministic and not the result of stochastic synchronization [20–24], i.e. the entrainment of uncoupled oscillators driven by common noise.

In order to improve the solution of the least squares problem, we removed angular frequencies that differed by more than three standard deviations from the natural frequency. Outlying angular frequencies were removed by eliminating entire segments of the phase corresponding to those values, from both signals. This preserves the paring of the data points in time, thus preserving any interactions which were present prior to modifying the data. For clarity, no means of interpolation was used to fill in removed segments; they are simply removed in the same way from both signals. An example of the coupling functions for an experiment before and after vagotomy is presented in Figure 2.7a, and examples of the coupling functions for three experiments in the naïve state are presented in Figure 2.7b. Overall, the interaction functions are quite consistent across animals in terms of their undulated structure. This is because the dominant $A_{n,m}$ corresponds to the closest $n : m$ ratio of heartbeat to respiration.
Figure 2.7: Empirical coupling functions of CRC data. In both (a) and (b), left is the coupling function corresponding to the influence of heartbeat on the respiration, and right is the coupling function corresponding to vice versa. (a) Top is before vagotomy and bottom is after vagotomy. The coupling coefficients for this experiment correspond to 1 in Figure 2.9. (b) The coupling functions for three experiments are shown. Top, middle, and bottom corresponds to 2, 3, and 4 in Figure 2.9.
A comparison of the empirical and theoretical probability density functions is presented in Figure 2.8.

Figure 2.8: Empirical and theoretical joint probability distributions of the phases. The left panel is the joint probability of the empirical data. The right panel is the joint probability of the synthetic data.

The Kendall’s $\tau$, along with the associated p-value, and Pearson’s linear correlation coefficient is presented in Appendix A, and the coupling coefficients for these experiments are presented in Figure 2.9. Our results show that coupling in the heart-lung system in the anesthetized state is generally biased in the direction of respiration to heartbeat. Moreover, coupling in both directions diminishes to insignificant levels after severing the vagus nerve.
2.4 Discussion

We have presented a approach that combines mutual information with phase oscillator dynamics to quantify coupling in real oscillators. We have successfully tested our approach with a model of two coupled Stuart-Landau oscillators. In addition, we have applied our approach to investigate cardio-respiratory coupling in anesthetized rats. From a physiological perspective, we have shown that the interaction between heartbeat and respiration is reciprocal but predominantly manifested as an influence of respiration on heartbeat. While it is well known that the vagus nerve plays a critical role in mediating coupling in the direction from heartbeat to respiration.
to respiration, we have shown here for the first time that it affects the reciprocal interaction, thought to be mediated by arterial baroreceptors located in both vagal and other pathways.

Quite literally, the phase oscillator approach answers the question, can the fluctuations in instantaneous angular velocity of one oscillator be explained by the position of both oscillators? This is equivalent to determining if there exists positions on the unit circle that the oscillators prefer so that when the oscillators are not in these positions, they will speed up or slow down, depending on the location of both oscillators, to get to there. Since the phase oscillator model accounts for all the n:m phase ratios, the approach presented here is indiscriminate of the frequency ratios in which the two oscillators interact. A simple way to constrain the analysis to identify one particular n:m ratio, e.g. the ratio for the heart and lung interaction, is to only fit the model with a given n and m.

A natural concern with using mutual information as a measure of significance is its performance in the case of uni-directional coupling. It turns out that although the mutual information is a non-directional measure of dependence, it is still sensitive to uni-directional interactions. In other words, it can discriminate significant interactions even if coupling exists in only one direction. This is not difficult to see from the definition of mutual information and Bayes’s theorem. As mentioned previously, mutual information measures how separable or independent two random processes are. If the two processes are entirely independent one another, then the mutual information is zero. However, in the case where coupling exists in only one direction, the joint distribution is still inseparable, which
translates to the possibility of having some positive mutual information value. Nevertheless, there is still the chance that the strength of the unidirectional interaction is weak enough so that the empirical $I$ for this interaction falls in the confidence interval of the random $I$’s, which brings us back to the question of what is the best statistical measure for ruling out spurious coupling.

CRC is believed to be a good indicator of health, as it reflects a balance between the sympathetic and parasympathetic components of the autonomous nervous systems which control homeostasis and visceral function [25]. CRC interactions are defined and measured in different ways, the most popular is the so called respiratory sinus arrhythmia, by which inspiration tends to delay the upcoming heartbeat. This frequency modulation is apparent in the power spectrum of ECG signals as a second peak in the spectrum below 1 Hz corresponding to the heartbeat’s frequency modulation due to respiration. Consistent with the respiratory sinus arrhythmia, the phase-oscillator model obtained from the data reveals a dominant effect of respiration on the heartbeat. In addition, the model also resolves the reciprocal interaction: there is a weak but reproducible effect of the heartbeat on respiration suggesting that the baroreceptor pathway depicted in Figure 2.1 is also functionally relevant in anesthetized conditions.
Chapter 3

Adapting the Event Triggered Average to a Phase Framework

3.1 Background

Making the connection between individual neurons and advanced brain function requires an understanding of how neurons cooperate on a network level. The systems perspective is important because complex behavior is an emergent property of many interacting neurons. The distinction of functional connectivity is made to accommodate the observation that neuronal communication is dynamic. That is to say, anatomical knowledge of the neural network does not provide an accurate representation of how neurons are interacting to achieve a particular end [26, 27].

An experimental approach to study microcircuit architecture is to collect ensemble recordings of many neurons with micro arrays. The growing popularity of this method has prompted the development of diverse data analysis routines that can resolve functional connections with multi-electrode data [28–31]. Examples of such measures include the correlation coefficient (CORC), information theoretic measures, and the Granger Causality (GC) [32–34]. Each method has its own advantages and disadvantages. CORC is computationally efficient but may not resolve nonlinear correlations, lacks directionality and the ability to distinguish between excitatory and inhibitory interactions. Information theoretic measures
and the GC are capable of resolving directionality, but they are computationally expensive and may pose ill-suited assumptions about the data.

Classical measures well known to neurophysiologist have also been adapted to accommodate this new data type. These measures include the Spike Triggered Average (STA) and the crosscorrelogram (CCG). The STA is a measure often applied in sensory physiology studies. It is often used to characterize a direction in the stimulus space in which a neuron is likely to change its activity in response to a stimulus [35–37]. The data required for STA analysis requires a stimulus waveform, or trigger, and the output of the neuron that is being stimulated, also known as the target neuron. The STA is computed by extracting the stimulus waveform prior to each spike in the target neuron, and averaging the all the waveforms across all the spikes in the target neuron. In a statistical sense, if the stimulus waveform prior to a target neuron spike is a probability distribution, then the STA is the mean of this distribution. Another use for the STA is estimating the linear filter for a neuron’s Linear-Nonlinear-Poisson representation. The CCG, on the other hand, is used widely in pairwise interaction identification.

Slight modifications need to made to the STA for performing functional connectivity analysis. First, deem one neuron as the trigger and the other neuron as the target. Then, average the waveform of the target with respect to the spikes of the trigger. The intuition is that if the trigger is exciting the target, then there should be a significant increase (compared to random) in the number of spikes in the target following a spike in the trigger. On the other hand, an inhibitory interaction should lead to a significant decrease in the number of spikes in the
target following that of the trigger. The CCG relies on the same intuition. The difference in implementation between the STA and the CCG is that the CCG considers the output of the target as histograms. In a general sense, the STA and CCG compress information of the activity of a target around the spikes of the trigger. Also, since these measures rely on the average or the first moment of the target output relative to a trigger spike, they can only quantify linear relations between the trigger and target.

The STA and CCG belong to a family of methods that averages the waveform of one neuron with respect to a reference neuron. The main difference between these two methods is that the CCG is defined for binary signals, i.e. signals that take only values of 0 or 1, and the STA is defined for continuous signals.

The benefits of the STA and CCG are that they are easy to interpret, assume no underlying statistical model for the spiking dynamics, and can be easily implemented and applied by researchers without training in advanced statistics. The method proposed here is a variation of the theme of averaging the postsynaptic output relative to the spikes of a reference neuron. Just as the CCG takes the postsynaptic waveform as histogram, STAPP considers the postsynaptic waveform of the phase or the timing between spikes. The key difference in performance between STAPP and CCG is that STAPP can resolve the same interactions with less data.

With regards to interpretation, STAPP is directly connected to the concept of spike time reliability, which is often described as the tendency of neurons to fire with millisecond precision as well as responding consistently to repetitions of the
same stimulus. It is believed to be an important means of information encoding in the brain [38, 39]. In this framework, coupling strength is directly related to how a reference neuron can modulate the spike-time reliability of a target spike. To reiterate, the benefit of using STAPP is that it is computationally efficient, sensitive to weak coupling, and easy to interpret. We demonstrate its utility by comparing the STAPP with the correlation coefficient and an information theoretic approach, the directed information (DI) using simulated neural micro-networks composed of Hodgkin-Huxley neurons.

### 3.2 Methods

#### 3.2 Spike Triggered Average of the Postsynaptic Phase

Begin by transforming the post-synaptic spike train into a phase, given by

\[ \varphi(t) = 2\pi \left( \frac{t - t_k}{t_{k+1} - t_k} \right), \text{ for } t_k \leq t < t_{k+1} \]

where \( t_k \) is the spike times, and \( \varphi(t) \) takes values between 0 and 2\( \pi \) in between spikes. Then, define the target as \( c(t) = \cos(\varphi(t)) \). By construction, the peaks of the cosine coincide with the spike times of the target (Figure 3.1a).

Define the trigger as \( s(t) = \frac{1}{N} \sum_{i=1}^{N} \delta(t - t_i) \), where \( t_i \) is the time of the \( i \)-th out of \( N \) spike in the reference spike train. Let STAPP be denoted by \( \kappa(\tau) \), which
Figure 3.1: Continuous spike trains. (a) Continuous signal used by STAPP. b) Continuous signal used by the CORC. The continuous spike train in orange is overlaid on the discrete one in black.

is mathematically defined as

\[ \kappa(\tau) = \langle c(t)s(t + \tau) \rangle \]
\[ = \frac{1}{N} \int_{-\infty}^{\infty} c(t) \sum_{i=1}^{N} \delta(t - t_i + \tau) dt \]
\[ = \frac{1}{N} \sum_{i=1}^{N} c(t_i + \tau) \]
\[ = \langle c(t_i + \tau) \rangle \text{ for } 0 \leq \tau \leq M, \]

where is the effective memory of the synaptic interactions, and \( \langle \ldots \rangle \) stands for the average across spikes. Note that should be chosen to be less than the inter-spike interval of the trigger to prevent any overlaps while averaging. In other words, the STAPP can be obtained by averaging the target immediately following each spike in trigger across \( \{1, \ldots, n\} \) spikes.
The strength of the interaction is taken as the amplitude of the first peak or trough of the STAPP. This measure is bounded between -1 and 1 by construction. The sign of the interaction can be determined by the coincidence of the first zero derivative of the STAPP with either a peak or a trough. Peak means the connection is excitatory; trough means the connection is inhibitory. Significance is established by finding a confidence interval around the first peak or trough of the STAPP. The 99% confidence interval can be formed by taking the lower .5% and upper 99.5% percentile of STAPP’s of a target-trigger pair where the post-synaptic inter-event intervals are permuted. Notably, this randomization procedure preserves only coupling due to chance. Moreover, the mean and variance of the inter-event interval distribution remains unchanged. Coupling is significant if the peak or trough lies outside the confidence interval.

In some cases where neuron A is strongly exciting neuron B but B is not affecting A, the STAPP may exhibit a significant trough if B is taken as the trigger and A as the target. This is observed because A is most likely to be in the refractory period following a spike in B. The way to rule out these false positives is to re-compute the STAPP where the past and future of the target is included in the averaging, and then finding if the peak preceding the trough in the original STAPP is significant. In cases where B is inhibiting A, this peak is insignificant, and in cases where A is asymmetrically exciting B, this peak is significant.

3.2 Correlation Coefficient

Continuous versions of simulated recordings used to compute the correlation coefficient are obtained by convolving half-Gaussians with the spike trains (Figure 3.1b).
The standard deviation for the half-Gaussian was set to 5 ms so that subsequent spikes did not summate. The significance was determined by permuting the target 500 times, obtaining an 99% confidence interval for random CORC’s and checking if the empirical CORC falls beyond the confidence interval.

3.2 Crosscorrelogram

The crosscorrelogram for two spike trains is obtained by counting the number of spikes in the target surrounding a spike in the trigger and summing the counts across all the spikes in the trigger. In detail, begin by aligning the two spike trains and select one as the reference spike train. Then, consider the first spike in the reference train and create bins of arbitrary width around that spike until a certain memory, M, is reached. Repeat this process for the N spikes in the reference spike train. Lastly, sum all the histograms. The height of the tallest or lowest bin is taken as the measure for coupling between the two neurons. The bin is said to be significant if its height falls above or below a confidence interval obtained by permuting the spikes K times and computing the CCG for each permutation. If the reference neuron is exciting the target neuron, then a peak is often observed to the right of the zeroth bin. If the reference neuron is inhibiting the target neuron, then a trough is observed. Here, we use compute the CCG with 1ms bins with 500 permutations to determine the significance threshold.

3.2 Directed Information

We compute the directed information following [28, 29]. First, bin the trigger and target so that each bin has at most one spike. Then each bin is considered a
random variable. Let $X, Y \in \mathbb{R}^n$ where $X$ is the trigger and $Y$ is the target. The DI, denoted by $I(X \rightarrow Y)$, can be written as

$$I(X \rightarrow Y) = \sum_{i=1}^{n} I(X^i; Y_i|Y^{i-1}).$$

(3.1)

It can be shown that (1) converges to

$$\sum_{i=1}^{n} \log \frac{\pi(Y_i|Y^{i-1}, X^i)}{\pi(Y_i|Y^{i-1})},$$

where $\pi(x) \equiv P(X = x)$ [7]. A typical choice for $\pi(\ldots)$ is the Poisson distribution with a time dependent rate, denoted by $\lambda_i$, for $1 \leq i \leq n$, which makes

$$\pi(y_i|y^{i-1}, x^i) = \frac{\lambda_i^{y_i}}{y_i!} \exp(-\lambda_i).$$

(3.3)

In the above expression, is given by a GLM where the logarithm is the “link” function. That is,

$$\log \lambda_i = a_0 + \sum_{j=1}^{J} a_j Y_{i-j} + \sum_{k=1}^{K} b_k X_{i-(k-1)}$$

(3.2)

If $X$ and $Y$ are uncoupled, then $\lambda_i$ depends only on $Y$’s history. Thus, $\pi(Y_i|Y^{i-1})$ is given by

$$\pi(Y_i|Y^{i-1}) = \frac{\lambda_i^{y_i}}{y_i!} \exp(-\lambda_i),$$

(3.3)

with

$$\log \lambda_i = a_0 + \sum_{j=1}^{J} a_j Y_{i-j}.$$

(3.4)
In practice, the value of $J$ and $K$ in (2) can be determined via a model selection measure. For our analysis, we use the Akaike Information Criterion. Let $\theta = \{a_0, a_1, ..., a_J, b_1, ..., b_K\}$. Consider the likelihood function, $L(\theta)$, given by

$$L(\theta) = \prod_{i=1}^{n} \pi(y_i|y_{i-1}, x_i, \theta) = \prod_{i=1}^{n} \frac{y_i^{y_i}}{y_i!} \exp(-\lambda_i).$$  

(3.5)

An estimate for $\hat{\theta}$ can be obtained by finding

$$\hat{\theta} = \arg \min_{\theta} -\log L(\theta).$$  

(3.6)

The likelihood function for the intrinsic history of $Y$ is found by setting $b_1, ..., b_K$ to 0, and the DI is the ratio of the two likelihoods. Additionally a confidence interval can be defined for each parameter, $\hat{\theta}_j$, by

$$\hat{\theta}_j \pm \frac{1.96}{\sqrt{I(\hat{\theta}_{jj})}},$$  

(3.7)

where

$$I(\hat{\theta}_{jj}) = -\frac{\partial^2 L}{\partial \theta_j^2}\bigg|_{\hat{\theta}}.$$  

(3.8)

Significance is found by computing the 99th confidence bounds for all the parameters using (4), which also produces a confidence interval for the DI. We say the DI is significant if the 99th confidence bounds does not include zero.
3.3 Synthetic neural network

We simulate three Hodgkin-Huxley neurons coupled via inhibitory or excitatory connections, and driven by independent inhibitory and excitatory noise. Background activity was modeled as Poisson processes and introduced into the model through either excitatory or inhibitory synaptic connections. The Hodgkin-Huxley neuron model takes the form

\begin{align*}
C \frac{dV}{dt} &= -g_{Na} m^3 h (V - E_{Na}) - g_K n^4 (V - E_K) - g_L (V - E_L), \\
&\quad - g_{Ex} (t) (V - E_{Ex}) - g_{In} (t) (V - E_{In}) \\
\frac{dn}{dt} &= \alpha_n (V) (1 - n) - \beta_n (V) n, \\
\frac{dm}{dt} &= \alpha_m (V) (1 - m) - \beta_m (V) m, \\
\frac{dh}{dt} &= \alpha_h (V) (1 - h) - \beta_h (V) h,
\end{align*}

where \(g_{Ex} (t)\) and \(g_{In} (t)\), the synaptic currents, are given by

\begin{align*}
\frac{dg_{Ex}}{dt} &= \frac{1}{\tau_{Ex}} \left( \epsilon_{Ex} X + \epsilon_{noise} Y_{Ex} \right), \\
\frac{dg_{In}}{dt} &= \frac{1}{\tau_{In}} \left( \epsilon_{In} X + \epsilon_{noise} Y_{In} \right),
\end{align*}

In this model, \(X\) and \(Y\) are Boolean variables where \(X\) is 1 if the presynaptic neuron has fired and 0 otherwise, and \(Y\) is 1 when there is a background spike and 0 otherwise. The \(\epsilon\)'s serve the purpose of the synaptic weights. Lastly, the
remaining parameters are chosen based on the classic formulation. These values are reported in Appendix A.

For all of our simulations, the firing frequencies of the neurons fell between 18-30 Hz, and the same 120s segments were used to compare different methods. It is also important to note that STAPP was computed with a synaptic memory of 100 ms using 500 permutations to establish significance, and the DI was computed with a maximum history of 30ms at 5ms intervals. We constrained the search space to span 30ms because our choice of time constants placed the maximal interaction region within this time interval.

3.4 Results

We choose to test motifs that are common in large neural networks. First, we demonstrate the use of STAPP with direct excitatory and inhibitory connections. Then we compare its performance with that of the CORC, CCG and the DI.

3.4 Resolving pairwise interactions

Example voltage traces of simulated neurons coupled via excitation and inhibition are provided in Figure 3.2 along with the activity log of each neuron in the microcircuit.
Figure 3.2: Three body neural network. (a) Simulated membrane potential and net current flow of three neurons configured in the microcircuit presented top right. (b) Spike times of all three neurons. In the network schematic at the top, a filled in circle denotes an excitatory connection, and an empty circle denotes an inhibitory one.
We apply STAPP to resolve interactions in the same microcircuit but with higher synaptic weights for demonstrative purposes (Figure 3.3). We generated 500 samples to obtain a 99th percentile confidence interval used for significance testing.

Figure 3.3: STAPP of direct excitatory and inhibitory connections. Orange: STAPP for which 1 is the trigger and 2 is the target. Blue: STAPP for which 2 is the trigger and 3 is the target. The orange and blue bands are the 99th percent confidence intervals for each STAPP.

3.4 Comparison of methods

We evaluated the performance of STAPP and the CCG using direct excitatory and inhibitory connections Figure 3.4. It is evident that when coupling is weak, STAPP can resolve significant interactions with short data segments (60s) as compared to the CCG.
Figure 3.4: STAPP compared to CCG with short signals. (a) STAPP and CCG applied to a 60s recording where the trigger excites the target with a synaptic weight of 0.028. (b) STAPP and CCG applied to a 60s recording where the trigger inhibits the target with a synaptic weight of 0.052. The synaptic weights used to connect the trigger and target were less than the synaptic weight of the background noise. The two models used to test the inhibitory and excitatory cases differed only in the weight of inhibitory noise. In both cases, STAPP returned a significant value of coupling for the correct direction while the CCG did not.
To gauge the performance of multiple approaches, we constructed six three body microcircuits with different connectivity schemes, and attempt to resolve the interactions from the simulated time series. The results are presented in Figure 3.5.
Figure 3.5: Comparison of methods with different microcircuits. Left to right: schematic of test circuits, STAPP, DI, and CORC. Insignificant measures are set to zero. The theoretical connections, denoted by + for excitatory and - for inhibitory, are overlaid on the connectivity matrices. Colorbars at the very bottom go along with the matrices in each column.
We find that the STAPP accurately resolves causal interactions in all the test cases with exception of the 6th microcircuit, where one spurious interaction was also found. In contrast, the CORC worked well in resolving excitatory connections but offered no directional or sign information, and the DI seems to be insensitive to weak interactions as well as inhibitory ones.

We also simulated a network of 9 neurons to determine if multiple inputs weakens the ability of STAPP to recover significant interactions Figure 3.6. All

![Diagram of 9 neuron network](image)

**Figure 3.6: Evaluating connections in 9 neuron network.** (a) 9 Hodgkin-Huxley were connected according to the schematic in the left panel. (b) Coupling measures returned by STAPP for each target-trigger pair. The weights of these connections were generated randomly and took values of $\sim 0.05$ and $\sim 0.06$ for excitatory and inhibitory synapses, respectively. The weights for the background noise were $\sim 0.05$ and $\sim 0.03$ for excitatory and inhibitory noise, respectively.

the interactions built into model were recovered. However, an additional interaction that was not built in was also found. Lastly, to see how the performance scales with the strength of the synaptic connections, we simulated an asymmetric excitatory pairwise interaction with increasing synaptic weights (Figure 3.7). The results for the CORC and STAPP were comparable, both reflecting the increasing
Figure 3.7: Performance of methods under increasing excitation. The synaptic weight is denoted by $\epsilon$. The measure values are given as a ratio of the value for a given $\epsilon$ to the value returned by the last $\epsilon$.

The synaptic weight in the model. The DI was unreliable sometimes failing to resolve any interactions. Running time of the three methods in resolving one interaction are shown in Figure 3.8. Note that for a microcircuit with $n$ neurons, the running time will be scaled by $n(n - 1)$. As expected, CORC was found to be the fastest performer. STAPP took longer due to the cost of generating the random samples for significance testing, and DI took considerably more time due to the computationally burdensome model selection step. For our comparisons, we looked over a small parameter space with mesh defined by 1:5:30ms because the maximum time-scale of coupling was between 0-30ms by construction.
Figure 3.8: Comparison of running time. (a) Version used for STAPP. B) The mean running time of the three methods are shown for five realizations of the same model.

3.5 Discussion

We show that STAPP has strong potential for analyzing multi-electrode array data in functional connectivity studies. Compared to the CORC, STAPP provides the addition of directional and sign information without adding much cost. The running time of STAPP was between CORC and DI. Specifically, it took me minutes to compute STAPP for a pair of neurons with an Intel i7 quad-core machine, while the DI required hours to perform the same analysis. We also demonstrated that STAPP is less sensitive to sample size as compared to the CCG. Lastly, it is important to recognize that the simulations used in this study were designed to evaluate the efficacy of detecting weak coupling, i.e. scenarios where there is high levels of background activity, similar to real neural networks. Mathematically, this means
that the weights for the synaptic connections were chosen to be on the same order as that of the background noise.

The DI was included in our comparisons because we wanted to evaluate the performance of a measure based on the generalized linear model (GLM) [40]. The intuition of the GLM is that instantaneous firing rate of neurons can be explained by a linear combination of intrinsic (refractory period, etc.), and extrinsic (synaptic connections) covariates [40–42]. In practice, GLM based measures require fitting a Poisson regression model to the data, where the weights assigned to the extrinsic covariates account for the coupling. The parameters are typically found using both maximum likelihood methods and Bayesian approaches [43, 44]. The slowest step is the model selection step, and can vary greatly depending on the desired search space. The benefits of the DI are that is capable of resolving higher order interactions, directional, and sign information. However, there are several caveats that reduce its practicality. The best statistical model for given time series is not known a priori so a model selection criterion must be used. Furthermore, a function optimization strategy is needed to maximize the likelihood function obtained from data. Binning, non-stationarity, and the length of experimental data are also factors that will influence the outcome of the analysis.

STAPP can be viewed as the ability of one neuron to either boost or depress the baseline activity of another neuron. More precisely, ability is simply the likelihood of observing or not observing a spike in the target neuron at a given time point after the reference neuron has fired. Indeed, the intuition of STAPP is identical to the STA and CCG. The technical difference that separates STAPP
from the STA and CCG is that STAPP first transforms the data into phase space. Thus, the waveform averaging procedure performed in STAPP returns the expected position of the target on the unit circle when the trigger is at 0. And as we have shown, introducing this step yields a significance increase in performance.

It is important to recognize that the difference in implementation between the STAPP and STA allows STAPP to be sensitive non-linear coupling. In a statistical sense, STAPP returns the kernels of a linear filter of a given input and output like the STA. However, since the input and output are translated into a phase, the returned coupling measure should be sensitive to both linear and non-linear interactions, in a mathematical sense, underlying the process of interest. In essence, STAPP measures consistently observed phase relations between two oscillators, which will be present even when the oscillators are coupled with purely non-linear dynamics.

Caution should be exercised when translating the results of computational studies to physiological ones. That is to say, there needs to be a clear understanding of the assumptions and interpretation of different measures. Otherwise, the results will not be meaningful. The assumption made by STAPP is that the recordings are weakly stationary, i.e. the signal has finite variation, constant first and second moments, and the auto correlation function, $\gamma(s-t)$ depends on $(s-t)$ and not $s$ or $t$. These constraints are equivalent to saying that the biological processes which facilitate coupling do not drastically change during the recordings. For instance, it makes no sense to analyze recordings from an experiment during which the cells died halfway.
The limitations of STAPP are similar to that of other methods which averages a target output with respect to triggers in a reference. An important consideration is that only pairwise interactions are resolved, as opposed to simultaneously capturing the flow of information in the neural network. However, if functional connectivity is desired to be defined as the dependence of the activities between neurons, then this constraint does not weaken the results. Another important consideration is that this method is unable to capture interactions which occur on different time scales. Therefore, STAPP will not be useful for systems where coupling fluctuates on time scales that are less than the minimum length of data required to establish significance.
Table A.1: Model and Data Phase Distributions. Both coefficients are given for the 12 experiments with $I > I^*$. Statistical dependence is determined from the p-value of each $\tau$. Numbering of the experiments is consistent with that of Figure 2.6.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>R</th>
<th>$\tau$</th>
<th>Dependent (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.99</td>
<td>0.92</td>
<td>Y</td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
<td>0.79</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>0.80</td>
<td>0.52</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>0.99</td>
<td>0.95</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>0.99</td>
<td>0.96</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
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<td>0.95</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
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<td>0.79</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
<td>0.90</td>
<td>Y</td>
</tr>
<tr>
<td>9</td>
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<td>0.86</td>
<td>Y</td>
</tr>
<tr>
<td>10</td>
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<td>0.83</td>
<td>Y</td>
</tr>
<tr>
<td>11</td>
<td>0.92</td>
<td>0.77</td>
<td>Y</td>
</tr>
<tr>
<td>12</td>
<td>0.98</td>
<td>0.89</td>
<td>Y</td>
</tr>
</tbody>
</table>
Table A.2: Hodgkin-Huxley Neuron Model Parameter Values. The synthetic data used to compare the approaches mentioned were generated using the HH model with the following parameter values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
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<td>$g_{Na}$</td>
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</tr>
<tr>
<td>$g_k$</td>
<td>36mΩ$^{-1}$/cm$^2$</td>
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<tr>
<td>$g_l$</td>
<td>0.3mΩ$^{-1}$/cm$^2$</td>
</tr>
<tr>
<td>$E_{Na}$</td>
<td>$-60$mV</td>
</tr>
<tr>
<td>$E_{K}$</td>
<td>$-77$mV</td>
</tr>
<tr>
<td>$E_L$</td>
<td>0mV</td>
</tr>
<tr>
<td>C</td>
<td>1 $\mu$F</td>
</tr>
<tr>
<td>$\epsilon_{Ex}$</td>
<td>0.03 – 0.15</td>
</tr>
<tr>
<td>$\epsilon_{In}$</td>
<td>0.03 – 0.15</td>
</tr>
<tr>
<td>$\epsilon_{\text{noise}}$</td>
<td>0.04 – 0.08</td>
</tr>
<tr>
<td>$\tau_{Ex}$</td>
<td>2ms</td>
</tr>
<tr>
<td>$\tau_{In}$</td>
<td>4ms</td>
</tr>
</tbody>
</table>


