Published in final edited form as:

J Comput Neurosci. 2011 October ; 31(2): 401–418. doi:10.1007/s10827-011-0315-2.

Effects of conduction delays on the existence and stability of one to one phase locking between two pulse-coupled oscillators

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Abstract

Gamma oscillations can synchronize with near zero phase lag over multiple cortical regions and between hemispheres, and between two distal sites in hippocampal slices. How synchronization can take place over long distances in a stable manner is considered an open question. The phase resetting curve (PRC) keeps track of how much an input advances or delays the next spike, depending upon where in the cycle it is received. We use PRCs under the assumption of pulsatile coupling to derive existence and stability criteria for 1:1 phase-locking that arises via bidirectional pulse coupling of two limit cycle oscillators with a conduction delay of any duration for any 1:1 firing pattern. The coupling can be strong as long as the effect of one input dissipates before the next input is received. We show the form that the generic synchronous and anti-phase solutions take in a system of two identical, identically pulse-coupled oscillators with identical delays. The stability criterion has a simple form that depends only on the slopes of the PRCs at the phases at which inputs are received and on the number of cycles required to complete the delayed feedback loop. The number of cycles required to complete the delayed feedback loop depends upon both the value of the delay and the firing pattern. We successfully tested the predictions of our methods on networks of model neurons. The criteria can easily be extended to include the effect of an input on the cycle after the one in which it is received.

Introduction

Synchronization between distal regions in the brain has been shown to be important for encoding, retention, and retrieval of information and proposed to underlie binding (Konig et al. 1995) as well as conscious perception (Melloni et al. 2007). Under the binding hypothesis, synchronization must occur early within a few tens of milliseconds at most (Singer 1999); such rapid synchronization requires strong coupling. The analysis presented in this paper does not assume, as many theoretical studies do, that the coupling is weak. Long distance synchronization is reduced in schizophrenia and epilepsy, despite an enhancement of local synchronization in epilepsy (Uhlhass and Singer 2006), and synchronization that occurs between distal areas is almost always associated with oscillatory activity (Konig et al. 1995). Although synchronization with nonzero phase lag has been observed between distal areas in human brains (Melloni et al. 2007), zero phase lag synchronization is of particular interest with respect to the binding hypothesis (Singer 1993; Womelsdorf et al. 2007). Strong inter-hemispheric phase locking at zero phase lag occurred in area 17 of cats that was disrupted by severing the corpus callosum (Engel et al. 1991). This is strong evidence that the synchronization arose via reciprocal connectivity rather than via locking to a common input.

Mechanisms for long distance synchronization have been proposed (Ermentrout and Kopell 1998), but how synchronization can take place over long distances in a stable manner is considered an open question (Karbowski and Kopell 2000). Phase lags equal to the conduction delay are expected (Canavier et al. 2009; Ernst et al. 1995, 1998) if the delayed arrival of an input triggers a spike. Conditions under which zero phase lag synchronization can occur have been given for particular models. For example, simulation results from a firing rate model (Konig and Schillen 1991) are often cited to support the idea that zero phase lag can be established with reciprocal coupling with conduction delays up to one third of the period. For models with sinusoidal interaction functions, synchrony is generally unstable if the delay exceeds a quarter of the period (Ko and Ermentrout 2009). On the other hand, for the class of models that include leaky integrate and fire neurons with inhibitory pulse coupling that decrements the potential by a fixed amount, in phase synchrony persists in the presence of longer delays (Ernst et al 1995, 1998; Timme et al 2002; Timme and Wolf 2008). In yet another model, delays allowed synchronization at weaker coupling values than in its absence (Dhamala et al. 2004). Neurons usually communicate in a pulsatile fashion using action potentials, so here we present a general, model-independent theoretical framework that encompasses any two pulse coupled oscillators at any value of delay.

Phase resetting curves (PRCs) keep track of how much an input advances or delays the next spike in an oscillatory neuron depending upon where in the cycle the input is applied. The assumption of pulsatile coupling requires that the effect of a synaptic input must dissipate before the next input is received, which for one-to-one locking means within a network period. Here, we use phase resetting theory to propose a general framework for synchronization of two reciprocally pulse coupled oscillators separated by conduction delays. The appropriate PRC to use for this application is one measured using an input that approximates that received in the closed circuit. If the appropriate PRCs for neural oscillators can be measured, then we do not require any additional assumptions regarding the intrinsic dynamics of the oscillator or the form of the coupling. These results can be extended to apply to two populations of reciprocally coupled oscillators (Achuthan and Canavier 2009; Chandrasekaran et al 2011) under additional assumptions regarding the dynamics of each population.

First we formulate existence criteria based simply upon the constraints imposed by periodicity on the relationships among the time intervals between events such as the firing of an action potential or receipt of an input. Then we use the pulsatile coupling assumption to reformulate these criteria in terms of a coupled map based on the PRC, from which we can extract stability criteria. We then use model neurons as examples to confirm that the predictions of existence and stability are correct provided the assumptions are valid. A key observation is that time for the firing of one neuron to affect a subsequent firing in the same neuron via the feedback pathway through the other neuron must be a multiple (k) of the network period. We further demonstrate that the criteria correctly account for the effect of k on stability and (in Appendix 1), for the effects of resetting on not just one, but two cycles after each input.

Methods

Phase Resetting Curves

Figure 1 shows how the PRCs were generated for each neuron by stimulating a single repetitively firing neuron by activating the post-synaptic conductance with a single action potential from a presynaptic neuron. The pre-synaptic model neuron is initialized at a phase of zero, then the coupling is turned on for a single cycle of the pre-synaptic neuron. We define zero phase to be when the membrane potential crosses -14 mV from below, because the synaptic conductance trace begins to noticeably increase above zero at that pre-synaptic

potential, and we would like spike onset in the presynaptic neuron to coincide with input onset at the postsynaptic neuron for the zero delay case. This type of PRC is often called a spike response curve (Acker et al 2003). The PRC is measured in the open loop condition, meaning there is no feedback from the partner neuron as shown in the diagram to the left of Fig. 1A. The stimulus interval t_s is the elapsed time between when a neuron fires and when it next receives an input. The recovery interval is the elapsed time between when a neuron receives an input and when the neuron next fires. T_0 is the unperturbed cycle length, T_1 is the length of the cycle containing the perturbation and T_2 is the length of the subsequent cycle. The phase at which a stimulus is received is $\phi = t_s/T_0$. This phase uniquely defines a position on the unperturbed limit cycle. This position can be reset (moved forward or backward on the limit cycle) by an input. The first order resetting is $f_1(\phi) = (T_1 - T_0)/T_0$ and the second order resetting is $f_2(\phi) = (T_2 - T_0)/T_0$. Second order resetting will be ignored in the body of the paper, but is considered in Appendix 1. In this paper we use P_i to represent the intrinsic period of neuron i , but T_j to represent cycle lengths relative to the cycle in which the perturbation is delivered (cycle 1), such that T_0 is equal to the intrinsic period (P_i) in the neuron whose PRC is being generated. Hence the phase can also be represented as $\phi = t_s/P_i$.

Predictions based on PRCs

Routines written in C find the fixed points of the mapping described in the results. The predicted phases at the fixed points were inferred by linear interpolation between the tabulated values that produced the intersection points. Routines written in C were also used to construct the k by k matrices (A) derived in the Results section and to calculate the eigenvalues of this matrix in order to determine the stability of the fixed points. (The k by k matrices included second order resetting as described in Appendix 1, otherwise only order $k - 1$ is required). In the discrete linear system $y = Ax$, y is a vector containing the values of the perturbed phases on one cycle, and x is a vector containing the corresponding perturbed phases on the previous cycle. The GNU Scientific Library (GSL) (Galassi et al 2009) was used to solve for the eigenvalues. The time lags were predicted by adding the appropriate delay to each of the predicted recovery times and then alternately subtracting a predicted network period from each of these two quantities until their sum was equal to the predicted network period.

Simulations

We tested the predictions derived and presented in the Results on networks consisting of two reciprocally connected Morris and Lecar (1981) or (in Appendix 2) Wang and Buzsaki (1996) model neurons. The differential equations describing these networks are given in Appendix 2. Similar results were obtained using a Runge-Kutta fourth order method and an adaptive Runge-Kutta-Felberg method (from the GSL) using a custom routine to incorporate delays. If the firing intervals remained constant to the sixth decimal place on successive cycles, it was assumed that 1:1 phase locking had been established.

Results

Existence and Stability Criteria in Terms of the Stimulus and Recovery Intervals

Figure 2 shows that there are potentially four different one to one phase locked firing patterns in a two neuron circuit with conduction delays. Four distinct events that occur in each cycle: the firing of neuron 1, the firing of neuron 2, the receipt of a delayed input by neuron 1 and the receipt of a delayed input by neuron 2. These events can occur in any order during a cycle, but they must occur in the same order on each cycle in a 1:1 locking. In schemes B and C, either neuron could fire first resulting in two additional firing patterns for a total of six. The analysis is identical no matter which neuron fires first, because we can

arbitrarily designate the neuron that fires first as neuron 1, so we only need analyze four of the six cases. Patterns that contain synchronous events are transitional between two patterns, one in which one neuron fires first, and another in which the other neuron fires first. For short, equal delays, only Schemes A and B can be realized, because scheme C requires unequal delays, specifically for the delay from neuron 2 to neuron 1 to be shorter than the delay from neuron 1 to neuron 2, and scheme D requires the sum of the delays to be longer than the network period.

We define the stimulus interval ($ts_i[n]$) as the time elapsed between the firing time of the i th neuron and the subsequent arrival of an input in the n th cycle, and the recovery interval ($tr_i[n]$) as the time elapsed between the arrival of an input at the i th neuron in the n th cycle and the subsequent firing time in the i th neuron. Figure 3A shows how the intervals are labeled for Scheme A for short delays. In the figures in this paper, the firing patterns are consistently presented with neuron 1 firing first in the n th cycle, followed by the n th cycle in neuron two. In Fig. 3A, the firing of neuron 1 in the n th cycle causes an input to be received by neuron 2 after the conduction delay δ_1 . Neuron 2 then fires after its recovery interval, which causes an input to be received by neuron 1 after the conduction delay δ_2 . The arrival of this input ends the stimulus interval in neuron 1. Therefore the two delays plus a recovery interval in neuron 2 equals the stimulus interval in neuron 1:

$$\delta_1 + tr_2[n-1] + \delta_2 = ts_1[n] \quad (1)$$

If we make the assumption that the PRC as described in Fig. 1 and the Methods allows us to calculate the recovery interval from the preceding stimulus interval, we can formulate a map from the intervals (see explicit map for this case in Appendix 3). First, we calculate $tr_1[n]$ from $ts_1[n]$, then we can use $tr_1[n]$ to calculate $ts_2[n]$. A expression similar to (1) allows us to obtain $ts_2[n]$ from $tr_1[n]$:

$$\delta_2 + tr_1[n] + \delta_1 = ts_2[n] \quad (2)$$

We then obtain $tr_2[n]$ from $ts_2[n]$, and can continue indefinitely, except that in practice there is no guarantee the firing order will remain constant (for a map that assumes no particular firing order see Canavier and Achuthan 2010). Nevertheless, Equations 1 and 2 together with the PRC define a mapping from the intervals on one cycle to those on the next that allows a reduction of the full system dynamics to a discrete coupled system. The system is nonlinear because the dependence of the recovery intervals on the stimulus interval is in general nonlinear, ie, the PRC is a nonlinear function. The fixed points of this reduced system correspond to periodic one to one locked firing modes of the full system that are characterized by this specific firing order. In general, the observables are not the stimulus and recovery intervals, but rather the time lags $tl_{12}[n]$ and $tl_{21}[n]$ between neural firings. In Fig. 3A, the time lag tl_{12} is defined as the elapsed time between a spike in neuron 1 and the next spike in neuron 2, and tl_{21} is the elapsed time between a spike in neuron 2 and the next spike in neuron 1. The time lags can be inferred from the stimulus as follows:

$$tl_{12}[n] = ts_1[n] - \delta_2 \text{ and } tl_{21}[n] = ts_2[n] - \delta_1.$$

Figure 3B shows how the analysis shown in Fig. 3A can be generalized to arbitrarily long delays with the same firing pattern. The sequence of events is the same, but each input is not necessarily triggered by the spike in the partner neuron that immediately precedes the input if delays are long. Therefore it takes k cycles rather than just a single cycle before the firing of a spike in neuron 1 affects the timing of the next spike in neuron 1 via the feedback loop

through neuron 2. Examples of modes with $k = 2$ are given in Supplementary Figures S1 and S2, and an example of $k = 3$ is given in Supplementary Fig. S3. In Fig. 3B, the firing of neuron 1 in the n th cycle again causes an input to be received by neuron 2 after the conduction delay δ_1 . Neuron 2 then fires after its recovery interval, which again causes an input to be received by neuron 1 after the conduction delay δ_2 . The arrival of this input ends the stimulus interval in neuron 1, but depending upon the length of the delay, neuron 1 may have spiked an integral number $(k-1)$ of times since it fired to begin the n th cycle. We define j_2 as the number of spikes in neuron 2 that occur during the delay period δ_1 and j_1 as the number of spikes in neuron 1 that occur during the delay period δ_2 . The definition of the n th stimulus interval in neuron 2 as occurring after the n th stimulus interval in neuron 1 causes an asymmetry in the equations such that the recovery interval in neuron 1 is indexed as $n+j_1$ but the recovery interval in neuron 2 is indexed as $n-1+j_2$. The integer k is equal to $j_1 + j_2 + 1$. Thus in Fig. 3A, j_1 and j_2 are both equal to zero, and k is one. In Fig. 3B1, during the arrow labeled “ k periods”, beginning with a spike in neuron 1, one can see that the following equality, analogous to the equality given by Equation 1, holds true:

$$\delta_1 + tr_2[n-1+j_2] + \delta_2 = ts_1[n] + tr_1[n] + \dots + ts_1[n+k-1] \quad (3)$$

Similarly, Fig. 3B shows that

$$\delta_2 + tr_1[n+j_1] + \delta_1 = ts_2[n] + tr_2[n] + \dots + ts_2[n+k-1] \quad (4)$$

The left hand side of Eq. 3 and 4 consists of intervals that span the elapsed time between two firings of the same neuron. In a phase locked mode, the sum of these intervals must be an integer multiple of the network period, which is the sum of the stimulus and recovery intervals for a given neuron. The stimulus and recovery intervals for each neuron do not vary from cycle to cycle in a steady phase-locked one to one mode but instead take on a steady value as n goes to infinity. Eq. 3 and 4 can be rewritten as the following two existence criteria that any periodic one to one locking must satisfy:

$$\delta_1 + tr_2[\infty] + \delta_2 = ts_1[\infty] + (k-1)(ts_1[\infty] + tr_1[\infty]) \quad (5)$$

$$\delta_2 + tr_1[\infty] + \delta_1 = ts_2[\infty] + (k-1)(ts_2[\infty] + tr_2[\infty]) \quad (6)$$

Any fixed point of the map of the stimulus and recovery intervals as defined by the PRC corresponds to a one to one locking and must satisfy the above two equations.

Application of the PRC to Predict the Existence of Phase-locked Modes

In order to apply Eqs. 5–6 to network analysis, the dependence of the stimulus and recovery intervals on the PRC as measured in Fig. 1 must be established under the assumptions of pulsatile coupling. These assumptions are that the perturbations received in a network are similar to those used to generate the PRC, and that each neuron returns to its unperturbed limit cycle by the time the next input is received. If the effect of a perturbation dies out before the next input is received, then all phase resetting must be complete and accounted for in the recovery and stimulus intervals immediately following an input, because the next input is received after the next stimulus interval. The first order resetting is incorporated in the recovery interval, because the first order resetting determines when the very next spike

will occur. Second and higher order resetting are neglected in the body of the paper, but second order resetting is considered in Appendix 1.

We call the circuit configuration (diagram at the top of Fig. 2) with two neurons reciprocally connected by delays the closed loop circuit, in contrast to the open loop circuit depicted in Fig. 1 that was used to measure the PRC. In order to find any possible phase locked modes satisfying the existence criteria given in Eqs. 5 and 6, we parameterize the stimulus and recovery intervals in terms of the phases from 0 to 1 of the respective oscillators. The stimulus interval is $ts_i[\varphi_i] = P_i\varphi_i$, where φ_i is the phase at which a synaptic input was applied as in Fig. 1. The recovery interval $tr_i[\varphi_i]$ is the time remaining until the next spike in the unperturbed case $P_i(1 - \varphi_i)$ plus the first order resetting such that $tr_i[\varphi] = P_i(1 - \varphi_i + f_i(\varphi_i))$. We designate the steady state values at which the constraints in Eqs. 5 and 6 are satisfied as $\varphi_i[\infty]$, $ts_i[\infty]$, and $tr_i[\infty]$. Since $ts_i[\infty]$ and $tr_i[\infty]$ can be calculated directly from $\varphi_i[\infty]$, there are exactly as many unknowns as there are equations. A graphical method similar to the ones employed for networks without delays (Oprisan et al 2004; Sieling et al 2009) can be used to find these steady values. We plot curves for each neuron that are parameterized by the phase from 0 to 1 in that neuron as follows. The left-hand side of Eq. 6 and the right-hand side of Eq. 5 ($tr_1[\varphi] + \delta_1 + \delta_2$, $k(ts_1[\varphi]) + (k-1)tr_1[\varphi]$) depend only on the phase in neuron 1, so we plot these pairs of values for each value of the phase in neuron 1 (black curves in Fig. 4C). Similarly, the right-hand side of Eq. 6 and the left-hand side of Eq. 5 ($k(ts_2[\varphi]) + (k-1)tr_2[\varphi]$, $tr_2[\varphi] + \delta_1 + \delta_2$) depend only on the phase in neuron 2, so we plot these pairs of values for each value of the phase in neuron 2 (red curves in Fig. 4C). If the values on the x-axis for the two curves are equal, the criterion in Eq. 6 is satisfied, whereas if the values on the y-axis for the two curves are the same, Eq. 5 is satisfied. Therefore, at the intersections the existence criteria are satisfied as graphically illustrated in Fig 4AB for $k = 2$ and Fig. 4DE for $k = 1$. The $ts_i[\infty]$ and $tr_i[\infty]$ values were determined from the intersection points. The predicted observable time lags were obtained from these intervals by noting that the delay plus the predicted recovery interval equals the predicted time lag plus an integer multiple of the predicted network period (Fig. 3 and Eqs. 5 and 6). The graphical presentation allows us to visualize what happens to the intersections as the delay is increased. The red curves are shifted upward and the black curves are simultaneously shifted to the right until the intersections are lost (or gained, in the case of higher values of k , not shown).

Application of the PRC to Predict Stability

We can rearrange terms and write Eq. 4 as:

$$ts_2[n+k-1] = tr_1[n+j_1] + \delta_1 + \delta_2 - \sum_{i=0}^{k-2} (ts_2[n+i] + tr_2[n+i]) \quad (7)$$

This expression generalizes to all firing patterns in Fig. 2 (see Supplemental Material Figs S1–3). The summation is only applied for k greater than or equal to two. Except for the term $tr_1[n+j_1]$, $ts_2[n+k-1]$ is written in terms of earlier intervals in the same cell. The following is also true:

$$ts_1[n] + tr_1[n] + \delta_1 = \delta_1 + tr_2[n+j_2-1] + ts_2[n+j_2] \quad (8)$$

as shown in Fig. 3C. Eq. 8 describes the interval between a spike in neuron 1 and the arrival of an input due to the next spike in neuron 1 at neuron 2 in two different ways, one using intervals from neuron 1 and the other using intervals from neuron 2. Equations 7 and 8 are

sufficient to construct a discrete-time system that expresses $ts_2[n+i+1]$ in terms of their values $ts_2[n+i]$ in the previous cycle as we have done in Appendix 3 for $k=1$ and 2. However, rather than deriving the explicit nonlinear map of the time intervals, it is simpler to obtain a linearized map directly from Eqs. 7 and 8. This can be accomplished by rewriting the equations in terms of phase rather than time intervals, assuming a perturbation from fixed point that corresponds to a one to one periodic mode, and cancelling steady terms on both sides to leave only the perturbations. This linearized system can be used to determine the stability of the fixed point and hence that of the periodic mode.

The phase $\varphi_i[n]$ designates the phase at which an input is received by neuron i in cycle n . The stimulus interval is $ts_i[n] = P_i \varphi_i[n]$. The recovery interval tr_i is the time remaining until the next spike in the unperturbed case $P_i(1 - \varphi_i)$ plus the first order resetting such that $tr_i[n] = P_i(1 - \varphi_i[n] + f_{1i}(\varphi_i[n]))$. We assume a steady locking such that as n goes to infinity, $\varphi_i[n] = \varphi_i[n-1]$ for all n , and we designate these steady state values as $\varphi_i[\infty]$. Then we assume a fixed point of the mapping $(\varphi_1[\infty], \varphi_2[\infty])$. In order to determine stability, we introduce a perturbation from steady-state $\varphi_i[n] = \varphi_i[\infty] + \Delta\varphi_i[n]$, for the n th cycle of the i th neuron. Then we linearize the PRC for each neuron at its locking point as $f_i'(\varphi_i[n]) = f_i'(\varphi_i[\infty]) + f_i''(\varphi_i[\infty])\Delta\varphi_i[n]$. Eq 7 becomes

$$\Delta\varphi_2[n+k-1] = \frac{P_1}{P_2} \Delta\varphi_1[n+j_1](m_1-1) - \sum_{i=0}^{k-2} m_2 \Delta\varphi_2[n+i] \quad (9)$$

and Equation 8 becomes:

$$m_1 \Delta\varphi_1[n+j_1] = \frac{P_2}{P_1} \Delta\varphi_2[n+j_1+j_2-1](m_2-1) + \frac{P_2}{P_1} \Delta\varphi_2[n+j_1+j_2] \quad (10)$$

where m_i is the slope of the PRC $f_i'(\varphi_i[\infty])$ evaluated at the locking point for the i th neuron. Since $j_1+j_2 = k-1$, we can use Eq 10 to rewrite Eq 9 only in terms of $\Delta\varphi_2[n+i]$ for $i = 0$ to $k-2$:

$$\Delta\varphi_2[n+k-1] = \Delta\varphi_2[n+k-2](m_1-1)(m_2-1) - \sum_{i=0}^{k-2} m_1 m_2 \Delta\varphi_2[n+i] \quad (11)$$

The summation terms are only valid for $k>1$. We then construct the linear system $y = Ax$ as follows. The vector y contains the elements $(\Delta\varphi_2[n+k-1], \dots, \Delta\varphi_2[n+1])$ and the vector x contains the values of the same elements on the previous cycle $(\Delta\varphi_2[n+k-2], \dots, \Delta\varphi_2[n])$. The stability of this linearized system determines the stability of the corresponding phase locked mode. For the special case of $k=1$, the dimension is 1, for all other values of k it is $k-1$. For $k>1$, the $k-1$ by $k-1$ matrix A has a very simple form. The first element in the first row is $1-m_1-m_2$; all subsequent entries are $-m_1 m_2$. The second row has a 1 in the first position; the third row has a 1 in the second position, and so on. All other entries in rows two and higher are zero. These ones correspond to the identity equations of the form $\Delta\varphi_2[n+i] = \Delta\varphi_2[n+i]$ for $i = 1$ to $k-2$. The eigenvalues of the matrix A determine the stability of the locking mode assumed prior to linearization. The dependence on the length of the delay is limited to the value of k associated with that delay for a particular firing pattern, which together with the slopes of the PRCs at the locking point thus determine the stability of any one to one phase locked mode. For example, when Eq. 11 is evaluated with $k=1$ (Scheme A in Fig. 2), a first order linear system is obtained, and the eigenvalue is equal to $\lambda_k = 1 =$

$(1-m_1)(1-m_2)$ which agrees with results for this firing pattern with no delay (Dror et al. 1999). When Eq. 11 is evaluated at $k = 2$ (scheme B in Fig. 2), again a first order linear system results, but the eigenvalue that determines stability is $\lambda_{k=2} = 1-m_1-m_2$. In Scheme B, synchrony is transitional between two firing orders (one in which neuron 1 leads versus one in which neuron 2 leads) that have the same stability result due to symmetry. In other words, the result is invariant when the order of the two neurons as reflected in the subscript index is switched. Therefore this eigenvalue is correct for the case of exact synchrony.

PRC- based methods predict stable modes as delays shift the locking point in a model network

We tested the PRC-based predictions in a network of two identical, identically coupled Morris-Lecar model neurons with reciprocal excitation. The delay was increased from zero to several times the intrinsic period of 85 ms with the parameters set in the Type II excitability regime as in Rinzel and Ermentrout (1998) (see Appendix 2), with $g_{syn} = 0.25$ mS/cm². Figure 5A shows good agreement between the time lags tl_{12} and tl_{21} predicted from the PRCs with pluses, and those observed by integrating the full set of delay differential equations with circles. In this example, the only stable modes predicted or observed were synchrony and antiphase. For synchrony (arrows labeled B at a delay of 0 ms), tl_{12} is zero and tl_{21} is the network period. The arrow labeled D points to an antiphase mode at a delay of 40 ms in which tl_{12} is equal to tl_{21} so that only a single interval is visible. The arrows labeled C and E indicate the coexistence of synchrony and antiphase at delays of 25 and 60 ms, respectively.

The slope of the phase resetting curve at the locking points determines the stability of the locking. For both $\lambda_{k=1} = (1-m_1)(1-m_2)$ and $\lambda_{k=2} = 1-m_1-m_2$, negative slopes for the resetting are destabilizing; if both are negative the eigenvalue is guaranteed to be greater than one, and if one is negative the other slope must be positive and bring the total magnitude of the eigenvalue down to less than one. For identical neurons with identical locking points, a negative slope guarantees instability. The destabilizing trend also holds for higher k . This is the key point required to understand the example in Fig. 5.

The PRCs shown in Fig. 5B, C, D and E have three branches: a leftmost stable (positive slope) branch, a middle unstable (negative slope) branch, and a rightmost (positive slope) branch. The stability results can in this case be simplified to the observation that a positive slope (less than one) of the first order PRC at the locking point generally implies stability and a negative slope generally implies instability. The repetitive nature of the solution structure results because increasing the delay moves each locking point to the right until a phase of one is reached, then resets the locking point to zero, and then moves the locking point to the right again. The reset of the locking point from one to zero corresponds to an increment in the value of k , the number of cycles elapsed before the feedback from a given neural firing impacts the firing time in the same neuron.

At a delay of zero (Fig. 5B), the synchronous solution (for $k = 2$) falls in the left branch and the antiphase solution (for $k = 1$) falls in the middle branch. As the delay is increased to 25 ms (Fig. 5C), both solutions move rightward on the PRC at different rates. When the antiphase solution arrives on the left branch before the synchronous solution leaves the right branch, the system is bistable. Figure 4 shows the result of the graphical method for this case, with antiphase (square) at $k = 1$ and synchrony (circle) at $k = 2$. The antiphase solution continues to move to the right, and then jumps to the leftmost branch as the phase resets from one to zero and k switches from 1 to 3. As the delay is increased to 40 ms (Fig. 5D) and the solutions continue to move rightward, the synchronous solution falls in the middle branch so only antiphase is stable. As they move farther right for a delay of 60 ms (Fig. 5E), bistability is reestablished with antiphase on the left branch and synchrony on the right.

Then the antiphase solution reaches the middle branch and once again there is only stable synchrony. Then the synchronous solution jumps back to the right branch and k switches to 4, and so on. The synchronous and antiphase solutions arise from the symmetry of a network with two identical, identically coupled neurons with identical delays as shown in the next section.

Synchrony and Antiphase are Generic Solutions for Identical Pulse Coupled Oscillators

A system of two identical, identically coupled oscillators will always have a synchronous solution because of the inherent symmetry (Golubitsky et al 1988), and may also have an antiphase solution, but the form and stability of these solutions for pulse-coupled oscillators with conduction delays has not previously been described. We begin by generalizing the definitions of the time lags given from Fig. 3A to the longer delays shown in Fig. 3B to give their steady values in a one to one phase-locked mode:

$$tl_{12}[\infty] = ts_1[\infty] + j_1(ts_1[\infty] + tr_1[\infty]) - \delta_2 \quad (12)$$

$$tl_{21}[\infty] = ts_2[\infty] + j_2(ts_2[\infty] + tr_2[\infty]) - \delta_1 \quad (13)$$

For an exact antiphase mode, the time lags are equal to each other and to half the network period:

$$tl_{12}[\infty] = tl_{21}[\infty] = (ts_1[\infty] + tr_1[\infty])/2 = (ts_2[\infty] + tr_2[\infty])/2 \quad (14)$$

We can use the expressions for the time lags to calculate the delays at which the exact antiphase mode can occur:

$$\delta_1 = ts_2[\infty] + (j_2 - 1/2)(ts_2[\infty] + tr_2[\infty]) \quad (15)$$

$$\delta_2 = ts_1[\infty] + (j_1 - 1/2)(ts_1[\infty] + tr_1[\infty]) \quad (16)$$

Note that for an exact antiphase mode with equal delays ($\delta_1 = \delta_2$), the network periods are equal ($ts_1[\infty] + tr_1[\infty] = ts_2[\infty] + tr_2[\infty]$) and by symmetry $ts_1[\infty] = ts_2[\infty]$, so j_1 must be equal to j_2 , which makes k odd since $j_1 + j_2 + 1 = 2j_1 + 1 = k$. Since the delays must be nonnegative so both j_1 and j_2 must be greater than or equal to one for this firing pattern. For a system such as the one illustrated in Fig. 5, with identical oscillators and identical delays, Eq. 5 and 6 can be written $2\delta + tr[\infty] = ts[\infty] + (k - 1)(ts[\infty] + tr[\infty])$, and Fig 6A illustrates a symmetric antiphase mode for $k = 1$. Noting that for identical, identically coupled oscillators $ts_1[\infty] + tr_1[\infty] = ts_2[\infty] + tr_2[\infty] = P\{1 + f(\varphi[\infty])\}$, Eqs. 15 and 16 can be written with the delay in an exact antiphase mode given in terms of the common phase φ at which each oscillator receives an input:

$$\delta = P_i \varphi[\infty] + (k/2 - 1)P_i \{1 + f(\varphi[\infty])\} \quad (17)$$

Eq. 17 can be rewritten as $(k-2)f(\varphi[\infty]) = 2\delta/P_i - 2\varphi - k + 2$, and is guaranteed to have a solution for a given δ if 1) $f(0)$ and $f(1)$ lie on opposite halves on the plane bisected by the line $(k-2)y = 2\delta/P_i - 2\varphi - k + 2$ and 2) both $(k-2)f(0)$ and $(k-2)f(1)$ are contained within

the range $(2\delta/P_i - k + 2, 2\delta/P_i - k)$, and 3) the PRC is continuous over the ϕ interval $(0,1)$. Most PRCs of interest easily satisfy these conditions. Any solution that exists for $k = 1$ also exists for any odd k at a delay that is incremented by the network period $(ts_i[\infty] + tr_i[\infty])$ each time k is incremented by two. This firing pattern (Scheme A in Fig 2) requires an odd k for equal delays.

Synchronization is not possible with scheme A in Fig. 2, but it can occur in scheme B as transitional between a pattern in which neuron 1 fires first and another in which neuron 2 fires first. In our convention, the n th stimulus interval in neuron 1 precedes that in neuron 2, so for equal delays in Scheme B in Fig. 2, it is always true that $j_2 = j_1 + 1$, because neuron 2 fires one more time during δ_1 than neuron 1 fires during δ_2 . An odd k is not possible for this firing pattern with equal delays because $k = 2j_1 + 2$. For synchrony, one time lag is defined as the network period and the other as zero. For short delays, $k = 2, j_2 = 1$ and $j_1 = 0$ so from Eqs. 12 and 13:

$$tl_{21}[\infty] = ts_2[\infty] + (ts_2[\infty] + tr_2[\infty]) - \delta_1 = ts_2[\infty] + tr_2[\infty] \text{ and } tl_{12}[\infty] = ts_1[\infty] - \delta_2 = 0$$

These conditions are satisfied if $\delta_2 = ts_1[\infty]$ and $\delta_1 = ts_2[\infty]$ as illustrated in Fig. 6B. For the symmetric case of identical neurons with identical coupling and identical delays, this condition as well as Eq. 17 for $k = 2$ reduces to $\delta/P_i = \phi[\infty]$. Eq. 17 also gives the delays that allow synchrony for longer delays. Any solution that exists for $k = 2$ also exists for any even k at a delay that is incremented by the network period $(ts_i[\infty] + tr_i[\infty])$ each time k is incremented by two. In the case of delays that differ by a network period or more due to different, possibly polysynaptic, pathways in the two directions, adding different multiples of the network period to each of the two delays breaks the link between the firing patterns in Schemes A and B in Fig. 2 and whether k is odd or even.

Delays not only shift locking point but also affect dynamics via the eigenvalues

As k is increased at the fixed antiphase and synchronous locking points identified in Fig. 4 and 5, the order of the system increases as does the number of eigenvalues. For the case of two identical, identically coupled oscillators with equal delay, the stability depends upon only two things: the value of k and the slope of the PRC at the single phase at which both neurons receive an input in the phase locked mode, the locking point. The stability of the solution is determined solely by whether the maximum absolute value of the eigenvalues of the matrix A described above exceeds one. Therefore, we have plotted the maximum absolute value of the eigenvalues versus k value and parameterized the curves by PRC slope in Fig. 7. We only compare odd k with odd k (Fig. 7A), and even k to even k (Fig 7B), since under these conditions only the former supports antiphase and only the latter supports synchrony. These plots hold for any two identical pulse coupled oscillators, the only information that is relevant is the slope of its PRC at the locking point. In the limit of large k , modes with locking points at which the slope of the PRC is between 0 and 2 converge to a maximum eigenvalue of one; those with PRC slopes in the range 0 to 1 converge from below whereas those with slopes between 1 and 2 converge from above. This condition represents neutral stability. For a system with only a single eigenvalue, if the absolute value of this eigenvalue is exactly one, the associated periodic locking neither attracts nor repels nearby trajectories, so in practice it is not robust to any amount of noise. For systems with multiple eigenvalues and eigenvectors, the rate of convergence or divergence is more complex. Modes with PRC slopes between 0 and 1 are stable at $k = 1$ or 2, but effectively lose stability in the presence of noise as the delays become very large. For small PRC slopes ($m = 0.1$ and 0.25 in Fig. 7) the eigenvalue with maximum absolute value does not monotonically decrease, but the rate of convergence or divergence is not captured by a single dominant eigenvalue. On the other hand, modes with PRC slopes between 1 and 2

may tend to repel trajectories more slowly as k becomes large and the maximum absolute value of its eigenvalues drops to one. Interestingly, antiphase (k odd) modes with slopes in the range 1 to 2 ($m = 1.2$ and 1.5 in Fig 7A) are stable at $k = 1$ but are destabilized by delay at k equal to 3 or greater. Note that these curves cross the horizontal dotted line corresponding to $y = 1$. This is the only case in which we observe an actual flip in the stability of a mode due to increasing the k value. Modes with locking points with PRC slopes outside of the range 0 to 2 are unstable. Empirically we observe that the maximum absolute value of the eigenvalues converges in the limit of large k to $|1-m|$ for these cases, where m is the slope of the PRC at the locking point.

The stability criterion must be based on the correct k value

For short, equal delays and an alternating firing mode such as the one shown in Fig. 2 scheme A in which the delayed input from one neuron reaches the other neuron before the next spike in other neuron, the presence of a delay does not change the stability criterion because k is one in the presence or absence of a delay. However this is not generally true. If the delayed input from one neuron reaches the other neuron after the next spike in other neuron (Fig. 2 scheme B) instead, the k value changes and therefore so does the applicable stability criterion.

The lowest k value for scheme A with equal delays is one. The eigenvalue for $k=1$ can be written as follows: $\lambda_{k=1} = 1 - m_1 (\varphi_1[\infty]) - m_2 (\varphi_2[\infty]) + m_1 (\varphi_1[\infty])m_2 (\varphi_2[\infty])$. The lowest k value that satisfies scheme B for equal delays is two. The eigenvalue for $k=2$ to be written as follows: $\lambda_{k=2} = 1 - m_1 (\varphi_1[\infty]) - m_2 (\varphi_2[\infty])$.

In scheme A each neuron affects the very next spike in the other, resulting in a term that contains the product of the slopes, whereas in scheme B, the lagging neuron, but not the leading neuron, affects the next firing time of its partner, resulting in the absence of the term that contains the product of the slopes.

The stability criterion for synchrony with no delays is the $k=1$ criterion, but in the presence of delays, the criterion switches to the $k=2$ value. Here we give an example for which the predictions of the old criterion for $k=1$ are different than the predictions for the novel criterion for $k=2$, and as expected, the predictions based on the correct firing order were verified by integrating the system of differential equations. In this case, the Morris Lecar model for two identical, identically coupled neurons with Type II excitability (Rinzel and Ermentrout 1998) and reciprocal excitation ($E_{\text{syn}} = 0$ mV) was utilized. The intrinsic period was 85 ms, the delay was 33 ms and g_{syn} was 0.8 mS/cm^2 , all other parameters are given for this case in Appendix 2.

The existence criteria were applied to the PRC for this case as shown in Fig. 8. An anti-phase mode with time lags of 41 ms in which each neuron received an input at a phase of 0.868 (open square on the PRC) and a synchronous mode with a period of 97.9 ms in which each neuron received an input at a phase of 0.383 (center closed circle on the PRC in Fig. 8) were found to exist at this delay value. In addition, a mode with unequal time lags equal to 6.9 and 85.4 ms was found to satisfy the existence criteria, in which one neuron received an input at a phase of 0.305 and its partner received one at a phase of 0.453 (closed triangles on the PRC in Fig. 8). Only the antiphase mode was observed when the differential equations for the system were solved numerically.

Both stability criteria (for $k=1$ and for $k=2$) correctly predicted the antiphase mode to be stable and the mode with unequal time lags to be unstable. However, the predictions differed for the synchronous mode. The slope of the first order resetting at the locking point, a phase of 0.383 for each neuron, was 1.21. Second order resetting was negligible in this example.

The criterion for $k=1$, $(m_1-1)(m_2-1)$, results in a stable eigenvalue of 0.044, which would result in very strong attraction and fast convergence to synchrony. On the other hand, the criterion for $k=2$, $(1-m_1-m_2)$, results in an unstable eigenvalue of -1.42 . The latter prediction is correct, and when the differential equations were initialized exactly at synchrony, the firing times diverged initially with an observed multiplier of -1.44 to -1.46 maintained for 25 cycles, then quickly converged on the antiphase mode. The negative sign of the observed multiplier indicates that the firing order switched on every cycle, and the perturbation from synchrony grew exactly as predicted. The close correspondence is a testament to the predictive power of the PRC methodology, and confirms that the stability criterion that is applied must correspond to the correct firing pattern.

If we examine a delay of 82 ms rather than 33, the circle at a phase of 0.383 in Fig. 8 now corresponds to an antiphase mode with $k=3$ and a time lag equal to 49 ms for a network period of 98 ms. No antiphase mode exists at this delay for $k=1$ because no phase satisfies Eq 17 for $\delta=82$ ms and $k=1$. Nonetheless, using the criterion for $k=1$ predicts a stable eigenvalue of 0.044 as described above. This prediction is not correct because the antiphase mode at 0.383 is unstable for a delay of 82 ms in the system of two coupled Morris Lecar oscillators. On the other hand, the criterion for $k=3$ gives the absolute value of the maximum eigenvalue as 1.21, correctly predicting that the mode is not stable. Therefore it is critical to use the correct stability criterion as determined by the k value of the periodic mode.

Discussion

The work presented in this study is most closely related to previous work on coupled oscillators with delay under weak coupling assumptions and to work on dynamical relaying in which distant brain regions are postulated to synchronize via symmetric connectivity to a hub region. Previous work on pulse coupled oscillators with delay (Ernst et al. 1995, 1998) is philosophically close to the work presented here, but not as general since they constrained the form of the oscillator and the nature of the coupling to that used in previous studies (Peskin 1975; Mirollo and Strogatz 1990). Oprisan et al. (2004) suggested a method to incorporate short delays into the assumptions of pulsatile coupling, and Pervouchine et al. (2006) applied similar methods to two oscillators with short delays, and used the stability criterion neglecting second order resetting for the case with no delay, which is the same criterion as the one for $k=1$. Pervouchine et al. (2006) also specifically stated that second order effects prevented them from correctly analyzing synchrony in a network of two model *oriens lacunosum-moleculare* interneurons. The results in Appendix 1 of this paper show how to handle second order effects correctly in the presence of delays.

As expected from the inherent symmetry, two oscillators can synchronize despite the presence of conduction delays, if the delays have similar magnitude, and the frequencies of the oscillations are sufficiently similar. Two examples of oscillatory synchronization despite sizable conduction delays motivated this study. One example of such synchronization was observed between pairs of multiunit responses from area 17 in the left and right hemispheres of cats. Strong inter-hemispheric phase locking occurred in between a third and a half of the pairs examined with an intact corpus callosum, and no strong locking was observed when the corpus callosum was severed (Engel et al 1991). The locking was at an oscillatory frequency of 40-50 Hz with zero phase lag with an SEM of 0.3 ms, and the presumably symmetric interhemispheric delays were on the order of 4-6 ms, or about a sixth to a third of a gamma cycle. In another example with presumably symmetric time delays, tetani simultaneously applied at sites separated by up to 4 mm in hippocampal slices induced gamma oscillations that were synchronized (<1 ms lag) between the two sites (Traub et al. 1996). For small unmyelinated fibers in the hippocampus, the conduction velocity is 300 $\mu\text{m/ms}$ (Andersen et al 1978), resulting in conduction delays up to 13 ms, plus about a 1 ms

synaptic delay, which implies delays up to more than half of a gamma cycle. In order for a mechanism based on symmetric oscillators to apply to these examples, the slope of the appropriate PRCs in the phase range determined by the delays should be positive by our convention.

Our results predict that delays can either disrupt or promote stable synchronization, or have no effect, depending upon the slope of the PRC at zero (no delay) compared to the slope of the PRC at a given delay value. We postulate that a similar symmetry-based mechanism may be responsible for synchronization observed in a computational model (Tort et al 2007) with conduction delays up to 8 ms in the presence of added noise. Subsets of gamma modules that were embedded in roughly symmetric networks synchronized only with other modules with similar frequencies. Synchronization was not evident at weak values for the connectivity between modules, likely due to the inability of weak coupling strengths to overcome the effects of noise. The applicability of the methods presented herein is limited only by the ability to measure the appropriate PRCs, by the requirement that the coupling be effectively pulsatile, and the restriction to only two oscillators unless the dynamics of the population are analogous to those of a component oscillator (Achuthan and Canavier 2009; Chandrasekaran et al 2011). For example, absence epileptic seizures have been postulated to arise from phase-locking with a small but noticeable phase lag between thalamic and cortical sites (Perez Velasquez et al 2007). The methods presented herein may be more appropriate to analyze such lockings compared to the methods based upon assuming weak coupling presented in that study.

Comparison to Weak Coupling Results

Much of the theoretical work assuming weak coupling with time delay was based on the assumption of a simple model (D'Huys et al 2008; Earl and Strogatz 2003; Schuster and Wagner 1989, 1990). The results presented herein are based solely on the PRC without assuming a priori a form for the PRC. This renders the results model independent, and directly applicable to actual neurons if the PRC can be measured. The work in the present study does not make any assumptions with respect to the strength of the coupling between oscillators, but does assume that the duration is sufficiently short that the effect of a synaptic input dies out within one network period. In contrast, averaging theory assumes nothing about the duration of the coupling but instead assumes that the coupling strength is weak. Nonetheless, the predictions under the weak coupling and pulsatile coupling assumptions should converge when the coupling is both weak and pulsatile. Under the assumptions of weak coupling, meaning that a phase model is sufficient to describe network dynamics, very long delays contribute to the network dynamics in a way that is qualitatively different from shorter delays (Ko and Ermentrout 2009; Izhikevich 1998). Specifically, for weak coupling short delays produce only a phase shift in the locking point, but the delay starts to play a significant role in the dynamics of the phase model when it is comparable to $1/\varepsilon$ periods, where $\varepsilon \ll 1$ is the coupling strength. Whereas our study is in agreement that a delay shifts the locking point, we also show that the delay exerts its effects on the dynamics through its effects on the eigenvalues as k is increased (Fig. 7). We show that increasing the delays by increasing the k value at a given locking point changes the eigenvalues that determine the stability of the locking, which can change the dynamics in a fundamental way. This is consistent with, but also an extension of, the results obtained assuming weak coupling (Ko and Ermentrout 2009; Izhikevich 1998). Our results are also consistent with results (Foss 1999; Foss and Milton 2000) for the case of pulsatile feedback to a single neuron with a fixed delay; the stability results depended upon the delay, and multistability was more likely with longer delays. We observed in Eq. 17 that as the delays (and therefore the possible k values) are increased, that solutions can exist at a higher k that did not exist at a lower k , but all solutions that exist at k exist at $k+2i$, where i is an integer. Since the number of solutions

can increase or stay the same as k as increased, but never decrease, multistability is more likely at higher delay values. Any set of phases that satisfies the existence criteria at a given delay δ also satisfies them at delays $\delta + iP_N$ where P_N is the network period $P_1(1 + f(\varphi_1)) = P_2(1 + f(\varphi_2))$ and i is an integer. This fact does not imply anything about what happens to the number of solutions as δ is incremented by δ less than a network period. However, over a range of delays corresponding to large k , new solutions may emerge that were not present at small k , but no solution present at small k will be lost, so on average there will be more solutions in the range of delays corresponding to large k compared to a similar range corresponding to small k . However, it is possible for the stability of solutions to change in either direction as the delay is increased. Based on Fig. 7, increasing the delays only causes a flip between stability and instability in certain limited cases, but sufficiently large delays do decrease the rate of attraction to the limit cycle so that noise might more easily prevent a locking from being established in practice.

Comparison to Dynamic Relaying Hypothesis

It has been suggested recently that zero phase synchronization between two neuron populations can emerge via their mutual connectivity with a third area (Fischer et al. 2006). The third area is a central hub that is not synchronized with the two outer regions but instead links the other two populations in a symmetrical manner reminiscent of the symmetry that underlies synchrony in the present paper because the symmetry between the two oscillators is preserved if they are identical and identically coupled via a third oscillator rather than directly to each other. The result is zero time lagged activity in the two outer regions over a wide range of axonal delays (Vicente et al 2008). The advantage of this mechanism is that it can be generalized to multiple outer areas with a central hub. It has been proposed that the role of a central hub in synchronizing cortical regions may be played by thalamic nuclei (Uhlhass et al. 2009). The analysis in this paper can be extended to synchronize multiple regions in a similar manner. An interesting possibility is that since axonal delays can be modulated by the regulation of the conduction velocity (Fries 2005), that delays within such a network could self-regulate to compensate for heterogeneity and promote synchronization.

Summary

The most important result obtained in this study is that the existence and stability of any one to one phase locked solution in a network of two pulse coupled oscillators can easily be inferred from the phase resetting curve for delays of any duration and any firing pattern. The stimulus intervals (between neural firing and the receipt of a delayed input) determine what time lags will be observed between neural firings in areas separated by a delay. A key observation is that the time for the firing of one neuron to affect a subsequent firing in the same neuron via the feedback pathway through the other neuron must be a multiple (k) of the network period. This leads to the understanding that for a network of identical, identically coupled neurons with equal delay, stimulus intervals that are equal to the delay produce zero time lag. Furthermore, delays that are equal to the stimulus interval plus half the network period produce exact antiphase. Adding the network period to each of the two delays increments k by two but does not change the time lag that is produced, although it may change the stability. Thus, we have described the generic synchronous solution to two pulse coupled oscillators with delay, and shown that antiphase can also emerge as a generic solution depending upon the shape of the PRC. A mechanistic explanation was provided for switches between these solutions that were observed as the delay was increased. Similar switches have been noted in neural models (Tort et al 2007) as well as in other diffusively coupled systems (Prasad et al 2008) with delays and in systems in which an effective delay is introduced by the filtering properties of dendritic cables (Crook et al 1998; Remme et al 2009).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Thanks to Lakshmi Chandrasekaran for a careful reading of an earlier draft and to Shuoguo Wang for assistance with the figures. This work was supported by NIH grant 5R01MH085387-03 to CCC under the CRCNS Collaborative Research in Computational Neuroscience program.

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Appendix 1

The presence of second order resetting, or an effect on the second spike after the perturbation, implies that the trajectory in the state space has not returned to the limit cycle by the time of the first spike after the perturbation. To correct for the effect on the timing of the second spike, the phase immediately after the first spike is not presumed to be reset to zero, but rather to a value that will cause the second spike to occur at the proper time. Therefore the second order resetting must be included in the following stimulus interval (Achuthan and Canavier 2009; Oprisan and Canavier 2004; Sieling et al 2009), and be complete by the end of this interval. Third and higher order resetting cannot be accommodated in this formalism and must be negligible in order for the assumptions and methodology to be valid.

The stimulus interval in the closed loop is then defined based on the open loop stimulus interval, but modified to account for the fact that neurons in the closed circuit are perturbed multiple times as opposed to a single time in the open loop circuit. Therefore, $ts_i[n] = P_i(\varphi_i[n] + f_{2i}(\varphi_i[n-1]))$, where $\varphi_i[n]$ is the phase at which the input is received by neuron i in cycle n and the second order resetting (indicated by the 2 in the first subscript) term accounts for the possibility that the trajectory has not fully recovered to the limit cycle at the time of the spike initiating the stimulus interval.

In order to derive stability results from Eqs. 7 and 8, the PRC for both first and second (j th) order resetting is linearized as $f_{j,i}(\varphi_i[n]) = f_{j,i}(\varphi_i[\infty]) + f'_{j,i}(\varphi_i[\infty])\Delta\varphi_i[n]$. Equations 9 and 10 with second order resetting become

$$\begin{aligned}\Delta\varphi_2[n+k-1] &= \frac{P_1}{P_2}\Delta\varphi_1[n+j_1](m_{11}-1) - m_{22}\Delta\varphi_2[n-1] - \sum_{i=0}^{k-2} (m_{12}+m_{22})\Delta\varphi_2[n+i] \\ m_{11}\Delta\varphi_1[n+j_1] &= \frac{P_2}{P_1}\Delta\varphi_2[n+j_1+j_2-1](m_{22}+m_{12}-1) + \frac{P_2}{P_1}\Delta\varphi_2[n+j_1+j_2] - m_{21}\Delta\varphi_1[n+j_1-1]\end{aligned}$$

where m_{ji} is the slope of the j th order PRC $f'_{j,i}(\varphi_i[\infty])$ evaluated at the locking point for the i th neuron. Again, the summation terms are only valid for $k>1$.

$$\begin{aligned}\Delta\varphi_2[n+k-1] = & \Delta\varphi_2[n \\ & +k-2](m_{11}-1)(m_{12}+m_{22}-1)+(m_{11}-1)m_{21}\Delta\varphi_1[n \\ & +j_1-1] - m_{11}m_{22}\Delta\varphi_2[n \\ & -1] - \sum_{i=0}^{k-2} m_{11}(m_{12}+m_{22})\Delta\varphi_2[n+i]\end{aligned}$$

The addition of second order resetting increases the order for $k=1$ from 1 to 2, and adds two for all other k for an order of $k+1$. When the linear system constructed from the equation above is evaluated with $k=1$, $j_1=0$ and $j_2=0$ (Scheme A in Fig. 2), a second order linear system is obtained, and the eigenvalues are the roots of the following quadratic polynomial:

$$\lambda^2 - ((m_{11}-1)(m_{12}-1) - m_{21} - m_{22})\lambda + m_{21}m_{22} = 0$$

which agrees with results for this firing pattern with no delay (Oprisan et al. 2004).

On the other hand, when the linear system is evaluated at $k=2$, $j_1=0$ and $j_2=1$ (scheme B in Fig. 2), the three eigenvalues that determine stability are the cubic roots of the following polynomial:

$$\lambda^3 + (m_{11}+m_{12}+m_{21}+m_{22}-1)\lambda^2 + (m_{12}m_{21}+m_{11}m_{22}+m_{21}m_{22})\lambda + m_{21}m_{22} = 0.$$

The introduction of second order resetting complicates the analysis. However, it gives the advantage that we no longer require that the trajectory return to the limit cycle between the time a neuron receives an input and when it fires next (the end of the next recovery interval) but rather by the time it next receives an input (the end of the next stimulus interval). Therefore although the “observed phase” when a neuron spikes is one, or equivalently zero, if the trajectory has not yet returned to the limit cycle, the “true” phase is determined by the isochron on which the trajectory lies. The correct phase at the time of the first spike observed after an input can be inferred by observing the shift in the timing of the second spike after the input, and even negative phases which are not on the original limit cycle can be accommodated by this method (see also Oh and Matveev 2009). Second order resetting can be important especially when inputs are received at late phases and bleed over into the second cycle.

Second order resetting is negligible for the Morris Lecar model used in Figs. 5 and 8, but this is not always true. Here we give an example in which second order resetting cannot be neglected. We used two identical mutually inhibitory Wang and Buzsaki model neurons with parameters given in Appendix 2 and an intrinsic period of 16.75 ms. The predicted modes at a delay of 16 ms are indicated by symbols on the first order PRC (solid lines Fig. A1), and on the second order PRC (dashed lines). A stable antiphase mode (open squares) with a time lag of 9.48 and a stable synchronous mode synchrony (open circles) with a network period of 16.77 ms were predicted, and each was observed exactly at the predicted values when the system of differential equations was initialized with their respective basins of attraction. For the antiphase mode, second order resetting was negligible. However, the slope of the second order resetting at a phase of 0.962 corresponding to synchrony was 0.765 compared to the -0.52 for the slope of the first order resetting, so second order resetting is clearly not negligible, and in fact exerted a powerful stabilizing influence on

synchrony. The k value for this mode was 1, so the full polynomial expression was used to find the eigenvalues in this case: $\lambda^2 - ((m_{11}-1)(m_{12}-1) - m_{21} - m_{22})\lambda + m_{21}m_{22}=0$.

When second order resetting was included, all eigenvalues had absolute value less than one: a real eigenvalue of -0.76 and a complex conjugate pair with an absolute value of 0.87 . On the other hand, ignoring second order resetting moves the locking point to a phase of 0.955 , changes the predicted network period to 16.96 ms and results in an eigenvalue of -2.6 that incorrectly predicts that synchrony is not stable at a delay of 16 ms.

Appendix 2 Model Equations and Parameters

Morris-Lecar Model Network

In Figs 5, we simulated a model network composed of two Morris Lecar (1981) oscillators with Type II excitability (Rinzel and Ermentrout 1998), reciprocally coupled by identical, excitatory synapses. The differential equations for each oscillator are

$$C \frac{dV}{dt} = -g_{Ca} \bar{m}(V)(V - E_{Ca}) - g_K w(V - E_K) - g_L(V - E_L) - g_{syn} s(V - E_{syn}) - I_{stim,i}$$

$$\frac{dw}{dt} = \phi \frac{\bar{w}(V) - w}{\tau_w(V)}$$

where $\bar{m}(V) = 0.5\{1 + \tanh((V - m_{half})/m_{slope})\}$, $\bar{w}(V) = 0.5\{1 + \tanh((V - w_{half})/w_{slope})\}$, and $\tau_w(V) = 1/\cosh((V - w_{half})/(2 w_{slope}))$. C_m and V are the membrane capacitance and potential, and t is time. Constants g_{Ca} , g_K , g_L and g_{syn} and E_{Ca} , E_K , E_L and E_{syn} are the maximal conductances and reversal potentials for the calcium, potassium, leak and synaptic currents. Potassium activation is denoted by w , and $\bar{w}$ is the steady-state value of w ; $\bar{m}$ is the steady-state activation of the calcium current. ϕ is a time-scale factor.

Post-synaptic activation is modeled by the equation:

$$ds/dt = \alpha[1/(1 + \exp(-(V_{pre}(t - \delta)/2)))(1 - s) - s/\tau_{syn}],$$

where α is the presynaptic activation rate, τ_w is the synaptic decay constant, and $V_{pre}(t - \delta)$ is the delayed presynaptic voltage.

C_m was set to $20 \mu\text{F}/\text{cm}^2$; I_{stim} , $100 \mu\text{A}/\text{cm}^2$; g_{Ca} , $4.4 \text{ mS}/\text{cm}^2$, g_K , $8 \text{ mS}/\text{cm}^2$; g_L , $2 \text{ mS}/\text{cm}^2$; E_{Ca} , 120 mV ; E_K , -84 mV ; E_L , -60 mV ; E_{syn} , 0 mV ; ϕ , 0.04 ; α , 6.25 ms^{-1} ; τ_{syn} , 1 ms^{-1} ; m_{half} , -1.2 mV ; m_{slope} , 18 mV ; w_{half} , 2 mV ; w_{slope} , 30 mV .

Wang and Buzsaki Model Network

In Fig. 7B, we simulated a model network composed of two Wang and Buzsaki (1996) model neurons, reciprocally coupled by identical, inhibitory synapses. The differential equations for each oscillator are:

$$CdV/dt = -I_{Na} - I_K - I_L - I_{syn} + I_{stim,i}$$

$$dh/dt = \phi\{\alpha_h(V)(1 - h) - \beta_h(V)h\}$$

$$dn/dt = \phi\{\alpha_n(V)(1 - n) - \beta_n(V)n\}$$

where the capacitance $C = 1 \mu\text{F}/\text{cm}^2$, V is the cell membrane voltage in millivolts and t is time in milliseconds. The leak current is given by $I_L = g_L(V - E_L)$. The sodium current is

given by $I_{Na} = g_{Na} m_{\infty}^3 h (V - E_{Na})$. The steady state activation is $m_{\infty} = \alpha_m / (\alpha_m + \beta_m)$ where $\alpha_m(V) = -0.1 (V + 35) / \{ \exp[-0.1(V + 35)] - 1 \}$ and $\beta_m(V) = 4 \exp[-(V + 60)/18]$.

The scale factor ϕ was set to 5. (The symbol was changed from ϕ to Φ to avoid confusion with the symbol for phase). The rate constants for the inactivation variable h are given by $\alpha_h(V) = 0.07 \exp[-(V + 58)/20]$ and $\beta_h(V) = 1 / \{ \exp[-0.1(V + 28)] + 1 \}$. The potassium current is given by $I_K = g_K n^4 (V - E_K)$. The rate constants for n are $\alpha_n(V) = -0.01(V + 34) / \{ \exp[-0.1(V + 34)] - 1 \}$ and $\beta_n(V) = 0.125 \exp[-(V + 44)/80]$. The reversal potentials E_{Na} , E_K and E_L were set to 55, -90 and -65 mV, respectively. The maximal sodium (g_{Na}), potassium (g_K) and leak (g_L) conductances were set to 35, 9 and 0.1 mS/cm², respectively. $I_{stim,i}$ is the applied current and was set at 1.0 μ A/cm². The synaptic current is given by $I_{syn} = g_{syn} s (V - E_{syn})$, where g_{syn} is the maximum synaptic conductance equal to 0.15 mS/cm² and E_{syn} is equal to -75 mV. Synaptic activation was modeled as described above for the Morris Lecar network.

Appendix 3 Example Interval Maps

k=1 (scheme A)

From Eq 7 and 8 in main text:

$$\begin{aligned} ts_1[n] &= \delta_1 + tr_2[n-1] + \delta_2 \\ ts_2[n] &= \delta_1 + tr_1[n] + \delta_2 \end{aligned}$$

Dependence of recovery interval on stimulus interval is given by the PRC under the assumptions of pulsatile coupling:

$$\begin{aligned} tr_1[n] &= P_1 - ts_1[n] + P_1 f_1(ts_1[n]/P_1) \\ tr_2[n] &= P_2 - ts_2[n] + P_2 f_2(ts_2[n]/P_2) \end{aligned}$$

The above step can only be performed if second order resetting is ignored; otherwise the map must be formulated in terms of phase and not time intervals. Substituting for the recovery intervals, then eliminating $ts_1[n]$, we obtain the following nonlinear map.

$$ts_2[n] = ts_2[n-1] + P_1 + P_1 f_1((P_1 - P_2 + ts_2[n-1] + P_2 f_2(ts_2[n-1]/P_2) + \delta_1 + \delta_2)/P_1) - (P_2 + P_2 f_2(ts_2[n-1]/P_2))$$

The above nonlinear map contains all information required to extract the stimulus and recovery intervals for both neurons on each cycle as long as the firing pattern remains constant. Linearizing the above expression about the fixed point by setting $ts_2[n] = ts_2[\infty] + \Delta ts_2[n]$, linearizing the PRC in the neighborhood of the fixed point as described in the main text, and cancelling steady terms we obtain the 1D linear map:

$$\Delta ts_2[n] = (1 - f_1'((2\delta_1 - ts_2[\infty])/P_1))(1 - f_2'(ts_2[\infty]/P_2)) \Delta ts_2[n]$$

where $(P_1 - P_2 + ts_2[n-1] + P_2 f_2(ts_2[n-1]/P_2) + \delta_1 + \delta_2)/P_1 = \varphi_1[\infty]$ and $ts_2[\infty]/P_2 = \varphi_2[\infty]$. This is exactly equivalent to the eigenvalue $\lambda_{k=1} = (1 - m_1)(1 - m_2)$ derived in the main text.

Map for k=2 (scheme B)

From Eq 7 and 8 in main text:

$$\begin{aligned}ts_1[n+1] &= \delta_1 + tr_2[n] + \delta_2 - ts_1[n] - tr_1[n] \\ts_2[n+1] &= \delta_1 + tr_1[n] + \delta_2 - ts_2[n] - tr_2[n]\end{aligned}$$

Additional Constraint

$$ts_2[n+1] = ts_1[n] + tr_1[n] - tr_2[n]$$

Substituting the additional constraint in the Equation for $ts_2[n+1]$ above results in the equality:

$$ts_1[n] = \delta_1 + \delta_2 - ts_2[n]$$

Making the appropriate substitutions for $tr_1[n]$ then $ts_1[n]$ into the equation for $ts_2[n+1]$ we obtain:

$$ts_2[n+1] = ts_2[n] + P_1 f_1((\delta_1 + \delta_2 - ts_2[n])/P_1) + P_1 - (P_2 f_2(ts_2[n]/P_2) + P_2)$$

The above nonlinear map again contains all information required to extract the stimulus and recovery intervals for both neurons on each cycle as long as the firing pattern remains constant. As before, we obtain the 1D linear map:

$$\Delta ts_2[n+1] = (1 - f_1'((2\delta_1 - ts_2[\infty])/P_1) - f_2'(ts_2[\infty]/P_2)) \Delta ts_2[n]$$

where $(2\delta_1 - ts_2[\infty])/P_1 = \varphi_1[\infty]$ and $ts_2[\infty]/P_2 = \varphi_2[\infty]$.

This is exactly equivalent to the eigenvalue $\lambda_{k=2} = 1 - m_1 - m_2$ derived in the main text.

Figure 1. Phase Resetting Curve (PRC)

The PRC (A) is generated using an action potential from the pre-synaptic neuron to drive the perturbation in synaptic conductance (dashed curve at bottom). The diagram to the left shows the open loop circuit configuration used to measure the PRC. The unperturbed cycle length is T_0 , that of the cycle that contains the perturbation is T_1 and the one after that is T_2 . The dashed trace shows the time course of a perturbation in synaptic conductance triggered by a spike in the presynaptic neuron. The vertical arrow indicates the time of the presynaptic spike. The solid trace shows the membrane potential in the postsynaptic neuron in which the PRC is being measured. The stimulus (ts) and recovery (tr) intervals are explained in the text. The phase ϕ at which a stimulus is received is the normalized stimulus interval, ts/T_0 . The i th order phase resetting is $f_i(\phi) = (T_i - T_0)/T_0$. Characteristic PRC first (solid curve) and second (dotted curve) shapes are shown (B) for a Morris Lecar model with excitatory synapses ($E_{syn} = 0$ mV, $g_{syn} = 0.8$ mS/cm²).

Figure 2. Firing patterns

The closed loop circuit schematic wiring diagram with delays δ_1 and δ_2 is shown at the top. The order of the spikes and inputs are shown for each firing pattern A–D where the upper trace in each panel represents neuron 1, and the bottom trace represents neuron 2. Vertical bar above the trace represents a spike, arrow underneath represents an input.

Figure 3. Firing time map for scheme A

A. Short delays. The delay between a spike in neuron 1 (2) and the receipt of an input by neuron 2 (1) was designated δ_1 (δ_2). Stimulus intervals (ts_i) denote the time elapsed between a spike in neuron i and the receipt of the next input by neuron i , whereas recovery intervals (tr_i) denote the time elapsed between the receipt of an input by neuron i and the next spike in neuron i . The time lag between a spike in neuron i and a spike in neuron j was designated tl_{ij} . The time intervals are variable and indexed by cycle number n . B. Arbitrarily long delays. B1. The quantities highlighted in gray sum to $k-1$ cycles in neuron 1 plus a stimulus interval. The number of spikes that occur in neuron 2 during δ_1 is j_2 . B2. The quantities highlighted in gray sum to $k-1$ cycles in neuron 2 plus a stimulus interval. The number of spikes that occur in neuron 1 during δ_2 is j_1 . C. The additional constraint given in Eq. 8 in the text.

Figure 4. Graphical Method to Predict Existence of Phase Locked Modes

A. For $k=2$ the quantities that sum to produce the x value for neuron 1 are shown in black and those that are summed to produce the x value for neuron 2 are shown in red. If the x values for the two curves are the same, Eq. 6 is satisfied. B. For $k=2$ the quantities that sum to produce the y value for neuron 1 are shown in black and those that are summed to produce the y value for neuron 2 are shown in red. If the y values for the two curves are the same, Eq. 5 is satisfied. C. At the intersections of the black (neuron 1) and red (neuron 2) curves, both criteria are satisfied, indicating a fixed point at which the periodicity criteria are satisfied. Parameters were as in the Methods for two identical Morris Lecar neurons with Type II excitability and reciprocal excitation at a delay of 25 ms: $g_{syn} = 0.25 \text{ mS/cm}^2$, $I_{stim} = 100 \text{ } \mu\text{A/cm}^2$. D. Same as A for $k=1$. E. Same as B for $k=1$.

Figure 5. The PRC Determines Observed Modes

A. Observed versus Predicted Firing Intervals. For two identical neurons coupled by identical delays, the synchronous solution branch is characterized by one short interval and one close to the network period of 85 to 90 ms. The antiphase branch has two identical intervals of about half the network period. The value of k is odd for the antiphase branch and even for the synchronous branch, and increments each time the phase of the solution passes through one to zero (for example between panels D and E). There is good correspondence between predicted (pluses) and observed (circles). B. For no delay, the fixed point corresponding to synchrony (circle) is stable but antiphase (square) is not. C. At a delay of 25 ms, both solutions move to the right and bistability results as antiphase (square) gains stability. D. At a delay of 40 ms, synchrony loses stability. E. Antiphase remains stable after switching branches and synchrony regains stability once again enabling bistability.

Figure 6. Schematic illustration of how symmetry leads to antiphase and synchrony in the presence of delays

A. Since symmetry implies the stimulus (t_s) and recovery (t_r) intervals are the same, antiphase at $k=1$ occurs when the stimulus interval is equal to the recovery interval plus twice the delay δ . B. Also by symmetry, synchrony at $k=2$ occurs when the stimulus interval is equal to the delay.

Figure 7. Increasing the delays at the same locking point affects the dynamics

The maximum absolute value of the eigenvalues of the matrix A are plotted versus the k value and parameterized by the slope m of the PRC at the locking point. The dotted line at $y=0$ demarcates the boundary of stability. A. Odd values of k. As k becomes very large, the maximum absolute value of the eigenvalue approaches 1 from below if $0 < m < 1$ and from above if $1 < m < 2$. On the other hand, small increases in k can destabilize a mode ($m=1.2$ and 1.5). In other cases ($m=0.1$ and 0.25), the value can dip before approaching one. B. Even values of k. The same trends with increasing k are observed for odd values of k except that no crossings of the stability boundary are observed.

Figure 8. Test of the stability criteria

Stable modes are open symbols, unstable are filled. They are marked at the appropriate phase on the first order PRCs (solid line). The second order PRC (dashed curve) is plotted to show it is negligible in this example. Changing the value of k changes the stability of the synchronous (filled circle) and unequal modes (filled triangles). The criterion for $k=2$ gives the correct stability results but the one for $k=1$ does not. The example shown is for two Morris Lecar oscillators coupled by excitation with a conduction delay of 33 ms and parameters as given in Appendix 2 except $g_{\text{syn}} = 0.8 \text{ mS/cm}^2$.

Figure A1.

In this case, neglecting second order resetting produces incorrect stability results for synchrony. Stability is only predicted if the second order term is considered. Note that the slope of the second order resetting is steeper than that of the first order resetting at synchrony (open circles). This example is for two Wang and Buzsaki neurons coupled by inhibition with a conduction delay of 16 ms and parameters as given in Appendix 2.