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Effect of phase response curve skewness on synchronization of electrically coupled neuronal oscillators

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Abstract

We investigate why electrically coupled neuronal oscillators synchronize or fail to synchronize using the theory of weakly coupled oscillators. Stability of synchrony and antisynchrony is predicted analytically and verified using numerical bifurcation diagrams. The shape of the phase response curve (PRC), the shape of the voltage time course, and the frequency of spiking are freely varied to map out regions of parameter spaces that hold stable solutions. We find that type-1 and type-2 PRCs can both hold synchronous and antisynchronous solutions, but the shape of the PRC and the voltage determine the extent of their stability. This is achieved by introducing a five-piecewise linear model to the PRC, and a three-piecewise linear model to the voltage time course, and then analyzing the resultant eigenvalue equations that determine the stability of the phase-locked solutions. A single time parameter defines the skewness of the PRC, and another single time parameter defines the spike width and frequency. Our approach gives a comprehensive picture of the relation between the PRC shape, voltage time course and the stability of the resultant synchronous and antisynchronous solutions.

1 Introduction

The theory of weakly coupled oscillators (Winfree, 1967; Neu, 1979b, 1979a; Kuramoto, 1984; G. B. Ermentrout & Kopell, 1986, 1991; Hoppensteadt & Izhikevich, 1997; Brown, Moehlis, & Holmes, 2004) provides a mechanism to relate the phase response curve (PRC) of a neuron and its voltage to the stability of the emergent phase-locked states such as synchrony of a network. The PRC and the voltage are not totally independent of one another (G. B. Ermentrout & Kopell, 1986, 1991; Hoppensteadt & Izhikevich, 1997; Brown et al., 2004) but at the same time their shapes are not easily predictable from each other. These shapes could be affected by a steady stimulus, drug application or modulation of ion channel conductances (B. Ermentrout, Pascal, & Gutkin, 2001; Netoff et al., 2005; Tateno & Robinson, 2007). For example causing the frequency of a neuron to change would also have caused a number of other changes in the shapes of the PRC and the voltage: a change of the spike width, spike height, spike maximum hyperpolarization, spike threshold, a possible change of the slope of the depolarizing phase, change of the PRC skewness, and a change of the maximum delay and advancement of the PRC. A detailed and extensive understanding of which of these parameters is more sensitive in changing the dynamical behavior of a network is generally lacking. Considerable progress is made when the neurons are synaptically coupled and are posited near bifurcation point (Van Vreeswijk, Abbott, & Ermentrout, 1994; Hansel, Mato, & Meunier, 1995; B. Ermentrout, 1996) where voltage time course does not significantly affect the stability of synchrony and antisynchrony, leading to a somewhat general theory that relates the PRC shapes to the network behavior.

However when the neurons are coupled by gap junctions or electrical connections, the task becomes more difficult. In fact very few general rules that relate the PRC and voltage shapes to the network behavior are available the literature. Most studies focused on leaky integrateand-fire and related models (Chow & Kopell, 2000; Lewis & Rinzel, 2003), and the

predictions are confined to specific forms of the PRCs corresponding to those models. This is still an unsolved problem requiring a detailed study. Lewis and Skinner (Lewis & Skinner, 2012) summarize the importance of this problem by stating that in order to obtain detailed insights into the dynamical and biophysical mechanisms underlying network behavior, we must "determine how the shapes of Z and V_{LC} affect phase-locking, i.e., study how the shapes of the functions Z and V_{LC} combine ... to influence the phase-locking states." (Z and V_{LC} are, respectively the PRC and the voltage profile of the neuron between two consecutive spikes.)

Cell-to-cell gap-junction mediated electrical coupling is important because it is not only found in a number of brain neurons including striatal fast-spiking interneurons (Koos & Tepper, 1999; Klaus et al., 2011) neocortex (Galarreta & Hestrin, 1999; Gibson, Beierlein, & Connors, 1999; Mancilla, Lewis, Pinto, Rinzel, & Connors, 2007), thalamic reticular cells (Landisman et al., 2002), thalamic relay neurons during development (Lee, Cruikshank, & Connors, 2010), and CA1 hippocampal neurons that could generate synchronous discharges characteristic of seizures (Valiante, Perez Velazquez, Jahromi, & Carlen, 1995; Carlen et al., 2000) but is also common in several other biological preparations such as sinoatrial node cells (Jalife, 1984; Verheijck et al., 1998; Demir, Clark, & Giles, 1999). When the neurons are in oscillatory state either autonomously or in response to external stimuli a synchronous state may emerge in the connected network (Kepler, Marder, & Abbott, 1990; Traub et al., 2003; Fuentealba et al., 2004; Hestrin & Galarreta, 2005; Mancilla et al., 2007) (also see simulations in (Gao & Holmes, 2007; Ostojic, Brunel, & Hakim, 2009)). Electrical coupling has also been found to result in a failure of synchrony (Bou-Flores & Berger, 2001). A number of models have been proposed to explain the mechanism of synchrony or its failure (Chow & Kopell, 2000; Lewis & Rinzel, 2003; Nomura, Fukai, & Aoyagi, 2003; Bem, Le Feuvre, Rinzel, & Meyrand, 2005; Pfeuty, Mato, Golomb, & Hansel, 2003). When neurons are coupled electrically, the coupling lasts the entire duration of the voltage time course. Although this dependence of the coupling on the voltage shape makes the task of obtaining general rules more difficult, some earlier studies succeeded in parameterization of spike width, spike height, and frequency while keeping the rest of the spike profile and the PRC shape intact (Chow & Kopell, 2000; Lewis & Rinzel, 2003).

In this study we are interested in the stability of phase-locked states of two coupled neurons that oscillate at identical natural frequency in their uncoupled state. The phase-locked states we are interested in are synchrony and antisynchrony. Synchronous state is characterized by the oscillating neurons maintaining no spike time difference, whereas the antisynchrony is characterized by the neurons maintaining a spike time difference equal to half their oscillation period. The model of the neuron however is not based on a dynamical evolution of independent variables. It is represented by its PRC and its voltage shape, which together with the knowledge of the coupling mechanism are sufficient to predict the emerging phaselocked states and their linear stability. Because we aim to obtain some general rules relating the PRC and the voltage shapes to the phase-locked states, we parameterize the shapes of both the PRC and the voltage, which is facilitated by not imposing any functional relationship between them in the analysis. This dissociation of the shapes would extend the applicability of the results to a wider class of PRCs and voltage shapes that are found both in experiments and models. This also gives the ability to independently evaluate the sensitivity of the phase-locked states to changes in the parameters that define the shapes of the PRC and the voltage. But we first need to make a reasonable choice of these shapes.

Phase response curves are usually classified as type-1 or type-2 (Hansel et al., 1995) depending on whether they show only phase advancement or that in addition to phase delay. The classic Hodgkin-Huxley neuron model, when driven using a steady current to oscillate, displays a type-2 PRC. We aim to capture not only type-2 PRCs of this kind but also other

type-1 PRCs that may be obtained by altering the shape parameters. Fitting experimental PRCs with Fourier modes (Galán, Ermentrout, & Urban, 2005; Tsubo, Teramae, & Fukai, 2007) or polynomials (Netoff et al., 2005) is a common practice in neuroscience. So it would seem an obvious choice to formulate shapes comprising of Fourier modes or polynomials. However the functional form of these shapes is less crucial than the ability to parameterize those shapes to span a wide range of PRCs. Considering that at least three Fourier modes are recommended for fitting most experimental PRCs, the number of parameters required to achieve a wide range of both type-1 and type-2 PRCs can be large. Similarly a third or higher order polynomial could be considered but it still suffers from the same disadvantage as that of the Fourier series.

Instead we use a piecewise linear functional form to model the PRCs requiring effectively only two independent parameters: a skewness parameter that determines how far the maximum phase advancement is from the spike initial phase, and a type parameter that determines the relative magnitude of the maximum phase delay with respect to the maximum phase advancement. The skewness parameter could range from zero when the maximum phase advancement of the PRC is at half oscillation period, to the oscillation period itself when the PRC has its peak near the oscillation period. The type parameter could be zero or positive making it either type-1, or negative making it a type-2. As will be demonstrated, this choice achieves our goals of spanning a wide range of shapes while being still accurate in predicting the nature of stability of the phase-locked states. Voltage profiles broadly comprise of spike downstroke, depolarization phase, and the spike upstroke. We again consider piecewise linear functional forms to model the voltage time course that is shaped by few parameters: the normalized spike width parameter that could range from 0 to its maximum allowed value, and the three amplitude parameters, viz., the spike width, spike height, and spike threshold. All these could be altered freely. Note that though linear in individual segments, the complete PRC and voltage shapes themselves are nonlinear. The PRC and the voltage shape parameters are fully explored in the permissible ranges of parameters to delineate the regions of stability of both synchrony and antisynchrony.

In Section 2, the PRC and the voltage shapes are formulated, and the method to determine the stability of the phase-locked states is described. The stability of synchronous and antisynchronous states is studied in Section 3 when the spike width is zero, and in Section 4 when the spike width is non-zero. The results are discussed in relation to the previous studies and are analyzed in Section 5. We obtain analytical results and provide explicit relations for the boundaries of the phase-locked states. And these boundaries are rigorously verified when feasible by examining the corresponding eigenvalue transitions. The results are summarized in Fig. 5 for zero spike width, and in Figs. 10 and 11 for non-zero spike width.

2 Model and methods

Coupled oscillatory model neurons that are intrinsically nonlinear in nature (such as those modeled by Hodgkin-Huxley equations) can be described by coupled phase evolution equations applying the theory of weakly coupled oscillators. The main idea behind such a reduction is that one would be able to study the collective behavior of coupled neurons with information that is easily obtainable in experiments. Instead of the full intrinsic dynamics that are necessary to model individual neurons, the phase coupled model requires only the knowledge of phase response curves, the voltage time course and the coupling mechanism, all of which are relatively easy to obtain. If $_1$ and $_2$ represent phases, i.e. times elapsed since their last respective spike times, of the two coupled neurons that are oscillating with nearly identical periods T_1 and T_2 , their collective behavior is described by the two phase

evolution equations (Winfree, 1967; Neu, 1979b, 1979a; Kuramoto, 1984; G. B. Ermentrout & Kopell, 1986, 1991; Hoppensteadt & Izhikevich, 1997; Brown et al., 2004):

$$\dot{\theta}_1(t) = \frac{1}{T_1} + \varepsilon H_1(\theta_2 - \theta_1), \dot{\theta}_2(t) = \frac{1}{T_2} + \varepsilon H_2(\theta_1 - \theta_2),$$

$$(1)$$

where is a small (because of the assumption of weak-coupling) constant parameter, and $H_{1,2}(\phi)$ are the mutual interaction functions that are essentially the instantaneous frequency increments. We assume that the oscillators are identical, and thus $T_1 = T_2 = T$, and $H_{1,2}(\phi) = H(\phi)$ where $H(\phi)$ is given by a convolution of the PRC, Z(t), that is characteristic of each of the oscillators, and the coupling function which in our case of electrical coupling is simply the difference of the voltages [V(t)] of the two neurons:

$$H(\phi) = \frac{1}{T} \int_{0}^{T} Z(\tilde{t}) [V(\tilde{t} + \phi) - V(\tilde{t})] d\tilde{t}.$$
 (2)

If $H(\varphi)$ is the interaction function of the first oscillator, the second oscillator's interaction is defined by $H(-\varphi)$. The voltage with phase advancement [$V(t + \varphi)$] is from the coupled oscillator, and is also the factor that will make the computation of the stability a complex task even within our assumption of piecewise linear functions. The dynamics of the two identical coupled oscillators can further be reduced to the study of single equation by writing an equation for the phase difference $\varphi = 2 - 1$ as

$$\phi(t) = \varepsilon [H(-\phi) - H(\phi)] = \varepsilon G(\phi(t)) \quad (3)$$

where

$$G(\phi(t)) = \frac{1}{T} \int_{0}^{T} Z(\tilde{t}) [V(\tilde{t} - \phi) - V(\tilde{t} + \phi)] d\tilde{t}.$$
 (4)

We will call the function $G(\varphi)$ the growth function, because it essentially quantifies the growth of the phase difference, or the rate of divergence of the phases. If there is no divergence, i.e. when $G(\varphi) = 0$ at some $\varphi = \varphi^*$, those phases represent equilibria of the original phase equations. These equilibria can be synchronous states ($\varphi^* = 0$), antisynchronous ($\varphi^* = T/2$), or any other phase-locked states. We can clearly see from Eq. 4 that $G(\varphi)$ becomes zero at $\varphi = 0$ and T/2, and thus synchronous and antisynchronous states always exist for this model. We are concerned in this study with these two states. However, to be of any practical utility, these states must be shown to be linearly stable. An equilibrium $\varphi = \varphi^*$ is stable if any perturbation imparted to the system subsides in time, i.e. the derivative of the growth function at the equilibrium must be negative, or the eigenvalue G

 (φ^*) , where $G'(\varphi^*) \equiv \frac{dG(\varphi(t))}{d\varphi}\Big|_{\phi(t)=\phi^*}$ must be negative. We represent this eigenvalue by if $\varphi^* = 0$, and if $\varphi^* = T/2$. We can directly express these eigenvalues from Eq. 3 and 4 as:

$$\lambda = \varepsilon G'(0) = -\frac{2\varepsilon}{T} \int_{0}^{T} Z(\tilde{t}) V'(\tilde{t}) d\tilde{t}, \quad (5)$$

$$\gamma = \varepsilon G' (T/2) = -\frac{2\varepsilon}{T} \int_{0}^{T} Z(\tilde{t}) V' (\tilde{t} - T/2) d\tilde{t}.$$
 (6)

In this study we compute and for various shapes of Z(t) and V(t), and map regions of stability of both synchronous and antisynchronous states. But first, we formulate V(t) and Z(t) below.

2.1 Model for the voltage time course

The voltage trace V(t) is periodic in time with period T(>0), and is formulated by three piecewise linear curves (Fig. 1) that use three parameters (V_p , V_{m} , and V_{th}) defining different voltage levels, and another parameter W(-0) that is closely related to the width of the spike that is asymmetric. This formulation is inspired by an empirical observation of the time course of the Hodgkin-Huxley (HH) model neuron (depicted as thin lines in Fig. 1 for an applied current of $I_{app} = 10\mu$ A/cm²). The three linear curves correspond to the spike upstroke, downstroke, and depolarization regimes. The number of free parameters is kept to a minimum and they are V_p , the peak value of the spike, V_m , the maximum hyperpolarization reached by the downstroke of the action potential, V_{th} , the spike threshold, and finally the parameter W. These parameters are now freely variable and no more correspond to the HH model alone. The voltage profile is thus given by

$$V(t) = \begin{cases} V_1(t) = V_p - \frac{V_p - V_m}{2W}t, & \text{if } 0 \le t < 2W\\ V_2(t) = V_m + \frac{V_{\text{th}} - V_m}{T - \frac{5}{2}W}(t - 2W), & \text{if } 2W \le t < T - \frac{W}{2}\\ V_3(t) = V_{\text{th}} + \frac{V_p - V_{\text{th}}}{\frac{W}{2}}(t - T + \frac{W}{2}), & \text{if } T - \frac{W}{2} \le t < T. \end{cases}$$
(7)

By observing the spike profile and the time course, we arrive at some simple conditions on the parameters defining V(t) as described below. The spike width and the refractory period together are accounted for by the rise time (W/2), and the fall time (2W), and we insist that the spike period (T) not smaller than this so that there is a finite time to recover before the

next spike onset: $\frac{W}{2} + 2W \leq T$, or

$$T - \frac{5}{2}W \ge 0. \quad (8)$$

The actual width of the spike could be considered either 5 W/2 or less, but for simplicity we term W in this study as the spike width. The spike peak V_p is bigger than the V_{th} , and hence

$$a_1 \equiv V_p - V_{\rm th} > 0.$$
 (9)

The spike peak V_p can be either positive or negative, but its magnitude is assumed to be not smaller than that of V_{m} , hence

$$a_2 \equiv V_p - V_m \ge 0. \quad (10)$$

The maximum hyperpolarization V_m is assumed to be negative, and the magnitude of V_{th} is smaller than that of V_m , such that

$$a_3 \equiv V_{\rm th} - V_m > 0.$$
 (11)

The shape of the voltage trace also imposes the condition

 $a_2 \ge a_3$, (12)

and

 $a_2 \ge a_1$. (13)

Of all the parameters that define the voltage shape, we will see that only W/T and a_3/a_2 are the truly independent parameters that affect the stability boundaries of synchrony and antisynchrony.

2.2 Model for the phase response curve

A popular method of measuring phase response curves experimentally is by computing the relative shifts of the spike times in response to brief current inputs placed during the time course in between the spike times. However such current inputs also cause similar phase shifts in other independent variables that define the spiking dynamics of the neuron. The profiles of these phase shifts are different in different variables, and together form different components of the adjoint solution that can be computed numerically for any spiking neuron model (Izhikevich, 2007). This is also referred to as the phase response curve, linear response function, or sensitivity function (Winfree, 1967). However, since the electrical coupling depends only on the voltage, the voltage component of the phase response curve [Z(t)] (i.e. the phase shifts measured in the voltage variable) is of interest to us, and we formulate it by five piecewise linear curves (Fig. 1). It is parameterized by three parameters A, B, and C. Of these three, A is a time parameter, and B and C (which can indeed be combined into a single parameter B/C without loss of generality) define the magnitude levels of the PRC. In addition to these three parameters, the time period T controls both the voltage and the PRC. Spike rise time W/2 is also used in specifying the PRC.

This formulation, as in the previous section, is again motivated by an empirical observation of the PRC shape of the HH model (thin lines in Fig. 1). Thus the piecewise linear formulation incorporates some general features of the HH model, but since the shape parameters are freely variable, our predictions based on the piecewise linear model are applicable to much larger set of models than those based on the HH model alone. The profile of Z(t) is given by

$$Z(t) = \begin{cases} Z_{1}(t) = 0, & \text{if } 0 \leq t < \frac{A}{2} \\ Z_{2}(t) = \frac{2B(t - \frac{A}{2})}{A}, & \text{if } \frac{A}{2} \leq t < A \\ Z_{3}(t) = \frac{(t - A)(C - B)}{\frac{T}{2} - \frac{A}{2}} + B, & \text{if } A \leq t < \frac{A + T}{2} \\ Z_{4}(t) = C - \frac{C(-\frac{A}{2} + t - \frac{T}{2})}{-\frac{A}{2} + \frac{T}{2} - \frac{W}{2}}, & \text{if } \frac{A + T}{2} \leq t < T - \frac{W}{2} \\ Z_{5}(t) = 0, & \text{if } T - \frac{W}{2} \leq t < T, \end{cases}$$
(14)

and is illustrated in Fig. 1 (thick lines). The parameter *B* is the type parameter that can convert the PRC to become completely non-negative $(B \ 0)$ and thus a type-1, or partially negative (B < 0) and thus a type-2. We term *A* the skewness parameter because the nearness of the maximum phase delay position to the center of the period is controlled by *A*. By this definition, A = 0 signifies a more symmetric PRC that has the maximum phase advancement

at half period. Since the maximum advancement occurs at $\frac{A}{2} + \frac{T}{2}$, and should be less than

 $T-\frac{W}{2}$ above which the PRC is zero, this leads to the following condition

$$T - A - W \ge 0. \quad (15)$$

The parameter C(>0) is the maximum phase advancement of the PRC. We will see that only B/C and A/T are the only independent PRC parameters that affect the stability boundaries of synchrony and antisynchrony.

PRC with large A is said to have large skewness, and that with no or zero skewness is characterized by A = 0. Many experimental PRCs show the maximum phase advancement tilted more toward higher values of the phases, i.e. they have large skewness. Mimicking the HH model that has very small response near early phases, we have assumed the PRC to be zero from spike peak time to a time half of maximum delay time of the PRC. Also, the PRC is assumed to be zero during the rise time of the spike. The zero regime during the action potential is essentially a depiction of the fact that the identical phase lines (i.e. isochrons) drawn in the phase plane of voltage versus any other variable are parallel to the voltage axis, thus perturbations imparted to the voltage (which are used in determining the PRC) cause negligible phase shifts.

2.3 Stability of synchrony and antisynchrony

In the synchronous state the phases of the two coupled oscillators are identical, i.e. the spike time difference of the two neurons is zero, and in the antisynchronous state the phase difference is equivalent to half the oscillation period. The stability of these two states is determined, respectively, by and defined in Eqs. 5 and 6. In computing and from these formulas, it is convenient to segment the parameter space of (W, A) depending on the relation between the V and Z segments. We have detailed this procedure in the Appendix A:. To help us compute the stability of synchronous state, the (W, A) parameter regime is split into four regions: a, b, c, and d. These regions and the relative position of the V and Z in each of these regions are displayed in Fig. 2(A). The eigenvalue in each region is written as

$$\lambda_x = \varepsilon (\lambda_{1x} + \lambda_{2x} + \lambda_{3x} + \lambda_{4x} + \lambda_{5x} + \lambda_{6x}), \quad x = a, b, c, d.$$
(16)

The expressions for each of these components are listed in the Appendix D:. Similarly to help us compute the stability of antisynchronous state (i.e. find from the integral in Eq. 6), we time shift the voltage by half period, and identify the parameter regimes where slopes are constant. This results in seventeen different regions (*a*, *b*, *c*, ..., *q*), and the eigenvalue in each region is written as

$$\gamma_x = \varepsilon (\gamma_{1x} + \gamma_{2x} + \gamma_{3x} + \gamma_{4x} + \gamma_{5x} + \gamma_{6x} + \gamma_{7x} + \gamma_{8x}), \quad x = a, b, c, \dots, q.$$
(17)

The regions and the relative placement of V and Z in some of these regions are illustrated in Fig. 2(B). We have detailed the procedure and the eigenvalue expressions for all the components in, respectively, the Appendix B: and Appendix E:. An examination of the relative placement of V and Z can directly give us an estimate of the sensitivity of the synchronous and antisynchronous states to the parameters that define the PRC and voltage shapes.

In the following two sections, we analyze these eigenvalues to determine where synchronous and antisynchronous states are located in the parameter regimes. Explicit curves for the

boundaries of these states are derived. When possible the derivation is substantiated by examining the actual transitions of the eigenvalues.

3 Zero spike width

In this section, conditions for synchrony and antisynchrony are derived analytically for the case of zero spike width (W=0). An example set of type-1 PRCs are displayed in Fig. 3(b) for a range of PRC skewness levels. These are obtained by setting B = 0. The parameter region is represented by the region (c) in the (W,T) plane of Fig. 2A, and is illustrated by an example in Case (c) Type I. We clearly see from the lack of any shaded region there (see Appendix A: for description) that no eigenvalue component is positive for any level of skewness, and the non-zero eigenvalue components 4_c and 5_c [displayed in Fig. 3(c)] and hence the total eigenvalue are negative and thus the synchrony is stable for all A. For the antisynchronous state we refer to regions (b) and (e) of (W,T) plane of Fig. 2B, and the corresponding illustrations in Case (b) and (e) of Type-I. There we see that the only eigenvalue component that is positive and hence contributes to instability of antisynchrony is due to the spike downstroke, $_{5b}(_{4e}$ becomes zero at B = 0). We will see that this is the biggest in magnitude among all the components due to the contribution of the downstroke with infinite slope in the limit of zero spike width. All the other components are negative. These are illustrated in Fig. 3(d). As the skewness is increased, the discontinuity in the voltage occurs at smaller and smaller levels of PRC leading to a diminishing effect of it, and thus the total eigenvalue becomes negative beyond certain level of skewness, causing the antisynchrony become stable. A numerical bifurcation diagram obtained by solving for the slopes of $G(\phi)$ directly from Eq. 4 [Fig. 3(e)] confirms these observations. The stable synchrony and antisynchrony regions as a function of the skewness are shown in Fig. 3(f) and will be rigorously shown in this section.

An example of type-2 PRCs for a range of A is shown in Fig. 4(b). B/C is set to -0.5 for illustration. For the eigenvalue components contributing to the stability of synchrony we refer to the Case (c) Type II in Fig. 2(A). There we see that the negative lobe of the PRC can potentially destabilize synchrony (see Appendix B: for description) if its contribution surpasses in magnitude that of the other PRC regions. Of the two shaded segments, the $Z_2(t)$ segment of the PRC results in a positive eigenvalue component (3c) for any level of skewness, and its magnitude increases linearly with skewness. At the same time, the other PRC segments span less range along the phase and thus their contribution to the negative eigenvalue diminishes [Fig. 4(c)], leading to the total eigenvalue becoming positive above a critical skewness causing the synchrony become unstable. For the stability of antisynchrony we refer to Cases (b) and (e) of Type II in Fig. 2(B). At small skewness the spike discontinuity occurs at a positive level of PRC, and thus it contributes a positive component to the eigenvalue (sum of $_{4b}$ due to upstroke, and $_{5b}$ due to downstroke) that overpowers the other stabilizing components of the eigenvalue. This effectively makes the antisynchrony unstable. But as the skewness is increased such that the discontinuity occurs closer to the zero crossing of the PRC, its effect in destabilizing the antisynchrony diminishes leading to a stable antisynchrony. At extremely large skewness, the discontinuity occurs at negative PRC level when the stabilizing roles of the spike upstroke and downstroke are reversed (represented now by $_{3e}$ and $_{4e}$). But at the same time the rising phase of the voltage convolved with the negative PRC regime $(5_e \text{ and } 6_e)$ adds to the positive level of the eigenvalue. Consequently at very large skewness, the antisynchrony could become unstable again [Fig. 4(d)]. A numerical bifurcation diagram as a function of skewness [Fig. 4(e)] confirms that the synchrony becomes unstable at large skewness whereas antisynchrony is unstable for small A/T, but becomes stable for large A/T before becoming unstable again at extremely large A/T. The analytical boundaries for synchrony (2) and the antisynchrony (8) and 10 that are derived later in this section are depicted in Fig. 4(f). We in fact derive the

stability regions in the plane of skewness and type parameter; These are depicted in Fig. 5(a); The type-1 PRCs always show stable synchrony, and type-2 PRCs are capable of displaying stable synchrony at all skewness levels. Both type-1 and type-2 PRCs exhibit stable antisynchrony at large skewness with type-2 PRCs showing instability at very large skewness levels. Type-2 PRCs may also lose stability at very large skewness. These are verified by numerically computed $G(\varphi)$ in Figs. 5(b,c,d). We next present the analytical stability boundaries.

3.1 Synchrony

Neurons with type-1 PRCs which have finite zero segments at either end always display synchrony as there are no eigenvalue components that can make the synchrony unstable [Fig. 2(A), Case (c) Type I]. But if the PRC is of type-2, then synchrony can become unstable due to negative PRC regime [Fig. 2(A), Case (c) Type II]. Since W = 0, the only eigenvalue components that are non-zero are $_{3c}(>0)$, $_{4c}$ that may become positive for large *B*, and $_{5c} < 0$ [Fig. 4(c)]. Combining these components, we get the eigenvalue

 $\lambda_c = \frac{-\varepsilon a_3 C}{2T^2} [BT + 2C(T - A)].$ We see that $\lambda_c|_{B=0} = \frac{-\varepsilon a_3 C}{T^2} < 0$ [Fig. 3(c)], and hence the synchrony is stable at B = 0. A critical state of stability will be reached when c becomes 0.

By setting the eigenvalue to zero, we obtain $B^* = -2C \left(1 - \frac{A}{T}\right)$. And on this critical

curve, $\frac{d\lambda_c}{dB} = \frac{-\varepsilon a_3}{2T} < 0$. That is this critical value acts as a lower boundary for stability. Increasing *B* across *B** causes the eigenvalue go through 0 with a negative slope, and hence the eigenvalue is positive for *B* < *B** and negative for *B* > *B** and is zero at *B* = *B**. Thus the region of stable synchrony is given by

$$\left(\frac{B}{C}\right) > \left(\frac{B}{C}\right)^* \equiv \rho_1 = -2 \left(1 - \frac{A}{T}\right), \quad \text{if} \quad W=0, \quad (18)$$

where we have also normalized *B* with *C*. This curve is negative for *A* between 0 and *T*. Consequently, all type-1 PRCs that have zero segments at the edges display stable synchrony [Fig. 3(f)], but type-2 PRCs (B < 0) do not necessarily lead to unstable synchrony. The maximum delay of the PRC (*B*) must be sufficiently long to counter the skewness in order to destabilize the synchrony. But PRCs with large skewness are closer to the unstable boundary than those with small skewness.

The above critical condition for stability can be inverted to obtain an expression in terms of the skewness. Thus the stable synchrony is obtained when

$$\left(\frac{A}{T}\right) < \left(\frac{A}{T}\right)^* \equiv \rho_2 = 1 + \frac{B}{2C}, \quad \text{if} \quad W = 0.$$
 (19)

The above condition [shown in Fig. 4(f)] predicts the value of upper boundary on skewness for synchrony to be stable. For the HH model discussed earlier, B/C = -0.5, and hence the upper limit of skewness for synchrony is A/T = 0.75. Numerical bifurcation diagrams were computed using functional forms of V(t) and Z(t), and are illustrated for type-1 [Fig. 3(e)] and type-2 [Fig. 4(e)] which verify the above analytical prediction.

3.2 Antisynchrony

Two stability criteria will emerge for antisynchrony, corresponding to the case of small skewness [Case (b), Fig. 2(B)], and the case of large skewness [Case (e), Fig. 2(B)]. In the

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first case, $0 \le A < \frac{T}{2}$, and the eigenvalue $_b$ determines the stability, and in the second case $\frac{T}{2} \le A \le T$ where $_b$ determines the stability. We will find that there are four segments that

 $\frac{T}{2} \le A < T$ where $_e$ determines the stability. We will find that there are four segments that form the boundary of stable antisynchrony. Type-1 PRCs at moderately large skewness

 $\left(\frac{T}{2} \le A < \frac{4T}{5}\right)$ may lead to unstable antisynchrony. They can also lead to stable

antisynchrony for very small skewness $\left(A < \frac{T}{5}\right)$ provided the type parameter is large

positive. Further we will see that at very large skewness $\left(A \ge \frac{4T}{5}\right)$, a type-2 PRC can lead to unstable antisynchrony. There are in all two disjoint regions of stability in (*A*, *B*) parameter space.

First consider the case of $0 \le A < \frac{T}{2}$. The eigenvalue components consist of 2b, 3b, 6b, 7b, T

and the integral across the voltage discontinuity at $t=\frac{T}{2}$ that can also be obtained by combining $_{4b}$ and $_{5b}$ in the limit of zero spike width. Combining these components and using the formula in Eq. 17, we write the eigenvalue as

 $\gamma_b = \frac{-\varepsilon a_3}{2T^2(T-A)} \left[2C \left(A^2 - T^2\right) + BT \left(T - 5A\right) + 4C AT \right].$ We directly see that for B = 0, the antisynchronous state is unstable for small skewness, and becomes stable for large skewness because

$$\gamma_b|_{B=0} = \frac{-\varepsilon a_3 C}{T-A} \left[\left(\frac{A}{T} + 1\right)^2 - 2 \right] \begin{cases} >0, & \text{if } A < (\sqrt{2} - 1)T, \\ =0, & \text{if } A = (\sqrt{2} - 1)T, \\ <0, & \text{if } A > (\sqrt{2} - 1)T. \end{cases}$$

Thus the criterion for stability when B = 0 is

$$\frac{A}{T} > \left(\frac{A}{T}\right)^* \equiv \sigma_1 = \sqrt{2} - 1, \text{ if } B = 0, W = 0, (20)$$

and is illustrated in Fig. 3(f). As *B* is increased or decreased from 0, antisynchrony may become stable. The sign of $_b$ could change across a critical curve (*B**) which is obtained by solving the equation $_b = 0$:

$$\left(\frac{B}{C}\right)^* = 2 \left(\frac{\left(\frac{A}{T}\right)^2 + 2\frac{A}{T} - 1}{5\frac{A}{T} - 1}\right), \quad (21)$$

where C is used to normalize B. On this critical curve, the transition of the eigenvalue is given by

$$\left. \frac{d\gamma_b}{dB} \right|_{B=B^*} = \frac{a_3(T-5A)}{2T(A-T)} \quad \left\{ \begin{array}{cc} <0, & \text{if } A < \frac{T}{5}, \\ >0, & \text{if } A > \frac{T}{5}. \end{array} \right.$$

Thus for very small skewness levels $\left(A < \frac{T}{5}\right)$, the eigenvalue becomes negative when *B* is increased past *B**. Thus the region of stable antisynchrony is given by

$$\frac{B}{C} > \left(\frac{B}{C}\right)^* \equiv \sigma_2, \quad \text{if } 0 \le A < \frac{T}{5}, W = 0, \quad (22)$$

where B^* is given by Eq. 21. So when there is no skewness in the PRC (A = 0), the typeparameter must be twice bigger than the maximum PRC advancement (B > 2C) for the antisynchrony to become stable. For slightly bigger A, the stability boundary increases quadratically as seen in Eq. 21. This curve, 2, appears in the top left corner of Fig. 5(a).

For $\frac{T}{5} < A < (\sqrt{2} - 1) T$, stable synchronous region lies below B = 0, and crossing $B = B^*$ from below the eigenvalue becomes positive. Hence the stability region is defined by

$$\frac{B}{C} < \left(\frac{B}{C}\right)^* \equiv \sigma_3, \quad \text{if} \quad \frac{T}{5} < A < \sqrt{2} - 1, W = 0, \quad (23)$$

where B^* is given by Eq. 21. This curve is shown in Fig. 5(a).

In the region $\left(\sqrt{2}-1\right) < A < \frac{T}{2}$, antisynchronous state is already stable when B = 0, and across the critical curve $B = B^*$, it loses stability. Hence the curve $B = B^*$ lies above B = 0. Thus the stability region is again given by

$$\frac{B}{C} < \left(\frac{B}{C}\right)^* \equiv \sigma_4, \quad \text{if } \sqrt{2} - 1 < A < \frac{T}{2}, W = 0, \quad (24)$$

where B^* is given by Eq. 21. The curve $_4$ and the region represented by the above relation is shown in Fig. 5(a).

Next consider the case of $\frac{T}{2} \leq A < T$ where the eigenvalue components [Fig. 2(B) Case (e)] are given by $_{2e}$, $_{5e}$, $_{6e}$, $_{7e}$, and the contribution from the voltage discontinuity that can in turn be computed by taking the limit of spike width going to zero from $_{3e}$ and $_{4e}$. Combining all the eigenvalue components, and using the formula in Eq. 17, we get the total

eigenvalue as $\gamma_e = \frac{\varepsilon a_3}{2AT^2} \left[2A^2C - A(5B+2C)T + 4BT^2 \right]$. This eigenvalue is negative at $a_2C(T-A)$

B = 0 in this regime because $\gamma_e|_{B=0} = -\frac{a_3C(T-A)}{T^2}$. Thus the antisynchronous state is already stable. A critical curve that may lie above or below the B = 0 level is obtained by solving for *B* from the equation e = 0 which gives,

$$\left(\frac{B}{C}\right)^* = \frac{\frac{A}{T} \left(1 - \frac{A}{T}\right)}{2 \left(1 - \frac{5A}{4T}\right)}.$$
 (25)

This clearly lies above B = 0 when $A < \frac{4T}{5}$, and below B = 0 level when $A > \frac{4T}{5}$. The transition of the eigenvalue is determined by

$$\left. \frac{d\gamma_e}{dB} \right|_{B=B^*} = \frac{2a_3 \left(T - \frac{5A}{4}\right)}{AT} \qquad \begin{cases} >0, & \text{if} \quad A < \frac{4T}{5}, \\ <0, & \text{if} \quad A > \frac{4T}{5}. \end{cases}$$

Thus when $A < \frac{4T}{5}$, the stable antisynchronous state becomes unstable when *B* is increased above *B*^{*}. Thus the stable region for antisynchrony is given by

$$\frac{B}{C} < \left(\frac{B}{C}\right)^* \equiv \sigma_5, \quad \text{if} \quad \frac{T}{2} \le A < \frac{4T}{5}, W = 0, \quad (26)$$

where B^* is given by Eq. 25. This region is shown in Fig. 5(a).

When $A > \frac{4T}{5}$, because the eigenvalue transitions to negative value across B^* , the stable region lies above the critical curve, and thus the stable region for antisynchrony is given by

$$\frac{B}{C} > \left(\frac{B}{C}\right)^* \equiv \sigma_6, \quad \text{if} \quad \frac{4T}{5} < A < T, \quad W = 0, \quad (27)$$

where B^* is again given by Eq. 25. This region is shown bounded by the curve $_6$ in Fig. 5(a). Thus type-2 PRCs with very large skewness can lose both synchrony and antisynchrony.

The critical curves can also be written in terms of A, and the regions can be inferred by solving the equations $_b = 0$ and $_e = 0$. We list the critical curves and the regions below but infer the regions by simply matching them with those already derived above instead of repeating such an analysis. For a specific value of B/C = -0.5, the eigenvalue components and the total eigenvalue are shown in Fig. 4(d) and the stable antisynchrony region derived from the eigenvalue is marked in Fig. 4(f). The computed numerical bifurcation diagram [Fig. 4(e)] verifies this region. From the equations for $_b$, critical curves are obtained as

$$\left(\frac{A}{T}\right)^* \equiv \sigma_7 = \frac{1}{4} \left(5(B/C) - 4 - \sqrt{25(B/C)^2 - 48(B/C) + 32} \right), \quad (28)$$
$$\left(\frac{A}{T}\right)^* \equiv \sigma_8 = \frac{1}{4} \left(5(B/C) - 4 + \sqrt{25(B/C)^2 - 48(B/C) + 32} \right) \quad (29)$$

And from the equation for _e, the following critical curves are obtained:

$$\left(\frac{A}{T}\right)^* \equiv \sigma_9 = \frac{1}{4} \left(5(B/C) + 2 - \sqrt{25(B/C)^2 - 12(B/C) + 4} \right), \quad (30)$$
$$\left(\frac{A}{T}\right)^* \equiv \sigma_{10} = \frac{1}{4} \left(5(B/C) + 2 + \sqrt{25(B/C)^2 - 12(B/C) + 4} \right). \quad (31)$$

We list below the critical regions in terms of *A* that can be verified with those already given above by numerically plotting them. The antisynchrony is stable in the following regions:

$$\begin{aligned} &\frac{A}{T} < \sigma_7, \text{ and } \frac{A}{T} > \sigma_9, & \text{if } B/C > 2, W = 0, \quad (32) \\ &\frac{A}{T} > \sigma_9, & \text{if } 1/3 < B/C < 2, & W = 0, \quad (33) \\ &\frac{A}{T} > \sigma_8, & \text{if } 0 < B/C < 1/3, & W = 0, \quad (34) \\ &\sigma_8 < \frac{A}{T} < \sigma_{10}, & \text{if } B/C < 0, & W = 0. \quad (35) \end{aligned}$$

For B/C = -0.5 as in Fig. 4, the last condition gives us the stable range of skewness as 0.347 < A/T < 0.883. This region is depicted in Fig. 4(f).

4 Non-zero spike width

In this section, we investigate the effect of spike width and the dependence of stability criteria on it. The effect of the spike width in type-1 PRCs is illustrated in Fig. 6 (cf. Fig. 3). The parameter W/T is set at 0.15 in the figure. For studying the stability of synchrony, in the limit of zero spike width we could consider the parameter point either belonging to region (c) as we did earlier or to region (a). But for finite spike width we must consider regions (a) and (d) in the (W, A) space of Fig. 2(A), and the corresponding illustrations in Cases (a) and (d). When A/T = 0, the PRC is non-zero near early phases, and thus the spike downstroke could cause instability of synchrony [Fig. 6(c)]. As the skewness is increased, the spike downstroke effect diminishes because of either small or zero level of the PRC, and consequently the synchrony acquires stability. Again in contrast to the case of zero spike width, the antisynchrony can acquire stability even at A/T = 0. At finite spike width the spike downstroke [Case (a) Type I in Fig. 2(B)] that earlier destabilized antisynchrony could become less effective [$_{6a}$ in Fig. 6(d)] if it extends to the region of the PRC that has negative slope. Consequently the total eigenvalue can become slightly negative for certain W/T leading to a stable antisynchrony. But as the skewness is increased the spike downstroke that contributes to positive eigenvalue occurs at PRC levels that are larger than that during the spike upstroke, leading to unstable antisynchrony. At extremely large spike width stability can return as quantified by the eigenvalue components in Fig. 6(d). A numerical one-parameter bifurcation diagram as a function of A/T obtained by computing the $G(\phi)$ from Eq. 4 [Fig. 6(e)] confirms these observations. The corresponding boundaries of stability are shown in Fig. 6(f). In the above illustration we have set B/C = 0. For finite positive B/C, as will be seen from the expressions derived later, the movement of the boundaries are as indicated in the side panel of Fig. 6(f).

The effect of spike width on type-2 PRCs is illustrated in Fig. 7. *W*/*T* is again set to 0.15 and B/C = -0.5 [Fig. 7(a,b)]. At these parameter values, the stability of synchrony is similar to that at zero spike width. The spike downstroke could still cause instability of synchrony [_{3a} in Case (a) Type II of Fig. 2(A)] even at small skewness, but due to the narrow region between the zero crossing of the PRC and time of the maximum hyperpolarization that contributes to the positive part of _{3a}, it would require a large negative *B*/*C* to cause instability. But in the regions (b) and (c), part or the entire negative lobe of the PRC [Fig. 2(A) Cases (b) and (c) Type II] contributes to a positive eigenvalue [Fig. 7(c)] causing the synchrony become unstable. The effect of spike width on the antisynchrony could be more

drastic than on synchrony. The antisynchrony becomes unstable for most of the skewness except at large and very small skewness. The components $_{5a}$ and $_{6a}$ [Fig. 7(d)] (and their corresponding segments in the regions (f), (d), (g), and (e)) together dominate the contribution to the total eigenvalue in causing the instability. A numerical one-parameter bifurcation diagram in Fig. 7(e) as a function of skewness confirms these observations. The stability boundaries and their dependence on the level of B/C are depicted in Fig. 7(f).

Before we present the analytical results, we illustrate the role of spike threshold together with spike width at a small (Fig. 8, A/T = 0.2) and a large (Fig. 9, A/T = 0.6) value of skewness. Comparing Figs. 3(e) and 6(e), we see that finite spike width could cause an instability of synchrony at small skewness. From these figures we also notice that the range of stable antisynchrony appearing near large skewness levels is moved further to larger skewness. The movement of eigenvalues for antisynchrony is shown in Fig. 8(a), and the corresponding bifurcation diagram in the space of W/T and a_3/a_2 is shown in Fig. 8(b). When the synchrony is unstable, increasing the spike threshold such that a_3/a_2 crosses a critical level causes the synchrony become stable because the destabilizing effect of downstroke is countered by the contribution of the stabilizing segments of the PRC that are now amplified by a larger slope of the voltage segment. $G(\varphi)$ computed at a parameter point where both the synchrony and antisynchrony are unstable is shown in Fig. 8(c), and a oneparameter bifurcation diagram [Fig. 8(d)] verifies the stability diagram. A stability diagram at the same level of skewness for a type-2 PRC (here by setting B/C = -0.5) is shown in Fig. 8(e) and is numerically verified in Fig. 8(f).

Large skewness causes the spike downstroke have less effect on synchrony, and thus is generally favorable to stable synchrony. Except when the spike threshold is small such that the slope of the depolarizing phase is very small, we find a stable synchrony [Fig. 9(a)] for all values of W/T. Large skewness coupled with small or zero spike width also makes the spike profile itself be less effective [see Cases (d) and (e) in Fig. 2(B)] in the antisynchrony; The spike downstroke contributes to instability in type-1 PRCs but is now diminished, and contributes to stability in type-2 PRCs. Thus we may expect a stable antisynchrony at small spike width. It becomes unstable at large spike width/frequency [Fig. 9(a)]. A numerical bifurcation diagram in Fig. 9(b) verifies this. The eigenvalue components illustrated for a type-1 PRC [Fig. 9(c)] for the antisynchrony clearly reveal that the stabilizing segments [see $_{6e}$ and $_{7e}$] at small spike width/frequency are not countered by the spike contribution. A numerical computation of $G(\varphi)$ [Fig. 9(d)] reveals that the antisynchrony is stable at small W/T and becomes unstable at large W/T, while the synchrony is stable at all W/T.

4.1 Synchrony

All the four cases (a-d) depicted in (W, A) space in Fig. 2(A) are treated here, and the corresponding regions of stability for synchrony are derived. Since each case constitutes only a portion of the parameter space, the critical curves in the space of (W, A) or (A, B) are composed of one or more of these critical curves. The eigenvalues are linear in the type parameter, B, but even then the expressions are not as simple as those in the previous section, and the eigenvalue transition conditions cannot be easily ascertained except in the case of very large skewness [Case (c)]. In the other three cases, we provide the critical curves by solving the critical eigenvalue equations, and list out expressions for the eigenvalue transitions. The regions may be verified by directly plotting the eigenvalue and checking for regimes where it is negative. The results from this section are presented in the Figs. 6, 7 that also display the explicit movement of eigenvalues as one of the parameters is varied, and also in Figs. 8, 9, 10, and 11 that are plotted after verifying the eigenvalues (not displayed).

To illustrate the effect of finite spike width on the phase-locked states, for type-1 [Fig. 6(b)] and type-2 [Fig. 7(b)] PRCs, we compute numerically one-parameter bifurcation diagrams as a function of PRC skewness for B/C = 0 [Fig. 6(e)] and for B/C = -0.5 [Fig. 7(e)] at W/T = 0.15. Type-1 PRCs showed loss of synchrony at small skewness when the effect of spike downstroke dominates ($_{3a}$), and type-2 PRCs showed loss of synchrony at large skewness where the effect of the negative PRC lobe dominates ($_{3c}$). The stability of synchrony in these diagrams is also verified by actually plotting the eigenvalues, respectively, in Fig. 6(c) and Fig. 7(c). Corresponding stability regions as a function of PRC skewness are shown in Fig. 6(f) and Fig. 7(f). The boundaries for type-1 neurons are defined by $_a$ [Case (a) below] and $_b$ [Case(b)] and for type-2 neurons the stability boundaries are defined by $_a$, and $_d$ [Case (d)]. The stability regions are derived exactly, but in the other three cases the regions are not derived but only the boundary curves are listed due to the inherent complexity in the analysis, but we show the stability regions in (A/T, B/C) and (W/T, B/T) parameter spaces in Figs. 10 and 11 based on the eigenvalue movements.

Very large skewness (A \geq 4W), Case (c)—This region extends all the way to A = 0, but can be termed the case of very large skewness because this region extends beyond the maximum skewness in the other three cases. The Hodgkin-Huxley model (see Fig. 1) falls in this regime. The arrangement of Z(t) and V(t) is shown for type-1 and type-2 in Case (c) of Fig. 2(A). The spike profile does not affect the stability because it occurs during the zero phases of the PRC. Only three eigenvalue components are non-zero, $_{3c}$ $_{4c}$ and $_{5c}$ (computed in the Appendix D:). Combining these three, and using the formula in Eq. 16, we get the eigenvalue as

$$\begin{aligned} \lambda_c &= \varepsilon(\lambda_{3c} + \lambda_{4c} + \lambda_{5c}) \\ &= \frac{-\varepsilon a_3 C}{T(2T - 5W)} \left[\frac{B}{C} T + 2(T - \frac{W}{2} - A) \right]. \end{aligned}$$

Utilizing the conditions in Eq. 15 and 8, we directly see that c < 0 for B = 0. That is if the parameter W/T is small enough or if the skewness is large enough such that 4W < A, then all type-1 PRCs lead to synchronous state, and no instability occurs at larger A. In fact synchrony is also stable for type-2 PRCs, and the condition for stable synchrony is obtained directly from the above equation when we insist that c < 0 which results in the following region:

$$\frac{B}{C} > \left(\frac{B}{C}\right)^* \equiv \rho_c = -2 \left(1 - \frac{W}{2T} - \frac{A}{T}\right), \quad \text{if } 4W \le A. \quad (36)$$

Whenever the spike width is less than one quarter of the skewness, the above condition provides the lower boundary for synchrony, and there is no upper boundary. As the spike width is increased the regime of existence of the curve $_c$ decreases as can be seen from the panels in Fig. 10. Since the skewness is limited by T - W(Eq. 15), as the spike width is increased, the skewness regime for the existence of $_c$ falls in the forbidden region, and hence this curve will not define boundary any more as seen in Fig. 10(d). On the other hand from the condition 4W - A where $_c$ exists, we see that as the skewness is increased, the span of W/T increases as is also seen in the (W/T, B/C) plots in Fig. 11. We can express the condition in terms of the skewness as well. From the eigenvalue equation above, we see that it becomes negative if A < T - W/2 + BT/(2C). Given that A must be bigger than 4W and also smaller than T - W, we write the sufficient condition for stable synchrony as:

$$\frac{4W}{T} \le \frac{A}{T} < \min \begin{cases} 1 + \frac{B}{2C} - \frac{W}{2T}, \\ 1 - \frac{W}{T}. \end{cases}$$
(37)

This condition complements other conditions from the other three cases in defining the complete picture of stability. For the example shown in Fig. 6, the parameter values are B/C = 0, W/T = 0.15, and thus the lower and upper limits in the above relation become 0.6 and 0.85. Since 0.6 is the lower limit of the present case the lower boundary will have be complemented with the results from the other cases (studied below), but the upper limit on A/T is 0.85 [Fig. 6(e)]. Similarly for the example shown in Fig. 7, B/C = -0.5 and W/T = 0.15, and thus the lower and upper limits in the above relation becomes 0.6 and 0.675. Thus the upper boundary for synchrony is defined by A < 0.675 [Fig. 7(e)].

Large skewness (2W \leq A < 4W), Case (b)—The arrangement of V(t) and Z(t) are shown for type-1 and type-2 PRCs respectively in Case (b) Type I and Case (b) Type II of Fig. 2(A). The non-zero eigenvalue components are $_{2b}$, $_{3b}$, $_{4b}$ and $_{5b}$ and are listed in the Appendix D:. The critical curve is obtained by solving the equation $_{b} = 0$ that results in the following equation in terms of the normalized type parameter:

$$\left(\frac{B}{C}\right)^* \equiv \rho_b = \frac{8Aa_3W(T - A - \frac{1}{2}W)}{e_1A^2 - 4W(2e_1 + a_3T)A + 16W^2e_1}, \quad \text{if} \quad 2W \le A < 4W, \quad (38)$$

where $e_1=2a_2(T-\frac{5}{2}W)+4a_3W$, and the derivative of the eigenvalue on the critical boundary is

By observing the behavior $_b$ in (W/T, A/T) plane (Fig. 10), we conclude that there are two segments to the curve $_b$, and they form boundaries of the synchronous state. These two segments fall on either side of the singularity that is in between the segments. The right segment lies in the regime where B/C < -2 + 9 W/T, and the left segment lies in the regime where $B/C < e_2$, and both segments reach a singularity when the denominator of the $_b$ reaches 0, which is when the abscissa, A/T, asymptotes the following value:

$$\frac{2\left(W^{'}\left(e_{3}+a_{3}^{'}\right)-\sqrt{a_{3}^{'}W^{'2}\left(4e_{3}+a_{3}^{'}\right)}\right)}{e_{3}}=e_{4}W^{'}+O\left(W^{'2}\right),$$

where $e_2 = \frac{2(a_3/a_2)(2 - 5W/T)}{2 - 5W/T + (a_3/a_2)(-2 + 4W/T)}$, $e_3 = 4a'_3 W' - 5W' + 2$, $e_4 = a'_3 - \sqrt{a'_3(a'_3 + 8)} + 4$, $a'_3 = a_3/a_2$, and W = W/T. Though the expression for $_b$ is an exact expression, it is difficult to see the dominant W terms. Using the above asymptote, we get simple sufficient conditions for stable synchrony in this regime:

$$e_4 W' + O(W'^2) < \frac{A}{T} < 1 - W', \text{ if } \frac{B}{C} > e_3,$$
 (39)

$$0 \! < \! \frac{A}{T} \! < \! e_4 W' \! + \! O(W'^2), \quad \text{if} \; \; \frac{B}{C} \! < \! -2 \! + \! 9 \frac{W}{T}. \tag{40}$$

The asymptote can be seen in all the panels in Fig. 10: For $a_3/a_2 = 0.2234$, using the boundaries predicted by the asymptotes for W/T = 0.02, we obtain the stability boundaries

as $0.57 < \frac{A}{T} < 0.98$ when B/C > 0.58, and $0 < \frac{A}{T} < 0.57$ when B/C < -1.82. For W/T = 0.05, the stability boundaries are obtained as $0.14 < \frac{A}{T} < 0.95$ when B/C > 0.58, and $0 < \frac{A}{T} < 0.14$ when B/C < -1.55. For W/T = 0.15, the stability boundaries are obtained as $0.40 < \frac{A}{T} < 0.85$ when B/C > 0.6, and $0 < \frac{A}{T} < 0.40$ when B/C < -0.65. And finally for W/T = 0.3, the asymptote results in a value of 0.7 which is also the boundary (1 - W/T) of existence of skewness, but the actual curve $_b$ shows that there is a small region of stable synchrony at this level of W/T. Thus the asymptote analysis predicts the boundaries for small W/T very well, and for large W/T the full expression for $_b$ must be used.

Intermediate skewness (4W – T ≤ A < 2W), Case (a)—The arrangement of V(t) and Z(t) for this case are shown for type-1 and type-2 PRCs respectively in Case (a) Type I and Case (a) Type II of Fig. 2(A). The non-zero eigenvalue components are $_{2a}$, $_{3a}$, $_{4a}$, and $_{5a}$. The critical curve is obtained by solving $_a = 0$ equation, and is given in terms of *B* as,

$$\left(\frac{B}{C}\right)^* \equiv \rho_a = \frac{4(c_1 A^2 - W c_2 A + W c_3)}{(c_1 + 2a_3 W) A^2 + d_2 A + 4W d_3}, \quad \text{if } 4W - T \le A < 2W, \quad (41)$$

where $c_1 = 2a_2 \left(T - \frac{5}{2}W\right) + 2a_3 W$, $c_2 = 4\left(T - \frac{5}{2}W\right) \left(2a_2 - a_3\right) + 7a_3 W$, $c_3 = 8a_2 W \left(T - \frac{5}{2}W\right) - 2a_3 T \left(T - \frac{W}{2}\right) + 16a_3 W^2$, $d_2 = 6a_2 \left(T - \frac{8}{3}W\right) \left(T - \frac{5}{2}W\right) + 8a_3 W \left(T - 4W\right)$, $d_3 = a_3 \left(T - 4W\right)^2 - 4a_2 \left(T - \frac{5}{2}W\right) \left(T - 2W\right)$. The derivative of the eigenvalue at $B = B^*$ is $\frac{d\lambda a}{dB}\Big|_{T = T_1} = \frac{(c_1 + 2a_3 W) A^2 + d_2 A + 4W d_3}{4TW(A - T)(2T - 5W)}$.

Small skewness (0 \leq A < 4W - T), Case (d)—And finally in this case, the arrangement of V(t) and Z(t) are shown for type-1 and type-2 PRCs respectively in Case (d) Type I and Case (d) Type II of Fig. 2(A). The non-zero eigenvalue components are _{2d} _{3d} _{4d} and _{5d}. The critical curve that is obtained by solving _{d} = 0 is given in terms of *B* **as,**

$$\left(\frac{B}{C}\right)^* \equiv \rho_d = \frac{2a_2A^2 - 4a_2(T - \frac{3}{4}W)A + f_1}{a_2T\left(T - A - W\right)}, \quad \text{if } 0 \le A < 4W - T, \quad (42)$$

where $f_1 = a_2 (17 TW - 2T^2 - 24W^2) - 8a_3 W (T - \frac{5}{2}W)$. The transition of the eigenvalue is given by $\frac{d\lambda_d}{dB} = \frac{a_2}{4W} > 0$.

The curves a, b, c and d are illustrated in Fig. 10 for select values of W/T at $a_3/a_2 = 0.2234$, and in Fig. 11 for two skewness levels for three values of a_3/a_2 . They are also illustrated in Figs. 8 and 9. Figures 8 and 9 essentially indicate that the stable synchronous region expands in size to larger W/T with increasing skewness. This fact is also corroborated by the two parameter stability regions in Fig. 11. Increasing the type parameter B/C to negative values also increases this range, but beyond some level (c which may be beyond realistic B/C levels in models or experiments), synchrony loses stability and is largely confined to higher values of W/T.

4.2 Antisynchrony

It is difficult to derive conditions for stability of antisynchrony in the general case due to the inherent complexity of the coefficients that arise in the stability conditions, but the critical curves can be written down easily by solving corresponding eigenvalue equations. We list them here without rigorous proof of the stable regions. The type parameter (*B*) appears linearly in all the eigenvalue equations, and thus the critical curves expressed in terms of *B* are simpler without multiplicity than those expressed in terms of *A* or *W*. The critical curves are expressed in each of the seventeen cases [Case (a), ..., Case (q)], which are all marked in the (*W*, *A*) space in Fig. 2. The arrangement of Z(t) and V(t) for some of the cases are also displayed. The main results are summarized in the two parameter stability regions in Figs. 10 and 11.

For small skewness [A < (T - W)/2 in (W, A) plot in Fig. 2(B)], six cases could form boundaries of antisynchrony: Cases (b, a, j, k, l, m). For example, four of these cases contribute to the boundary at A/T = 0.2 [Fig. 8(b,e)]. The combined value of the components ($_{5a}$ and $_{6a}$) due to the spike downstroke for A > 0 is comparable to that ($_{6a}$) for A = 0 but could be higher because part of the destabilizing downstroke occurs in the ramp-up phase of the PRC, and thus the stability of antisynchrony is delayed until larger W/T [Fig. 8(b)]. Similar effect is seen for negative B [Fig. 8(e)], as well as in Figs. 11 where the stability boundary is defined by $_{a}$, $_{b}$, $_{j}$, $_{k}$, $_{b}$ and $_{m}$. In each of these cases, the eigenvalue components are given in the Appendix E:, and using the eigenvalue equation 17 the critical curves are obtained by solving the equations $_{a} = 0, ..., _{m} = 0$. The critical curves written in

terms of normalized type parameter are given in Eqs. 43 when $0 \le A < \frac{T - W}{2}$.

The critical curve $_a$ at A/T = 0.2, B/C = 0.2 [Fig. 8(b)] can be approximated by the first term in the Taylor series: 4.9(W/T - 0.165). Or inverting this term, we obtain an approximate stability criterion as: $W/T > 0.165 + 0.2a_3/a_2$. Similarly the critical curve $_j$ at A/T = 0.2, B/C = -0.25 [Fig. 8(e)] can be approximated by the first term in the Taylor series: 4(W - 0.22). Again inverting this term, we get the approximate stability criterion as: $W/T > 0.22 + 0.25a_3/a_2$. The stability of antisynchrony at high frequencies is verified numerically in Fig. 8(d,f).

Finite spike width and frequency helped in stabilizing antisynchronous state even in the absence of skewness (Fig. 6) essentially due to the sharp spike upstroke ($_{4a}$). But the level of the PRC during the upstroke of V(t-T/2) decreases if the PRC acquires a finite skewness causing the negative eigenvalue component to reduce its magnitude [Fig. 7(d)] resulting in a loss of antisynchronous state [Fig. 7(e, f)]. But this loss can be delayed until larger values of A/T if we prevent the reduction of the PRC due to skewness, which can be achieved by

increasing the B/C value as depicted in the side panel of Fig. 7(f). Reducing the B/C to negative values has the opposite effect [Fig. 7(d,f)] because the PRC level during the upstroke is further reduced.

For intermediate levels of skewness, the stability is defined by eigenvalues in the Cases (c, f, i, n, o) [(W/T, A/T) space in Fig. 2(B). Similar to the curves derived above, we solve the equations $_{c} = 0, ..., _{o} = 0$, to obtain curves on which the eigenvalues are zero. Thus the

critical curves in terms of normalized type parameter *B* in the case when $\frac{T-W}{2} \le A < \frac{T}{2}$ are given in Eqs. 44. And finally for large skewness (A > T/2), the critical curves are derived from the Cases (e, d, g, h, p, q). Following the same procedure as described above, we arrive at the critical curves in Eqs. 45.

In Section 3.2 we have seen how antisynchrony might become stable for large skewness in the absence of spike width effects. For finite spike width this stability is still seen [$_d$ and $_e$ in Fig. 9(a), and in Figs. 10 and 11] due to the dominant effect of the positive lobe of the PRC [$_{6e}$ and $_{7e}$ in Fig. 9(c)], but the region becomes sensitive (for type-1 PRCs) or disappears (for both types of PRCs) at large *W*/*T*. This observation is also verified numerically in Fig. 9(b,d).

For small skewness the spike upstroke contributes a stabilizing eigenvalue component in both type-1 and type-2 PRCs, and the spike downstroke uniformly contributes a destabilizing component in both type-1 and type-2 PRCs because the sign of the PRC during spiking of V(t - T/2) is not altered [see Fig. 2(B) Case (a) Type I and Type II]. But as the skewness is increased, the spike up and downstrokes of V(t - T/2) begin to occur during the $Z_2(t)$ segment that is positive for type-1 and negative for type-2. And hence the role of spike up and downstrokes is reversed for type-2 PRCs [see Fig. 2(B) Case (e)]. Additionally, for type-1 PRCs, the boundary e becomes sensitive function of spike width because the segment $Z_2(t)$ is positive and the slope of the spike downstroke goes from infinity to a finite value quickly with W/T [Fig. 2(B) Case (e) Type I]. Thus the stable region bounded by dand e_{1} and 5 in Fig. 5(a)] shrinks drastically with increasing W/T (Fig. 10) for type-1 PRCs. As the skewness is increased, the contribution of the spike portion of the time course to the stability diminishes due to decreasing PRC levels, but the positive slope of the depolarizing phase that occurs during the negative PRC lobe contributes to the instability. Thus eventually for type-2 PRCs, the stability region at large skewness deceases in size. Figure 10 also reveals that the antisynchrony that is stable due to large skewness totally disappears at very high frequency for type-1 PRCs, and is mostly confined to large negative B/C.

For the HH voltage model parameter of W/T = 0.075, it can be verified that the stability diagram is similar to Fig. 10(b) with little change in $_d$ and $_e$, and the curves in the top left quadrant slightly moving up on the right and slightly moving down on the left. For the HH model's PRC parameters of A/T = 0.567, and B/C = -0.5, the system lies in the bistable region above the curve $_c$ and slightly to the right of $_d$. This is also verified numerically in Fig. 1. The system is closer to the boundary of antisynchrony ($_d$), and thus altering the parameters in the HH model that solely reduces skewness is likely to cause the system lose its stable antisynchronous state.

For the HH model's parameter $a_3/a_2 = 0.2234$, the stability diagram (for slightly bigger A/T) as a function of the product of spike with and frequency is almost identical to Fig. 11(d). At very low frequency both synchrony and antisynchrony are stable in a bistable manner, and as the frequency is increased only synchrony remains stable. We had earlier remarked that for models such as LIF a similar scenario happens, thus making the PRC skewness more

critical in determining the stability states than its type. Many neuronal models are likely to have B/C ranging from -0.5 to 0.5, and in this range, as we can see from Fig. 11(c,d), PRC skewness plays important role in stability. The PRC type plays a role in a qualitative manner, as for example, the stability curves are not vertical to the B/C axis, but are sloped at some angle such that changing the type of the PRC may have drastically different effect only at certain parameter points. Large negative B/C has of course different behavior than large positive B/C.

The stability structure as a function of W/T and B/C is not altered significantly when the spike threshold is increased [Fig. 11(e,f)], but if the threshold is decreased to very small value [Fig. 11(a,b)], then the PRC type can cause qualitative changes in the stability structure. At such small spike thresholds, the depolarizing part [$V_2(t)$] does not contribute much to the stability of either synchrony or antisynchrony. The spike up and down strokes dominate the eigenvalue components. And when the skewness is large, the effect is more tangible: A portion of the curve $_e$ is very close to B/C = 0 and thus type-1 neurons at low frequencies show only synchrony whereas type-2 neurons can show bistability. And at moderately high frequencies a portion of $_b$ becomes very close to B/C = 0 such that type-1 PRC neurons show neither synchrony nor antisynchrony, whereas type-2 PRC neurons show stable synchrony.

5 Discussion

Relation to previous works

Synchrony among pulse coupled neuronal oscillators received generic treatment earlier (Mirollo & Strogatz, 1990; Abramovich-Sivan & Akselrod, 1998; Goel & Ermentrout, 2002; Achuthan & Canavier, 2009) where the shape of the voltage was generalized by Mirollo and Strogatz, the slope of the PRC near zero phase was related to the stability of synchrony by Goel and Ermentrout, and Achuthan and Canavier, and the shape of a type-1 PRC was parameterized to study synchrony of non-identical oscillators by Aromovich-Sivan and Akselrod. But synaptic or electrical coupling has always been difficult to generalize because of the inherent complexities of the models and the ensuing shapes of the voltages and PRCs. For electrical interactions, leaky integrate-and-fire (LIF) models became attractive in the past because for them the voltage and PRC shapes can be derived analytically. Chow and Kopell (Chow & Kopell, 2000) and Lewis and Rinzel (Lewis & Rinzel, 2003) studied exhaustively the effect of oscillation frequency, and voltage shape on the phase-locked states either using the LIF model or modified versions of LIF model that incorporated spike and shape effects. Pfeuty et al. (Pfeuty et al., 2003) studied the effect of oscillation frequency and voltage shape parameter (that approximately corresponds to a_3 in our model) in a quadratic LIF model. Lewis and Rinzel found that electrical coupling led to synchrony at all frequencies of the LIF. Integrate-and-fire neurons are of type-1 with zero spike width, and the PRCs computed for very small perturbations possess large skewness (see, for example (Goel & Ermentrout, 2002)). Our results for type-1 neurons in the absence of spike width and large skewness (Fig. 9) are consistent with their conclusions. Lewis and Rinzel also implemented spike effects by adding a positive term to the voltage profile every time spike happens in the opposite neuron. This quantity emulates the missing spike profile in their model, and in our model such a term is equivalent to considering spike upstroke effects. But during the spike upstroke our PRC profile is zero, but if it were non-zero the synchrony region would be expanded to larger frequencies. In our model synchrony could become unstable due to the spike downstroke effect that was not part of their model. Lewis and Rinzel also found that antisynchrony becomes unstable at high frequencies. Our bifurcation diagram at large skewness (Fig. 9) is in agreement with that observation, but we also find that had the skewness been smaller, then antisynchrony would have been stable at higher frequencies instead of at lower frequencies.

Chow and Kopell (Chow & Kopell, 2000) studied an LIF model that again is of type-1 but with more complex structure to the voltage evolution that now incorporates not only spike amplitude, but also spike width, slope of spike upstroke, and spike frequency. Such an incorporation was done as an added kernel to the voltage evolutions. Their kernel has the effect of altering both the voltage spike profile and the PRC at the same time as the kernel parameters are altered. In our formulation, we change them independently. But their general conclusion on the synchronous state is that it is stable at low frequencies, and unstable at high frequencies. Our bifurcation diagrams for type-1 PRCs (Fig. 10) clearly map how such instability arises with increasing spike width or frequency. In Fig. 11 the loss of synchrony is seen beyond a critical frequency. Chow and Kopell found the antisynchrony in their model both at high as well as low frequencies. Our results are at some variance with theirs. We find the antisynchrony stable either at low or high frequencies, but not in general at both the frequencies (Fig. 11). It is possible that the PRCs corresponding to Chow and Kopell's LIF model are acquiring distinctly different shapes than those of pure LIF model because of the kernel affecting the voltage evolutions. At large skewness, for example, we do find within our model (Fig. 10) regimes of stable antisynchrony at low and high frequencies.

Pfeuty et al. (Pfeuty et al., 2003) studied a quadratic integrate-and-fire model which displays a type-1 PRC with more symmetry, albeit with jumps at the end, than that of an LIF model, but with small skewness. In particular Pfeuty et al. reported that as the magnitude of the ratio of reset voltage (V_T) to the spike threshold voltage (V_T) in increased stable synchrony is achieved, and reducing this ratio leads to stable antisynchrony (with perhaps regimes of bistability with synchrony). The PRC does not have as much skewness as the LIF does, and hence falls under low skewness. We have not incorporated edge effects of the PRCs, if any, in our current study. But within our model, we see from Fig. 8(b) that as the ratio a_3/a_2 is increased (that is the separation of reset and threshold levels increases and hence the magnitude of their ratio, V_T/V_T) we find stable synchrony at large a_3/a_2 , and stable antisynchrony at small a_3/a_2 and also at large frequencies.

Nomura et al. (Nomura et al., 2003) studied Erisir et al. (Erisir et al., 1999) model and discovered that the interneurons are capable of displaying synchrony even at high frequencies. The model displays a type-1 PRC with small skewness, and the voltage time course has a finite spike width. This may appear counter-intuitive because even in the Chow and Kopell's model, synchrony became unstable at high frequencies, and in our results it does become unstable for type-1 PRCs above a critical frequency [Fig. 11(c)] unless the PRC has large skewness [Fig. 11(d)]. We wanted to investigate this puzzle, and present the results in Fig. 12(a-f). The model (thin curves) does show stable synchrony (negative slopes of the growth functions) at high frequencies. But the PRC is no more of type-1 at high frequencies. The skewness is slightly increased (A/T from 0.17 to 0.27), but the type parameter (B/C) became negative (from 0.44 to -0.27) when the external steady current is increased to cause the frequency change from 64.3 Hz to 186.9 Hz. From Fig. 11(c) we see that increasing the frequency while decreasing the type parameter still keeps the system in stable synchronous state. We have also fitted this model's voltage [Fig. 12(a,d)] and PRC [Fig. 12(b,e)] with PWL functional forms (thick curves), and the resultant growth function [Fig. 12(c,f)] predicted the stability of the phase-locked states accurately at both these frequencies.

Mancilla et al. (Mancilla et al., 2007) studied neocortical interneurons that exhibited type-1 PRCs at low frequencies. The PRCs retained their type-1 character even at 50 Hz. The resultant growth functions predicted stable synchrony and unstable antisynchrony. We have fitted piecewise linear curves to the average voltages and PRCs recorded from these neurons to determine our fit parameters [Fig. 12(g-i)]. The spike width, skewness, and type parameters are all within the ranges of our model parameters. As the frequency is increased

from 28 Hz to 50 Hz, the W/T factor is increased twice, the skewness is not altered much, but the type parameter B/C decreased from positive to 0. In both cases, the growth function computed from the PWL fits [Fig. 12(i, lines)] predicts the experimentally determined [Fig. 12(i, points)] stability of synchronous and antisynchronous states accurately. The reduction in the type parameter perhaps also indicates that increasing the frequency further might result in a type-2 PRC (with negative B/C) just as in the Erisir et al. model.

Effect of spike upstroke and downstrokes

In type-1 PRC neurons, spike downstroke helps destabilize both synchronous and antisynchronous states [Fig. 2]. In our PRC model, the segment at large phases is set to zero $(Z_5 = 0)$, thus its contribution is not visible in the case of synchrony. But making this segment non-zero (but positive) causes both the synchrony and antisynchrony enhance their ability to become stable due to the PRC being positive and the corresponding voltage segment having also a positive slope. The sign of the contribution of the upstroke segment ($_{6x}$) can also be inferred from Fig. 2 by imagining the $Z_4(t)$ segment extending all the way to *T*. The sign would be the same as that of $_{5x}$ because the slope of the upstroke [$V_3(t)$] has the same sign as that of the depolarizing phase [$V_2(t)$]. The spike upstroke helps stabilize the antisynchrony in all the cases considered [Fig. 2(B)].

In type-2 PRCs neurons, spike upstroke always contributes to stabilizing the synchronous state (since the sign of $_{6x}$ is the same as $_{5x}$ as explained above), but it can contribute to either stabilizing [Cases (a), (b), (j), (k), (l), (m) in Figs. 2(B)], or destabilizing (in the remaining Cases) the antisynchronous state. That is, if the skewness is small such that A/T < (1 - W/T)/2, then the upstroke contributes to stabilizing the antisynchronous state, otherwise it contributes to destabilizing it. On the other hand, spike downstroke contributes to stabilizing the synchronous state only if A > 2W [i.e. in cases (b) and (c)], otherwise its contribution toward stabilizing or destabilizing the synchrony depends on sign of the PRC segment during the downstroke. Again in contrast, the spike downstroke contributes to destabilizing the antisynchronous state if the skewness is small such that A/T < (1 - W/T)/2 [Cases (a), (b), (j), (k), (l), (m) in Figs. 2(B)]. Similar behavior occurs in Cases (n) and (o). The downstroke contributes to stabilizing the antisynchrony at large skewness and small W/T such that A > T/2 and W < A/4 [Cases (d) and (e)]. In all other cases, the contribution of the spike downstroke toward stability of antisynchrony is dependent on the signs of the PRC segments during the upstroke.

Role of spike width and spike frequency

Type-1 PRC neurons are always in stable synchronous state in the absence of the spike width effects for any level of PRC skewness (Fig. 5) because there is no factor that counters stable synchrony [see Fig. 2(A) Case (c) Type I]. But finite spike width [such that the product of the spike width and spike frequency (W/T) is large] can destabilize it [see $_{2b}$ in [see Fig. 2(A) Case (b) Type I]. For small or no skewness, instability occurs at smaller and smaller levels of W/T as the height of depolarizing voltage segment (a_3) becomes smaller and smaller [$_{ab}$ $_{b}$ in Fig. 8(b)]. When the expression for $_{a}$ is Taylor expanded, we get an

approximate expression for synchrony when B = 0 and $A=0: \frac{W}{T} > \frac{1}{4} \left(\frac{a_3}{a_2}\right) + \frac{1}{8} \left(\frac{a_3}{a_2}\right)^2$. Skewness helps increase the chances of synchrony in type-1 PRC neurons, competing against the influence of spike width. For finite skewness (A > 0), sharp spike downstrokes are encountered for small spike widths. And when the spike downstroke does not extend beyond a factor that is proportional to the skewness A, synchrony becomes unstable (Fig. 10). But stability is retained for some values of B even when the skewness is smaller than $2W[\text{curve}_{a} \text{ in Fig. 10}]$ provided B/C is below the curve a.

Type-1 PRC neurons can display antisynchrony either due to the dominant effect of spike upstroke or sharp PRC segments at large skewness. For small skewness, antisynchrony becomes stable only at sufficiently large frequencies [curves $_a$ and $_j$ in Fig. 8]. Again at A = 0 and B = 0, a polynomial can be fitted to $_a$ giving an approximate condition for stable

antisynchrony as $\frac{W}{T} > 0.35 \left(\frac{a_3}{a_2}\right) - 0.02 \left(\frac{a_3}{a_2}\right)^2 - 0.1 \left(\frac{a_3}{a_2}\right)^3$. Antisynchrony does not necessarily immediately become stable after the loss of stable synchrony. Other phase-locked states could mediate the in-between regime [Figs. 8(d)]. As the skewness (A) is increased the slope of the spike upstroke encounters smaller levels of the PRC, leading to its (upstroke's) diminishing effect on stabilizing the antisynchrony. Thus the stable antisynchronous region that occurs at large frequencies (contributed to by the spike upstroke) decreases and disappears as the skewness is increased. As the skewness is increased the slopes of the PRC segments to the left [Z₃(t)] and to the right [Z₄(t)] of the peak increase leading to an increase of the negative eigenvalue components ($_{6e}$, $_{7e}$). This results in stabilizing the antisynchronous region is confined to smaller stabilizing effect diminishes. Thus the stable antisynchronous region is confined to smaller values of B/C at large skewness.

Type-2 PRC neurons, like those of type-1, can display both stable synchrony and stable antisynchrony. In addition to the spike width countering the synchrony as in type-1 PRC neurons, the PRC delay could also counter the synchrony [see Fig. 2 Case (b,c) Type II]. In the absence of spike effects (W= 0), unlike type-1 PRC neurons, type-2 PRC neurons do not display synchrony for all levels of skewness. Synchrony fails at large skewness because of the increasingly destabilizing effect of the negative segments of the PRC [$_{3c}$ and positive portion of $_{4c}$ in Fig. 2 Case (c) Type II]. If *B* is large negative, these segments contribute more, and instability occurs at even smaller *A*. In particular, synchrony is stable [Eq. 19,

Fig. 5] only if $\frac{B}{C} > -2 \left(1 - \frac{A}{T}\right)$. So, for example, if maximum PRC delay is equal in magnitude to maximum PRC advancement, then synchrony fails if skewness is bigger than half of the spike period. Comparison of Type I and Type II plots in Cases (a,b,d) of Fig. 2 reveals that some of the positive eigenvalue contribution that existed in type-1 neurons within the time span of spike downstroke is being removed in the type-2 neurons, and thus for small W/T, type-2 neurons are likely to remain synchronous in the presence of skewness. That indeed is the case as can be seen in Fig. 10(a,b). However, as the spike width and frequency increase, and if *B* is not sufficiently large negative, the gain in the form of the removed contributions referred to above can be countered by the effect of spike downstroke in combination with the positive segment of the PRC leading to unstable synchrony at large W/T. Thus in theory we could have two boundaries for stable synchrony, one at small skewness, and the other at large skewness. But for most of the negative *B* range, either upper limit defined by $_c$ and $_b$ or lower range defined by $_a$ and $_d$ constitute the boundaries (Fig. 10).

Type-2 PRC neurons display antisynchrony, and its region in the parameter spaces can become fragmented into two just as in the case of type-1. In the absence of spike width effects (Section 3.2), spike downstroke effect inherent in the discontinuity of V(t - T/2) at t = T/2 counters the stability. The combined effect of the spike discontinuity (the sum of $_{4b}$ and $_{5b}$ which is $2a_3 [AB + C(T - 2A)] / [T(T - A)]$ could contribute either a positive or a negative component to the eigenvalue. For A = 0, this term is positive and helps destabilize the antisynchrony. For non-zero A, unless B is large negative (less than -C(T - 2A)/A), the term continues to be positive, and thus contributes to destabilizing the antisynchrony. This destabilizing effect is overcome by reducing the level of PRC at t = T/2 which can be

achieved by increasing the skewness and thus pushing the PRC to the right. Thus it requires a finite skewness (A > 3) for stabilizing antisynchrony when W = 0. But increasing the skewness to big levels has the opposite effect because then the spike upstroke and downstroke fall in the negative lobe regime of the PRC causing the upstroke destabilize (due to its positive eigenvalue component), the downstroke stabilize in contrast to what happened at smaller A. Additionally, a considerable amount of the depolarizing phase could also fall in the negative PRC lobe regime. These factors together increase the chances of destabilizing the antisynchrony, and the instability occurs when A > 6 (Fig. 5). Thus we obtain stable antisynchrony when 3 < A < 6 in the absence of spike width effects. Now consider the competing effects at a non-zero W[see Fig. 2(B) Case(b) Type II] where the spike upstroke and downstroke assume less sharp slopes, but at the same time the upstroke spreads toward higher levels of PRC, and the downstroke toward lower levels of PRC. In effect, the effect of the upstroke (which contributes to instability) dominates, making it slightly harder to achieve stable antisynchrony. Thus the stability will be lost as W/T is gradually increased [the stable region bounded by d in Fig. 11(d)], and also the level of A at which stability occurs (due to countering the spike effect by skewness) moves to larger values of A at finite W[b, c, d, p in Fig. 10]. Another mechanism could lead to stable antisynchrony at small A. When B is negative, but not very large in magnitude, the reduction in the PRC level encountered by the spike upstroke may not be very significant [see Fig. 2(B) Case (a) Type II]. This results in a sizeable stabilizing effect contributed by portions of the depolarizing phase and the spike upstroke to counter the destabilizing effect due to the spike downstroke and the negative PRC lobe. This results in a stable antisynchronous state occurring at small skewness levels. This effect lasts until the skewness sufficiently diminishes the PRC level during the spike upstroke [a_{i} m_{i} b_{i} k in Fig. 10].

Distinction between type-1 and type-2 PRCs

The above discussion makes it clear that both stable synchrony and stable antisynchrony occur in both type-1 and type-2 PRCs, but the amount of skewness, the type parameter, and the spike width or frequency control where these phase-locked states are located. For example, large positive B at large skewness, and large negative B at small skewness hold stable synchrony in large parameter areas for some spike frequencies [Fig. 10(c)]. Similarly small skewness with large positive B, and large skewness with large negative B hold stable antisynchronous solutions [Fig. 10(a-d)].

But at the level of neuron pairs, any critical line that starts at B = 0 and runs perpendicular to the *B*-axis would constitute a clear distinction between type-1 and type-2 PRCs in terms of their ability to display stable synchrony and antisynchrony. Such critical lines can be found ($_b$ and $_e$) when the voltage time course has zero slope [i.e. when $a_3/a_2 = 0$ which is closer to the cases depicted in Fig. 11(a,b)] where brief parameter ranges along *W*/*T* exist that clearly distinguish type-1 and type-2 PRCs. Consider the eigenvalue corresponding to Case (b) for synchrony ($_b$). Examining the components (in the Appendix D:), we find that only

one component $\begin{pmatrix} 2b \end{pmatrix}$ becomes non-zero when $a_3 = 0$, and it is equal to $\frac{a_2 (A - 4W)^2}{4ATW} B$ (curve b) which clearly changes its sign causing a change of stability of synchrony when B is increased from negative to positive. This eigenvalue regime is defined (see the definition of Region b in Appendix A:) by the range 2W A < 4W. Rewriting this range, we conclude that when $a_3 = 0$, and the frequency is high enough such that the spike width is bigger than a

quarter of the skewness but less than half of skewness $\left(\frac{A}{4T} < \frac{W}{T} < \frac{A}{2T}\right)$, type-2 PRC neurons synchronize, and type-1 PRC neurons lose synchrony.

Now consider the eigenvalue corresponding to Case (e) for antisynchrony ($_{e}$). Examining its components (in the Appendix E:) by setting $a_3 = 0$ reveals that there are only two non-zero components ($_{3e}$ and $_{4e}$ corresponding to the spike up and downstrokes) which add up

to become $\frac{5a_2W}{AT}B$. This clearly changes its sign as *B* is moved across 0, and is negative (leading to stability) for B < 0 and positive (leading to instability) for B > 0. The eigenvalue

regime (see the definition of Region e in Appendix B:) is $\frac{T}{2} + 2W \le A < T - W$. Rewriting this range, we conclude that when $a_3 = 0$, and when the spike frequency is small enough

such that $W/T < \frac{A}{2T} - \frac{1}{4}$, antisynchrony is stable for type-1 PRCs, and is unstable for type-2 PRCs.

There is also a range of skewness for certain frequencies that comes close to distinguishing between type-1 and type-2 PRCs. The boundary of antisynchrony at large skewness for type-1 PRCs is sensitive to changes in frequency ($_e$ in Fig. 10). For low frequencies around W/T = 0.05, $_e$ is positive and is near B = 0. This clearly acts like a threshold for making the antisynchrony unstable.

In the specific cases mentioned above, the parameter ranges near crossings of the critical boundaries across B = 0 become regimes where crossing from type-1 to type-2 brings in qualitative change in the behavior of coupled neurons. Except in these cases, the stable boundary lines cross the B = 0 axis with a non-zero angle, and thus in general, the PRC skewness and the voltage profile must also be considered in characterizing the PRC behaviors.

6 Conclusions

The main question we address in this study is when electrically coupled neurons synchronize under the assumption of weak coupling. Conventionally such a question is addressed by investigating the dynamics of the internal gating currents, and then relating the mechanism to the emerging collective behavior of the coupled networks. Such investigative methods include drug application to block or enhance the activation of a selected ion channel type, and application of steady current to cause a change in the neuron's oscillating frequency. These methods in addition to causing the desired effect on physiological behavior of the neurons, also alter a number of other observables of interest such as spike width, spike frequency, spike height, PRC type, and PRC skewness. Although these observables are inter-related, insights into the effect of each of them on the network behavior could only be detailed if there was a mechanism to parameterize each of them. Such a task is indeed difficult to carry out experimentally. But we can take advantage of the theory of weakly coupled oscillators to address this in a comprehensive manner.

Earlier studies that aimed at such generalizations largely focused on integrate-and-fire models (Chow & Kopell, 2000; Lewis & Rinzel, 2003; Pfeuty et al., 2003; Lewis & Skinner, 2012; Hansel, Mato, & Pfeuty, 2012) while principally working with fixed relationships between voltage time course and the PRC. In this study we have taken the liberty to make these parameters independent, i.e. make the PRC and the voltage independent, and study the emerging collective states based on these shapes. This task would have been difficult but for the weakly coupled oscillator theory that is already being used widely in neuroscience (Van Vreeswijk et al., 1994; Hansel et al., 1995; B. Ermentrout, 1996; Netoff et al., 2005; Preyer & Butera, 2005; G. B. Ermentrout, Galán, & Urban, 2007; Tateno & Robinson, 2007; Cui, Carmen, & Butera Robert, 2009; Smeal, Ermentrout, & White, 2010). However, parameterizing the shapes independently would inevitably produce some parameter regimes

that may be of less physiological interest, but at the same time it exhaustively covers all the possible and physiologically relevant voltage and PRC shapes within our model assumptions. The predictions would now become more general based on these two functions. In the current approach only one independent time parameter (A/T), the PRC skewness), and one independent type parameter (B/C) define the PRC. The voltage spike train is again defined by just one independent time parameter (W/T, the spike width parameter), along with the spike peak, maximum spike hyperpolarization, and the spike threshold level. But the latter three parameters collectively result in one truly independent parameter, a_3/a_2 , that affects the stability of synchrony and antisynchrony. The stability is studied by segmenting the (W, A) parameter spaces (Fig. 2) such that each regime contains segments of the voltage and the PRC with constant slopes. This minimalistic formulation is possible because we have employed piecewise linear functions to model the voltage and the PRC shapes. Note however that the functional form of these shapes is less important than the ability to parameterize the shapes. We examined exhaustively whether the conventional categorization of PRCs into type-1 and type-2 had bearing on their role in synchrony. Or more specifically we addressed how the amplitude of the negative lobe in the PRC affects synchrony. We also investigated the role of PRC shape skewness as the maximum phase advancement of the PRC is systematically moved to longer phases. The effect of voltage depolarization and spike frequency was also investigated.

All the analytical results relating the shape parameters are given in Sections 3 and 4, and are summarized for zero spike width in Fig. 5, and for non-zero spike width in Figs. 10 and 11. These results explain and put in perspective the previous results obtained using leaky integrate-and-fire (Chow & Kopell, 2000; Lewis & Rinzel, 2000), quadratic integrate-and-fire (Pfeuty et al., 2003), and Hodgkin-Huxley model equations (Nomura et al., 2003). The leaky integrate-and-fire model exhibits large PRC skewness making a two-neuron LIF network exhibit antisynchrony at small spike width/frequency (Fig. 9). The coupled network of oscillating Hodgkin-Huxley model neurons exhibit bistability [Fig. 10(b), Fig. 1] again because of the large skewness. Altering the PRC of the HH model such that the maximum PRC delay occurs at earlier phases would eliminate the antisynchrony. We also found [Fig. 11] that if the PRC skewness is small or the spike height is large $(a_3/a_2 \text{ small})$, then the synchronous state could be preserved even at high frequencies or large spike widths provided the type parameter *B* becomes sufficiently negative. Such possibility occurs in some models (Nomura et al., 2003).

In simulations it may be possible to devise parameters or parameter combinations that could lead to an independent control of the PRC and voltage shape parameters. But such a control may be more difficult in experimental preparations. For example, increasing a steady applied current or incrementally controlling the maximum ionic conductance of a selected channel could cause multiple changes in the PRC and voltage shapes, traversing some curvilinear path in our parameter spaces. But a simple assessment of the PRC and the voltages to acquire their shape parameters could be made. The current results provide guidance to the network behavior when such shape parameters are determined. The results when spike width is zero [Fig. 5] are the simplest to interpret: For PRCs whose normalized type parameter is bigger than -2(1 - A/T) [curve 1 in Fig. 5] the coupled network displays stable synchrony. That is all type-1 PRCs lead to synchrony. Type-1 PRCs whose normalized skewness exceeds some threshold [Eqs. 32-35] lead to antisynchrony [curves 4 and 5 in Fig. 5]. Type-2 PRCs may cause loss of synchrony if the maximum PRC delay is large with sufficient skewness [curve 1 in Fig. 5]. Large (bigger than 3) but not very large (less than 6) skewness in the type-2 PRCs causes stable antisynchrony. At zero spike width, the slope of the voltage depolarization does not determine the stability of synchrony or antisynchrony.

For finite spike width, the stability boundaries [Figs. 10 and 11] are more complicated. As discussed in Section 5, the boundary of antisynchronous state, particularly when the PRC is of type-1, depends sensitively on spike width [curve $_e$ in Fig. 10]. For sufficiently large spike width or at sufficiently high frequency, type-1 and type-2 PRCs can lead to an unstable synchrony, but the threshold of instability for the type-2 PRCs is higher than that for the type-1 PRCs. At high frequencies or large spike width stable antisynchrony may disappear if the PRC has large skewness, and instead it may appear at small PRC skewness.

Limitations

The limitations of our model come in the form limitations of the voltage and PRC profiles, and the basis of the weak coupling among oscillators. The voltage time course with three piecewise linear profile described time courses of Hodgkin-Huxley (Fig. 1), Erisir et al. [Fig. 12(a,d)], and even some experimental recordings [Fig. 12(g)]. The piecewise linear formulation of the PRC profile also described satisfactorily the PRCs of Hodgkin-Huxley's (Fig. 1) and the experimental recordings of Mancilla et al. [Fig. 12(h)], but some deviations are prominent between the piecewise curves and the Erisir et al.'s model [Fig. 12(b,d)]. These deviations are at longer input phases. Though these deviations did not affect in predicting the stability of the phase-locked states, it is also a reflection of the limitations of our five-segment piecewise linear PRC model in being unable to capture perhaps a large class of other PRCs. This model is also obviously unsuitable for PRCs with more than one peak (see some examples reported in (Perez Velazquez et al., 2007; Devlin & Kay, 2001)). In fact the profile of the PRC that we chose that has zeros at the ends may not be suitable for all experimental data. For example a polynomial fit to the PRC that would have finite values at the ends may be more appropriate for some experimental recordings (Netoff et al., 2005; Tateno & Robinson, 2007). Also, because the coupling via electrical interactions uses all the voltage profile, deviations from the three piece-wise linear profile can have significant effect on the stability of the phase-locked states, particularly when those deviations impart slopes with opposite signs. Finally the interactions are assumed to be weak, and thus the results reported here cannot explain effects due to strong coupling. We have also not considered the role of heterogeneities and noise (for such studies in LIF models see (Ostojic et al., 2009)) on the phase-locked states. In fact the synchronous state considered here is a perfect synchronous state where the spikes align with no phase difference. The regions of unstable synchrony bordering the curves of stability contain phase-locked states that are near synchronous.

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Appendix A

Computing eigenvalue for the stability of synchrony

We can use the profiles of Z(t) and V(t) to compute using Eq. 5. Since both Z(t) and V(t) are piecewise linear, the resultant will have piecewise contributions. As a typical case that we must deal with in computing the eigenvalue, consider the figure panel marked Case (c) Type II in Fig. 2(A) that corresponds to the arrangement of Z(t) and V(t) for models such as the HH model. The time point at which the spike downstroke ends (at t = 2W) is less than the point at which the PRC becomes non-zero (t = A/2), and hence we obtain the condition, A = 4W. The line A = 4W is depicted in the (W, A) plot of Fig. 2(A), and the condition A = 4W is represented by the region (c). The parameter point for HH model itself is marked by a

square symbol. There are six regimes that are separated by the change of slopes of these curves. Each regime contributes a portion ($_{1o}$ $_{2o}$ $_{3o}$ $_{4o}$ $_{5o}$ and $_{6c}$), to the eigenvalue, and together all the six regimes will combine to determine the stability of the synchronous state. In this particular case, we can directly see that 1_c , 2_c , and 6_c are 0 because Z(t) is zero in those regimes. The other eigenvalue components will have either positive or negative values depending on the product Z(t) V(t) and its integral in those regimes. We shaded the regimes or parts of regimes that contribute to positive value of the eigenvalue component. In this figure, we see that $_{3c}$ is completely positive because Z(t) [i.e. $Z_2(t)$ in particular] is negative in this regime and the slope of the voltage is positive. Hence the product Z(t) V(t)is negative resulting in a negative value of the integral over this regime. Since there is a minus sign already outside the integral in Eq. 5, the eigenvalue component becomes positive, hence the region is shaded. In the adjacent regime that contributes to 4c the product Z(t) V(t) changes its sign when Z(t) goes from negative to positive, and thus the positive eigenvalue portion that is marked by negative Z(t) is shaded. The sign of the component 4_c itself depends on the magnitude of the maximum delay B, the maximum advancement C, and the skewness A. These two components together determine whether the synchronous state can become unstable because the other components 2c and 5c are completely negative since the product Z(t) V(t) is positive in those regimes. But if the PRC becomes type-1, in this case [Fig. 2(A) Case (c) Type I], all the eigenvalue components become negative, and thus the synchronous state cannot be destabilized.

As the skewness becomes smaller than 4 W such that the maximum depolarizing time point (t = 2W) is between the point at which the PRC becomes non-zero (t = A/2) and maximum delay (t = A) we obtain the condition 2 W A < 4W [region (b) in (W, A) plane of Fig. 2(A)]. The corresponding arrangement of Z(t) and V(t) are shown for type-1 and type-2 PRCs in Case (b) of Fig. 2(A). When the product Z(t)V(t) is negative, the resultant portion of the eigenvalue becomes positive contributing to the instability of the synchronous state. Such regions along time axis are shaded. In this case, both type-1 and type-2 can potentially cause the synchronous state become unstable. Reducing the parameter A further such that the maximum delay (t = A) in the PRC occurs within the spike downstroke (t = 2W) but the downstroke ends before the maximum phase advancement (t = A/2 + T/2), we arrive at the condition 4W - T A < 2W [region (a) in (W, A) plane of Fig. 2(A)]. This condition occurs when the frequency is high. The corresponding arrangements of Z(t) and V(t) for type-2 and type-1 are shown respectively in Case(a) Type II and Case(a) Type I in Fig. 2(A). The regions that contribute to positive eigenvalue components are shaded. Finally when the frequency of oscillation is very high such that the spike downstroke (t = 2W) ends after the PRC acquires its maximum advancement (t = A/2 + T/2), we arrive at the condition A < 4W-T[region (d) in (W, A) plane of Fig. 2(A)]. An example of the arrangement of Z(t) and V (t) are displayed for type-2 and type-1 PRCs in Case (d) Type II and Case (d) Type I of Fig. 2(A). There are now larger regions shaded that mark the regions contributing to positive eigenvalue which in turn destabilizes synchronous state. We summarize the four parameter regions discussed above as follows:

Region (a) Intermediate skewness: 4W - T A < 2W:

Region (b) Large skewness: 2W A < 4W:

Region (c) Very large skewness: A = 4W:

Region (d) Small skewness: 0 A < 4W - T:

where $_{x}$ is given in Eq. 16. The expressions for $_{a}$ $_{b}$ $_{c}$ and $_{d}$ are listed in the Appendix D: for all the four cases. The value $_{1x}$ corresponds to the full or part of $Z_{1}(t)$, and $_{6x}$ corresponds to the contribution of $Z_{5}(t)$. Hence both these are zero for all the cases. Consequently, the rising phase of the action potential has no effect on the stability of

я

h

synchrony in our model. If we were to consider the PRC to be non-zero during the rising phase, that would contribute to more stabilizing eigenvalue because the slope of the voltage is positive and PRC is always positive in that region. The effect of the falling phase of the action potential will have diminishing effect as the skewness of the PRC increases. The parameter region of *W* above 2T/5 is forbidden by the condition in Eq. 8.

Appendix B

Computing eigenvalue for the stability of antisynchrony

The eigenvalue for the antisynchronous state is found using Eq. 6, but this case turns out to be more complex than that for . comprises of piecewise contributions from Z(t) and V(t - T/2). Depending on the value of the skewness (A) in relation to the spike width parameter W, the relative arrangement of Z(t) and V(t - T/2) changes while keeping the spike peak position of the voltage time course fixed at T/2. Four such arrangements are displayed in Fig. 2(B). At any given such arrangement of Z(t) and V(t - T/2) we will have to evaluate eight integrals corresponding to the eight different time segments during which the slopes of Z(t) and V(t - T/2) are constant. We refer to these integrals as eigenvalue components.

At A = 0, for example, the spike peak and the positive peak of the PRC coincide, and for small positive A, the regions marked (a) and (b) in (W, A) plane of Fig. 2(B) arise. Examples of the arrangement of the PRC and V(t) in these two regions are shown, respectively, in Cases (a) and (b). Consider the Case (a) where the positive peak position

 $\left(\frac{A}{2} + \frac{T}{2}\right)$ of the PRC is slightly shifted toward longer phases, but still the spike width is big enough that the peak occurs during the downstroke of the spike and before the spike

minimum (at $\frac{T}{2} + 2W$). That is we have the relation A < 4W, and if A is increased beyond 4W, another set of regions along the time axis contribute to the eigenvalue. But W is small

enough that the spike minimum (at $\frac{T}{2}+2W$) occurred within the $Z_4(t)$ branch and before $Z_5(t)$ began (at $t=T-\frac{W}{2}$). That is we must have $W < \frac{T}{5}$. And A is also small enough that

the position of PRC minimum (at A) occurs before the spike upstroke initiates (at $\frac{T}{2} - \frac{W}{2}$).

Hence we also have the condition that $A < \frac{T-W}{2}$. If these conditions are violated then we will have to rewrite the conditions for the validity of the corresponding arrangement of the *Z* (*t*) and V(t-T/2). These three conditions are valid in the region (a) in the (*W*, *A*) space of Fig. 2(B), and the region is bounded by A = 4W, W = T/5, and A = (T - W)/2 which are also drawn in the figure. The Case (a) Type II and Type I panels also show the regimes during which the slopes of neither Z(t) nor V(t - T/2) change. These regimes from left (starting at t = 0) contribute to the eigenvalue components $_{1a}, \ldots, _{8a}$. Since the slopes of V(t - T/2) and Z(t) are constant the sign of the eigenvalue component can be directly visualized from the panels. When the product Z(t) V(t - T/2) is negative either because of the negative voltage slope or because of the negative PRC segment, then it contributes to a positive eigenvalue (due to the extra negative sign outside the integral in Eq. 6). In Type-2, the negative part of the PRC contributes to positive eigenvalues ($_{2a}$ and part of $_{3a}$ are positive). In both Type-1 and Type-2 of Case (a), the spike downstroke contributes to a positive eigenvalue, i.e. $_{5a}$ and $_{6a}$ both become positive. The spike down stroke even in the form of a voltage discontinuity when the spike width is zero contributes significant amount of positiveness to the eigenvalue due to the sharp voltage gradient. Thus we will see that the antisynchronous

state is unstable for small Weven when A = 0, and only becomes stable for sufficiently long W such that the downstroke contribution diminishes due to decreased slope.

Starting from conditions of region (a), when *A* is increased slightly we will arrive at three other possible arrangements of Z(t) and V(t - T/2). We will arrive at region (b) when the maximum PRC (at $\frac{A}{2} + \frac{T}{2}$) occurs after the spike minimum at $t = \frac{T}{2} + 2W$, which results in the condition A > 4W while still obeying $A < \frac{T - W}{2}$. Instead we could have the PRC minimum (at *A*) occur after the spike upstroke event (at $t = \frac{T}{2} - \frac{W}{2}$) but before the spike peak (at $t = \frac{T}{2}$), and thus defining the bottom and top boundaries of the region (f): $A = \frac{T - W}{2}$ and $A = \frac{T}{2}$. As a third possibility we could have both the above occurring at the same time, i.e. the PRC minimum (at *A*) occurring after the spike upstroke initiation (at $\frac{T}{2} - \frac{W}{2}$) but before the spike peak (at $\frac{T}{2}$), and the PRC maximum occurring after the spike minimum (at $\frac{T}{2} + 2W$). Together this gives the region of validity of this scenario at the intersection of the previous two regions and results in the region (c). In the example of Case (b) the regions along the time axis that contribute to a positive eigenvalue component on account of the product Z(t) V(t - T/2) in two [(c) and (f)] of the above four regions define

The arrangements of Z(t) and V(t - T/2) in two [(c) and (f)] of the above four regions define T

the maximum value of A which is smaller than $\frac{1}{2}$ on account of the PRC minimum (at A) occurring before the half period (at T/2). The Hodgkin-Huxley model discussed earlier is an example of its PRC minimum occurring above its half period point [the filled square mark in region (d) in the (W, A) panel of Fig. 2(B)]. But in general when A is increased further such that the PRC minimum occurs after the half period point, the arrangement of the PRC and Z(t) in region (c) transforms into that of region (d), and region (f) into that of region (g). And when A increased further such that the PRC minimum (A) occurs not only after the half

period point as shown in Case (d) but occurs after the spike minimum (at $t=\frac{T}{2}+2W$), then we arrive at region (e) for which Case (e) shows an example. All the above seven regions

discussed so far occur when the spike width is less than one fifth of the time period, $W < \frac{T}{5}$. The arrangements of the PRC and V(t) in region (d) and region (e) are illustrated, respectively, in Fig. 2(B) Case (d) and Case (e). The conditions for these seven regions are summarized below:

Region (a) $A < 4W, A < \frac{T}{2} - \frac{W}{2}, W < \frac{T}{5}$:

Region (b) $4W \le A < \frac{T}{2} - \frac{W}{2}$.

Region (c) $A \ge \frac{T}{2} - \frac{W}{2}$, 4 W A < T/2: c

Region (d) $\frac{T}{2} \le A < T - W, 4W \le A < \frac{T}{2} + 2W$: Region (e) $\frac{T}{2} + 2W \le A < T - W$:

Region (f)
$$\frac{T}{2} - \frac{W}{2} \le A < \frac{T}{2}, A < 4W, W < \frac{T}{5}$$
:
Region (g) $\frac{T}{2} \le A < 4W, W < \frac{T}{5}$:
 \mathcal{F}

where x is defined by Eq. 17. The eigenvalue components nx in the Eq. 17 are computed using the same integration formula as in Eq. 6 with the limits adjusted according to the regions (a-g). The algebraic expressions for x are listed in the Appendix E:. The values 1xand $_{8x}$ are contributed by either part or whole of the PRC segments $Z_1(t)$ and $Z_5(t)$ respectively, and thus they are zero. The other segments contribute either positively or negatively to the eigenvalue, and thus decide the critical boundary that defines the stability region of the antisynchronous state.

Regions (a,f,g) defined above border the maximum W that can occur in all the seven regions by requiring $W < \frac{T}{5}$, and other regions also obey this relationship. This condition arises because of the existence of the zero phase regime in the PRC at later phases, $Z_5(t)$. In all

these three regions the spike minimum (at $t=\frac{T}{2}+2W$) occurred before the $Z_5(t)$ segment began. When the spike width is increased such that the spike minimum occurred within the

 $Z_5(t)$ segment of the PRC (i.e. after $t=T-\frac{W}{2}$ and before t=T), then the arrangement of the PRC and V(t) in regions (a), (f), and (g) respectively become candidates for regions (j), (i), and (h). Thus the conditions for these three regions are given by:

Region (h) $\frac{T}{2} \leq A < T - W$, $\frac{T}{5} \leq W < \frac{T}{4}$: Region (i) $\frac{T-W}{2} \le \frac{T}{2}, \frac{T}{5} \le W < \frac{T}{4}$. Region (j) $A < \frac{T-W}{2}, \frac{T}{5} \le W < \frac{T}{4}$:

where x_i , x = h, *i*, *j* is the sum of the eight individual eigenvalue components in each region. The sum is as defined in Eq. 17, and the expressions for the individual segments are given in the Appendix E:.

Extremely large spike width with Wabove $\frac{T}{4}$ leads to some more interesting cases. Consider the parameter region when the spike upstroke (at $t=\frac{T}{2}-\frac{W}{2}$) occurs after PRC minimum (at A) in the segment $Z_3(t)$ as in the region (a, b, j), i.e. $A < \frac{T-W}{2}$. If the spike width grows long enough such that it is now bigger than a quarter of the period, the spike minimum of V (t - T/2) will occur beyond the $Z_3(t)$ segment, i.e. either in the segment $Z_1(t)$ [resulting in region (k)], in the segment $Z_2(t)$ [resulting in region (l)], or in the segment $Z_3(t)$ itself [resulting in region (m)]. If the spike upstroke occurred in the segment $Z_2(t)$ instead of $Z_3(t)$ because of elevated A that moves the PRC to longer phases, then for long spike widths there will be two cases corresponding to the discussion above: one when the spike minimum (now

at $t=2W-\frac{T}{2}$ occurs in the segment $Z_1(t)$ [resulting in region (n)], and when the spike minimum occurs in the segment $Z_2(t)$ [resulting in region (o)]. And finally when the skewness is large enough that the spike peak occurs before the PRC minimum but within the segment $Z_2(t)$, then for large enough spike widths the minimum of V(t - T/2) can occur

either in the PRC segment of $Z_1(t)$ leading to region (p) or in the segment of $Z_2(t)$ itself leading to region (q). All the above seven regions occur when the spike width is bigger than

 $\frac{T}{4}$ but still smaller than $\frac{2T}{5}$ that is defined by Eq. 8. The conditions for the above seven regions are given by:

where x, x = k, l, m, n, o, p, q is the sum of the eight individual components as before as defined in Eq. 17. The expressions for the individual components are given in the Appendix

E:. The region $W > \frac{2T}{5}$ that is not displayed in (*W*, *A*) plot in Fig. 2(B) is forbidden due to condition in Eq. 8.

The spike downstroke or, when the spike width is zero, the discontinuity that is associated with the spike due to its sharp slope contributes maximally to the positive eigenvalue, and can by itself have bigger magnitude over the sum of all the other negative eigenvalue components. And thus even when there is no spike width (W=0), the antisynchronous state can become unstable due to the sharp voltage drop at t = T/2. When the spike width increases, its effect in destabilizing the antisynchrony decreases, and the antisynchronous state has more chance of becoming stable.

Appendix C

Boundaries of antisynchrony when W > 0

The critical curves defining the antisynchronous state discussed in Section 4.2 are listed below.

$$\left(\frac{B}{C}\right)^{*} = \begin{cases} \sigma_{b} = \frac{b_{12} A^{2} + b_{11} A + b_{10}}{b_{21} A + b_{20}}, & \text{if } 0 \leq W < A/4, \\ \sigma_{a} = \frac{a_{13} A^{3} + a_{12} A^{2} + a_{11} A + a_{10}}{a_{23} A^{3} + a_{22} A^{2} + a_{21} A + a_{20}}, & \text{if } \frac{A}{4} \leq W < \frac{T}{5}, \\ \sigma_{j} = \frac{j_{12} A^{2} + j_{11} A + j_{10}}{j_{22} A^{2} + j_{21} A + j_{20}}, & \text{if } \frac{T}{5} \leq W < \frac{T}{4}, \\ \sigma_{k} = \frac{k_{12} A^{2} + k_{11} A + k_{10}}{l_{22} A^{2} + k_{21} A + k_{20}}, & \text{if } \frac{T}{4} \leq W < \frac{A+T}{4}, \\ \sigma_{l} = \frac{l_{13} A^{3} + l_{12} A^{2} + l_{11} A}{l_{22} A^{2} + l_{21} A + l_{20}}, & \text{if } \frac{A+T}{4} \leq W < \frac{A}{2} + \frac{T}{4}, \\ \sigma_{m} = \frac{m_{12} A^{2} + m_{11} A + m_{10}}{m_{21} A + m_{20}}, & \text{if } \frac{A}{2} + \frac{T}{2} \leq W < \frac{2T}{5}. \end{cases}$$

The coefficients on the right hand sides of the above expressions and similar expressions below are listed in the Appendix F:.

$$\begin{pmatrix} \frac{B}{C} \end{pmatrix}^* = \begin{cases} \sigma_c = \frac{c_{13}A^3 + c_{12}A^2 + c_{11}A}{c_{22}A^2 + c_{21}A + c_{20}}, & \text{if } 0 \le w < a/4, \\ \sigma_f = \frac{f_{14}A^4 + f_{13}A^3 + f_{12}A^2 + f_{11}A}{f_{24}A^4 + f_{23}A^3 + f_{22}A^2 + f_{21}A + g_{20}}, & \text{if } \frac{A}{4} \le W < \frac{T}{5}, \\ \sigma_i = \frac{i_{13}A^3 + i_{12}A^2 + i_{11}A}{i_{23}A^3 + i_{22}A^2 + i_{21}A + i_{20}}, & \text{if } \frac{T}{5} \le W < \frac{T}{4}, \\ \sigma_n = \frac{n_{13}A^3 + n_{12}A^2 + n_{11}A}{o_{22}A^2 + a_{21}A + a_{20}}, & \text{if } \frac{T}{4} \le W < \frac{A+T}{4}, \\ \sigma_o = \frac{o_{13}A^3 + o_{12}A^2 + o_{11}A}{o_{22}A^2 + a_{21}A + a_{20}}, & \text{if } \frac{A+T}{4} \le W < \frac{A}{2} + \frac{T}{4}. \end{cases}$$

$$\left(\frac{B}{C}\right)^{*} = \begin{cases} \sigma_{e} = \frac{e_{12}A^{2} + e_{11}A}{e_{21}A + e_{20}}, & \text{if } \frac{T}{2} + 2W \leq A < T - W, 0 \leq W < \frac{A}{2} + \frac{T}{4}, \\ \sigma_{d} = \frac{d_{13}A^{3} + d_{12}A^{2} + d_{11}A}{d_{22}A^{2} + d_{21}A + d_{20}}, & \text{if } \frac{T}{2} \leq A < \frac{T}{2} + 2W, \frac{A}{2} - \frac{T}{4} \leq W < A/4, \\ \sigma_{g} = \frac{g_{13}A^{3} + g_{12}A^{2} + g_{11}A}{g_{23}A^{3} + g_{22}A^{2} + g_{21}A + g_{20}}, & \text{if } \frac{T}{2} \leq A < \frac{T}{2} + 2W, \frac{A}{2} - \frac{T}{4} \leq W < A/4, \\ \sigma_{h} = \frac{h_{12}A^{2} + g_{11}A}{h_{22}A^{2} + h_{21}A + h_{20}}, & \text{if } \frac{T}{2} \leq A < T - W, \frac{T}{5} \leq W < \frac{T}{4}, \\ \sigma_{p} = \frac{p_{12}A^{2} + p_{21}A + h_{20}}{p_{22}A^{2} + p_{21}A + h_{20}}, & \text{if } \frac{T}{2} \leq A < T - W, \frac{T}{4} \leq W < \frac{A + T}{4}, \\ \sigma_{q} = \frac{q_{12}A^{2} + q_{11}A}{q_{21}A + q_{20}}, & \text{if } \frac{T}{2} \leq A < T - W, \frac{T}{4} \leq W < \frac{A + T}{4}, \end{cases}$$

$$(45)$$

Appendix D

Eigenvalue components for synchrony

.

Region (a)

The following are the expressions for the six components of the eigenvalue that determines the stability of synchronous state under case (a) as described in Appendix A:.

$$\begin{split} \lambda_{1a} &= \frac{-2}{T} \int_{0}^{\frac{A}{2}} Z_{1}(t) V_{1}'(t) dt = 0, \\ \lambda_{2a} &= \frac{-2}{T} \int_{A}^{A} Z_{2}(t) V_{1}'(t) dt = \frac{ABa_{2}}{4TW}, \\ \lambda_{3a} &= \frac{-2}{T} \int_{A}^{2W} Z_{3}(t) V_{1}'(t) dt = \frac{(A-2W)a_{2}(AC-BT+2BW-2CW)}{TW(T-A)}, \\ \lambda_{4a} &= \frac{-2}{T} \int_{2W}^{\frac{A}{2}+\frac{T}{2}} Z_{3}(t) V_{2}'(t) dt = \frac{a_{3}(A+T-4W)(A(B-3C)+B(T-4W)+C(T+4W))}{T(A-T)(2T-5W)}, \\ \lambda_{5a} &= \frac{-2}{T} \int_{\frac{A}{2}+\frac{T}{2}}^{T-\frac{W}{2}} Z_{4}(t) V_{2}'(t) dt = \frac{2Ca_{3}(A-T+W)}{T(4T-10W)}, \\ \lambda_{6a} &= \frac{-2}{T} \int_{T-\frac{W}{2}}^{T} Z_{5}(t) V_{3}'(t) dt = 0. \end{split}$$

Region (b)

As in region (a) the first and the last component become zero, and the fifth component is identical to that in region (a): $_{1b} = 0$, $_{6b} = 0$, and $_{5b} = _{5a}$. The other three components are given below:

$$\begin{aligned} \lambda_{2b} &= \frac{-2}{T} \int_{A/2}^{2W} Z_2(t) V_1'(t) \, dt = \frac{a_2 B (A - 4W)^2}{4ATW}, \\ \lambda_{3b} &= \frac{-2}{T} \int_{2W}^{A} Z_2(t) V_2'(t) \, dt = -\frac{8a_3 B W (A - 2W)}{AT(2T - 5W)}, \\ \lambda_{4b} &= \frac{-2}{T} \int_{A}^{\frac{A}{2} + \frac{T}{2}} Z_3(t) V_2'(t) \, dt = \frac{2a_3 (A - T) (B + C)}{T(4T - 10W)}. \end{aligned}$$

Region (c)

The first two and the last component become zero: $_{1c} = 0$, $_{2c} = 0$, and $_{6c} = 0$. The fourth component is identical to that in region (b), and the fifth component is identical to that in region (a): $_{4c} = _{4b}$, and $_{5c} = _{5a}$. The other component is given below:

$$\lambda_{3c} = \frac{-2}{T} \int_{\frac{A}{2}}^{A} Z_2(t) V_2'(t) dt = -\frac{2ABa_3}{T(4T - 10W)}$$

Region (d)

The first and the last components become zero: $_{1c} = 0$, and $_{6d} = 0$. The second component is identical to that in region (a): $_{2d} = _{2a}$. The other three components are given below:

$$\begin{split} \lambda_{3d} &= \frac{-2}{T} \int_{A}^{\frac{A}{2} + \frac{T}{2}} Z_3(t) V_1'(t) \, dt = -\frac{a_2(A-T)(B+C)}{4TW}, \\ \lambda_{4d} &= \frac{-2}{T} \int_{\frac{A}{2} + \frac{T}{2}}^{2W} Z_4(t) V_1'(t) \, dt = -\frac{a_2C(A+T-4W)(A-3T+6W)}{4TW(A-T+W)}, \\ \lambda_{5d} &= \frac{-2}{T} \int_{2W}^{T-\frac{W}{2}} Z_4(t) V_2'(t) \, dt = \frac{a_3C(2T-5W)}{T(A-T+W)}. \end{split}$$

Appendix E

Eigenvalue components for antisynchrony

The expressions for the eight components (see Eq. 17) comprising the eigenvalue in each of the seventeen parameter regimes in (W, A) plane a, \ldots, q [i.e. under region (a), ..., region (q)] for determining the stability of antisynchronous state described in Appendix B: are listed below.

Region (a)

$$\begin{split} \gamma_{1a} &= \frac{-2}{T} \int_{0}^{\frac{A}{2}} Z_1(t) V_2'(t) \, dt = 0, \\ \gamma_{2a} &= \frac{-2}{T} \int_{\frac{A}{2}}^{A} Z_2(t) V_2'(t) \, dt = -\frac{2Aa_3 B}{4T^2 - 10 TW}, \end{split}$$

$$\gamma_{3a} = \frac{-2}{T} \int_{A}^{\frac{T}{2} - \frac{W}{2}} Z_3(t) V_2'(t) dt = \frac{a_3(2A - T + W)(2AC - B(T + W) + C(W - T))}{T(A - T)(2T - 5W)},$$

$$\gamma_{4a} = \frac{-2}{T} \int_{\frac{T}{2} - \frac{W}{2}}^{\frac{T}{2}} Z_3(t) V_3'(t) dt = \frac{(a_2 - a_3)(2A(B - 2C) + BW + 2CT - CW)}{T(A - T)},$$

$$\gamma_{5a} = \frac{-2}{T} \int_{\frac{T}{2}+2W}^{A/2+\frac{T}{2}} Z_3(t) V_1'(t) dt = -\frac{Aa_2(A(B-3C)+2CT)}{4TW(A-T)},$$

$$\gamma_{6a} = \frac{-2}{T} \int_{\frac{A}{2}+\frac{T}{2}}^{\frac{T}{2}+2W} Z_4(t) V_1'(t) dt = -\frac{a_2C(A-4W)(A-2T+6W)}{4TW(A-T+W)},$$

$$\gamma_{7a} = \frac{-2}{T} \int_{\frac{T}{2}+2W}^{T-\frac{W}{2}} Z_4(t) V_2'(t) dt = -\frac{a_3 C (T-5W)^2}{T (2T-5W) (-A+T-W)};$$
$$\gamma_{8a} = \frac{-2}{T} \int_{T-\frac{W}{2}}^{T} Z_5(t) V_2'(t) dt = 0.$$

Region (b)

Two of the components become zero, and three others identical to those in region (a): $_{1b} = 0$, and $_{8b} = 0$, $_{2b} = _{2a}$, $_{3b} = _{3a}$, and $_{4b} = _{4a}$. The other three components are given below.

$$\begin{split} \gamma_{5b} = & \frac{-2}{T} \int_{\frac{T}{2}+2W}^{\frac{T}{2}+2W} Z_3(t) V_1'(t) \, dt = - \frac{2a_2(A(B-2C)-2BW+C(T+2W))}{T(T-A)}, \\ \gamma_{6b} = & \frac{-2}{T} \int_{\frac{T}{2}+2W}^{\frac{A}{2}+\frac{T}{2}} Z_3(t) V_2'(t) \, dt = \frac{a_3(A-4W)(A(B-3C)-4BW+2C(T+2W))}{T(A-T)(2T-5W)} \\ \gamma_{7b} = & \frac{-2}{T} \int_{\frac{A}{2}+\frac{T}{2}}^{T-\frac{W}{2}} Z_4(t) V_2'(t) \, dt = \frac{2a_3C(A-T+W)}{T(4T-10W)}. \end{split}$$

Region (c)

The components $_{1c} = 0$, and $_{8c} = 0$. Three other components are identical to those in region (b): $_{5c} = _{5b} _{6c} = _{6b}$, and $_{7c} = _{7b}$. The other three components are given below.

$$\begin{split} \gamma_{2c} &= \frac{-2}{T} \int_{\frac{A}{2}}^{\frac{T}{2} - \frac{W}{2}} Z_2(t) V_2'(t) \, dt = -\frac{a_3 B (A - T + W)^2}{A T (2T - 5W)}, \\ \gamma_{3c} &= \frac{-2}{T} \int_{\frac{T}{2} - \frac{W}{2}}^{A} Z_2(t) V_3'(t) \, dt = -\frac{B (a_2 - a_3) (T - W) (2A - T + W)}{A T W}, \\ \gamma_{4c} &= \frac{-2}{T} \int_{A}^{\frac{T}{2}} Z_3(t) V_3'(t) \, dt = \frac{(2A - T) (a_2 - a_3) (2AC - T (B + C))}{T W (A - T)}. \end{split}$$

Region (d)

The first and last components are zeros: $_{1d} = 0$, and $_{8d} = 0$. One component is identical to that in region (c): $_{2d} = _{2c}$, and two others are identical to those in region (b): $_{6d} = _{6b}$, and $_{7d} = _{7b}$. The other three components are given below:

$$\begin{split} \gamma_{3d} &= \frac{-2}{T} \int_{\frac{T}{2} - \frac{W}{2}}^{\frac{T}{2}} Z_2(t) V_3'(t) \, dt = \frac{B(a_2 - a_3)(2A - 2T + W)}{AT}, \\ \gamma_{4d} &= \frac{-2}{T} \int_{\frac{T}{2} - \frac{W}{2}}^{A} Z_2(t) V_1'(t) \, dt = -\frac{a_2 B(T - 2A)}{4AW}, \\ \gamma_{5d} &= -\frac{2}{T} \int_{A}^{\frac{T}{2} + 2W} Z_3(t) V_1'(t) \, dt = -\frac{a_2(2A - T - 4W)(2AC - B(T - 4W) - C(T + 4W))}{4TW(A - T)}. \end{split}$$

Region (e)

The first and last components are zeros: $_{1e} = 0$, and $_{8e} = 0$. The third and seventh components are identical to respectively those in regions (d) and (b): $_{3e} = _{3d}$, and $_{7e} = _{7b}$. The other four components are given below:

$$\begin{split} \gamma_{2e} &= \frac{-2}{T} \int_{-\frac{A}{2}}^{\frac{T}{2} - \frac{W}{2}} Z_2(t) V_2'(t) \, dt = -\frac{a_3 B (A - T + W)^2}{A T (2T - 5W)}, \\ \gamma_{4e} &= \frac{-2}{T} \int_{-\frac{T}{2}}^{\frac{T}{2} + 2W} Z_2(t) V_1'(t) \, dt = -\frac{2a_2 B (A - T - 2W)}{AT}, \\ \gamma_{5e} &= -\frac{2}{T} \int_{-\frac{T}{2} + 2W}^{A} Z_2(t) V_2'(t) \, dt = -\frac{a_3 B (T + 4W) (2A - T - 4W)}{A T (2T - 5W)}, \\ \gamma_{6e} &= -\frac{2}{T} \int_{-\frac{T}{2} + 2W}^{A} Z_3(t) V_2'(t) \, dt = \frac{2a_3 (A - T) (B + C)}{T (4T - 10W)}. \end{split}$$

Region (f)

The first and last components are zeros: $_{1f}=0$, and $_{8f}=0$. And all the other components are identical to previously computed expressions in either region (a) or region (c): $_{2f}=_{2o}$, $_{3f}=_{3o}$, $_{4f}=_{4o}$ and $_{5f}=_{5a}$, $_{6f}=_{6a}$, and $_{7f}=_{7a}$.

Region (g)

The first and last components are zeros: $_{1g} = 0$, and $_{8g} = 0$. Except the fifth component the other components are identical to expressions derived in either region (a), (c), or (d): $_{2g} = _{2c}$, $_{3g} = _{3d}$, $_{4g} = _{4d}$, $_{6g} = _{6a}$, and $_{7g} = _{7a}$. The remaining component is given below.

$$\gamma_{5g} = \frac{-2}{T} \int_{A}^{\frac{2}{2} + \frac{T}{2}} Z_3(t) V_1'(t) dt = -\frac{a_2(A - T) + (B + C)}{4TW}$$

Region (h)

The first and the last two components are zeros: $_{1h} = 0$, $_{7h} = 0$, and $_{8h} = 0$. Four other components are as derived in the previous cases: $_{2h} = _{2c}$, $_{3h} = _{3d}$, $_{4h} = _{4d}$, and $_{5h} = _{5g}$. The sixth component is given below:

$$\gamma_{6h} = \frac{-2}{T} \int_{\frac{A}{2} + \frac{T}{2}}^{T - \frac{W}{2}} Z_4(t) V_1^{'}(t) dt = -\frac{a_2 C (A - T + W)}{4 T W}$$

Region (i)

The first and the last two components are zeros: $_{1i} = 0$, $_{7i} = 0$, and $_{8i} = 0$. And all other components are as derived in the previous cases: $_{2i} = _{20}$, $_{3i} = _{30}$, $_{4i} = _{40}$, $_{5i} = _{5a}$, and $_{6i} = _{6h}$.

Region (j)

As in the previous two cases, the first and the last two components are zeros: $_{1j} = 0$, $_{7j} = 0$, and $_{8j} = 0$. And all other components are as derived in the previous cases: $_{2j} = _{2a}$, $_{3j} = _{3a}$, $_{4j} = _{4a}$, $_{5j} = _{5a}$, and $_{6j} = _{6h}$.

Region (k)

The first two and the last one component become zero: $_{1k}=0$, $_{2k}=0$, and $_{8k}=0$. All the other components are completely as derived in region (j) with shifted indices: $_{3k}=2_{a}$, $_{4k}=3_{a}$, $_{5k}=4_{a}$, $_{6k}=5_{a}$, and $_{7k}=6_{b}$.

Region (I)

The first and the last one component become zero: $_{1I}=0$, and $_{8I}=0$. Four components are identical those of the previous case: $_{4I}=_{3a}$, $_{5I}=_{4a}$, $_{6I}=_{5a}$, and $_{7I}=_{6h}$. The remaining two components are given below:

$$\begin{split} \gamma_{2l} &= \frac{-2}{T} \int_{\frac{A}{2}}^{2W - \frac{T}{2}} Z_2(t) V_1'(t) \, dt = \frac{a_2 B (A + T - 4W)^2}{4ATW}, \\ \gamma_{3l} &= \frac{-2}{T} \int_{2W - \frac{T}{2}}^{A} Z_2(t) V_2'(t) \, dt = \frac{a_3 B (T - 4W) (2A + T - 4W)}{AT (2T - 5W)} \end{split}$$

Region (m)

The first and the last one component become zero: $_{1m} = 0$, and $_{8m} = 0$. Three other components are as derived in the previous cases: $_{5m} = _{5b}$, $_{6m} = _{5a}$, and $_{7m} = _{6h}$. And the expressions for the third and fourth components are given below:

$$\gamma_{3m} = \frac{-2}{T} \int_{A}^{2W - \frac{T}{2}} Z_3(t) V_1'(t) dt = -\frac{a_2(2A + T - 4W)(2AC - 3BT + 4BW + CT - 4CW)}{4TW(A - T)},$$

$$\gamma_{4m} = \frac{-2}{T} \int_{2W - \frac{T}{2}}^{\frac{T}{2} - \frac{W}{2}} Z_3(t) V_2'(t) dt = \frac{a_3(2A(B - 2C) + 2BT - 3BW + 3CW)}{T(A - T)}.$$

Region (n)

The first two and the last one component become zero: $_{1n} = 0$, $_{2n} = 0$, and $_{8n} = 0$. And all other components are as derived in the previous cases: $_{3n} = _{2c}$, $_{4n} = _{3c}$, $_{5n} = _{4c}$, $_{6n} = _{5a}$, and $_{7n} = _{6h}$.

Region (o)

The first and the last component become zero: $_{1o} = 0$, and $_{8o} = 0$. Five other components are as derived in the previous cases: $_{2o} = _{2k} _{4o} = _{3c} _{5o} = _{4c} _{6o} = _{5a}$, and $_{7o} = _{6h}$. The remaining component is as given below:

$$\gamma_{3o} = \frac{-2}{T} \frac{\frac{T}{2} - \frac{W}{2}}{\int_{2W - \frac{T}{2}} Z_2(t) V_2'(t) dt} = -\frac{a_3 B (3W - 2A)}{AT}.$$

Region (p)

The first two and the last one component become zero: $_{1p}=0$, $_{2p}=0$, and $_{8p}=0$. All the other components are as derived in the previous cases: $_{3p}=_{2c}$, $_{4p}=_{3d}$, $_{5p}=_{4d}$, $_{6p}=_{5g}$, and $_{7p}=_{6h}$.

Region (q)

The first and the last component become zero: $_{1q} = 0$, and $_{8q} = 0$. And all the other components are as derived in the previous cases: $_{2q} = _{2h} _{3q} = _{3o} _{4q} = _{3d} _{5q} = _{4d} _{6q} = _{5g}$, and $_{7q} = _{6h}$.

Appendix F

Coefficients in the critical curve expressions for antisynchrony

These are the coefficients $a_{10}, ..., a_{13}, a_{20}, ..., a_{23}, b_{10}, ..., q_{11}, q_{12}, q_{20}, q_{21}$ that appear in the seventeen critical curve expressions for $\left(\frac{B}{C}\right)^*$ presented in Appendix C:. We use the definition $a'_3 = a_3/a_2$.

Region (a)

 $-4W(a'_{3}(-2T^{3}+3T^{2}W+11TW^{2}+4W^{3})+W(2T-5W)(3T+W))$ a_{10} = $4W(a'_{3}(-6T^{2}+20TW+5W^{2})+(2T-5W)(4T+W)) -48W^{2}a'_{3}-4T^{2}-20TW+75W^{2}$ $a_{11} =$ $a_{12} =$ $2(\overset{\circ}{8}Wa'_{3}+2T-5W) \\ 4W(T-W)\left(a'_{3}(T^{2}-2TW+4W^{2})+W(2T-5W)\right)$ $a_{13} =$ a_{20} = $-4W(3a'_{3}(2T^{2}-5TW+4W^{2})-4T^{2}+16TW-15W^{2})$ a_{21} = $\begin{array}{c} 4Wa_{3}^{'}\left(4T-7W\right)-\left(2T-5W\right)\left(T{+}7W\right)\\ 4Wa_{3}^{'}{+}2T-5W\end{array}$ a_{22} = $a_{23} =$

Region (b)

$$b_{10} = a'_{3}(-2T^{2}+TW-20W^{2})+5W(5W-2T)$$

$$b_{11} = a'_{3}(4T+W)$$

$$b_{12} = 2a'_{3}$$

$$b_{20} = 5W(5W-2T) - a'_{3}(T^{2}-2TW+20W^{2})$$

$$b_{21} = 5Ta'_{3}$$

Region (c)

$$\begin{array}{rcl} c_{11} &=& (2T-5W) \left(T^2-2TW-4W^2\right) - a_3' \left(2T^3-6T^2W+9TW^2+16W^3\right) \\ c_{12} &=& a_3' \left(8T^2-20TW+17W^2\right) - 4 \left(2T-5W\right) \left(T-W\right) \\ c_{13} &=& a_3' \left(18W-8T\right)+8T-20W \\ c_{20} &=& -T(T-W)^2 \left(2a_3' \left(T-2W\right)-2T+5W\right) \\ c_{21} &=& a_3' \left(8T^3-25T^2W+18TW^2-20W^3\right) - \left(2T-5W\right) \left(4T^2-4TW+5W^2\right) \\ c_{22} &=& -T \left(a_3' \left(8T-21W\right)-8T+20W\right) \end{array}$$

Region (d)

$$\begin{array}{rcl} d_{11} &=& 4Wa'_3\left(-T^2+9\,TW+16W^2\right)+(2T-5W)\left(T+4W\right)^2\\ d_{12} &=& -4(17W^2a'_3+(2T-5W)\left(T+4W\right))\\ d_{13} &=& 8Wa'_3+8T-20W\\ d_{20} &=& T\left((2T-5W)\left(T^2+8\,TW-4W^2\right)-4Wa'_3\left(3T^2-10\,TW+4W^2\right)\right)\\ d_{21} &=& 4Wa'_3\left(5T^2-18\,TW+20W^2\right)-4(2T-5W)\left(T-W\right)\left(T+5W\right)\\ d_{22} &=& 4T\left(-Wa'_3+2T-5W\right) \end{array}$$

Region (e)

$$e_{11} = a'_{3}(W - 2T)$$

$$e_{12} = 2a'_{3}$$

$$e_{20} = a'_{3}(-4T^{2} + 2TW - 20W^{2}) + 5W(5W - 2T)$$

$$e_{21} = 5Ta'_{3}$$

Region (f)

$$\begin{array}{rcl} f_{11} &=& 4T \left(a'_{3} \left(2T^{3}-8T^{2}W+15TW^{2}-25W^{3}\right)-\left(2T-5W\right) \left(T^{2}-3TW+6W^{2}\right)\right) \\ f_{12} &=& 4\left(2T-5W\right) \left(5T^{2}-6TW+6W^{2}\right)-4a'_{3} \left(10T^{3}-34T^{2}W+30TW^{2}-25W^{3}\right) \\ f_{13} &=& \left(16a'_{3}-17\right) \left(2T-5W\right) \left(2T-W\right) \\ f_{14} &=& -2\left(8a'_{3}-9\right) \left(2T-5W\right) \\ f_{20} &=& 4T\left(T-W\right)^{3} \left(2a'_{3} \left(T-2W\right)-2T+5W\right) \\ f_{21} &=& -4\left(T-W\right) \left(a'_{3} \left(10T^{3}-31T^{2}W+22TW^{2}-4W^{3}\right)-\left(2T-5W\right) \left(5T^{2}-5TW+W^{2}\right)\right) \\ f_{22} &=& 4\left(2T-W\right) \left(a'_{3} \left(8T^{2}-23TW+12W^{2}\right)-8T^{2}+26TW-15W^{2}\right) \\ f_{23} &=& \left(15T-7W\right) \left(2T-5W\right)-4a'_{3} \left(8T^{2}-20TW+7W^{2}\right) \\ f_{24} &=& 4Wa'_{3}+2T-5W \end{array}$$

Region (g)

g_{11}	=	$4Wa'_{3}(T-5W)^{2} - (2T-5W)(T^{2}+7TW-24W^{2})$
g_{12}	=	$\left(2T-5W\right)\left(4T-3W\right)$
g_{13}	=	10W-4T
g_{20}	=	$-(T-W)\left((2T-5W)\left(T^{2}+8TW-4W^{2}\right)-4Wa_{3}^{'}\left(3T^{2}-10TW+4W^{2}\right)\right)$
g_{21}	=	$\left(2T-5W\right)\left(4T-3W\right)\left(T\!+\!4W\right)-4Wa_{3}^{'}\left(5T^{2}-20TW\!+\!12W^{2}\right)$
g_{22}	=	$4Wa_{3}^{'}(T-7W)-8T^{2}{+}6TW{+}35W^{2}$
g_{23}	=	$4Wa_{3}^{'}{+}2T-5W$

Region (h)

h_{11}	=	$\left(2T-5W\right)\left(2T-W\right)$
h_{12}	=	10W - 4T
h_{20}	=	$(2T-5W)\left(T^2+8TW-4W^2\right)-4Wa'_3\left(3T^2-10TW+4W^2\right)$
h_{21}	=	$8Wa_3^{'}(T-4W)-6T^2-TW{+}40W^2$
h_{22}	=	$4Wa'_{3}+2T-5W$

Region (i)

i_{11}	=	$-T(2T-5W)(4Ta'_{3}-3T-W)$
i_{12}	=	$(2T-5W) \left(16T a_3^{'}-16T-W ight)$
i_{13}	=	$-2 (8a'_3 - 9) (2T - 5W)$
i_{20}	=	$-4T (T - W)^2 (2a'_3 (T - 2W) - 2T + 5W)$
i_{21}	=	$4\left(a_{3}^{'}\left(8T^{3}-25T^{2}W+18TW^{2}-4W^{3}\right)-\left(2T-5W\right)\left(W-2T\right)^{2}\right)$
i_{22}	=	$4(a'_{3}(-8T^{2}+21TW-8W^{2})+8T^{2}-24TW+10W^{2})$
i_{23}	=	$4Wa'_{3}+2T-5W$

Region (j)

j_{10}	=	$-4Wa_{3}^{'}\left(3T^{2}-10TW+4W^{2}\right)-\left(2T-5W\right)\left(T^{2}-9TW+4W^{2}\right)$
j_{11}	=	$W(16a_{3}^{'}(T-4W)-34T{+}85W)$
j_{12}	=	$2(8Wa'_{3}{+}2T-5W)$
j_{20}	=	$-4W\left(a_{3}^{'}(T^{2}-2TW+4W^{2})+W\left(2T-5W\right)\right)$
j_{21}	=	$4W\left(a_{3}^{'}\left(5T-8W ight)-4T{+}10W ight)$
j_{22}	=	$4Wa'_{3}+2T-5W$

Region (k)

$$\begin{array}{rcl} k_{10} &=& -4Wa'_3\left(3T^2 - 10\,TW + 4W^2\right) - \left(2T - 5W\right)\left(T^2 - 9\,TW + 4W^2\right) \\ k_{11} &=& W\left(16a'_3\left(T - 4W\right) - 34T + 85W\right) \\ k_{12} &=& 2\left(8Wa'_3 + 2T - 5W\right) \\ k_{20} &=& -4W\left(a'_3\left(T^2 - 2\,TW + 4W^2\right) + W\left(2T - 5W\right)\right) \\ k_{21} &=& 4W\left(a'_3\left(5T - 8W\right) - 4T + 10W\right) \\ k_{22} &=& 4Wa'_3 + 2T - 5W \end{array}$$

Region (I)

l_{11}	=	$4Wa'_{3}(3T^{2} - 10TW + 4W^{2}) + (2T - 5W)(T^{2} - 9TW + 4W^{2})$
l_{12}	=	$W(-16a'_{3}(T-4W)+34T-85W)$
l_{13}	=	$-2 \left(8Wa'_{3} + 2T - 5W \right)$
l_{20}	=	$-T(T-4W)^{2}(4Wa_{3}^{'}+2T-5W)$
l_{21}	=	$-8W^2a'_3(T-10W) - (2T-5W)(T^2-20W^2)$
l_{22}	=	$T(-16Wa'_{3}+2T-5W)$

Region (m)

m_{10}	=	$8Wa'_3(T-2W){+}2T^2-17TW{+}20W^2$
m_{11}	=	4T+W
m_{12}	=	2
m_{20}	=	$(T-2W) (8Wa'_3+3T-10W)$
m_{21}	=	5T

Region (n)

n_{11}	=	$-T(2T-5W)(4Ta'_{3}-3T-W)$
n_{12}	=	$(2T - 5W) (16T a'_3 - 16T - W)$
n_{13}	=	$-2 \left(8 a_{3}^{'}-9 ight) \left(2 T-5 W ight)$
n_{20}	=	$-4T(T-W)^2 \left(2a'_3(T-2W)-2T{+}5W ight)$
n_{21}	=	$4\left(a_{3}^{'}\left(8T^{3}-25T^{2}W+18TW^{2}-4W^{3}\right)-\left(2T-5W\right)\left(W-2T\right)^{2}\right)$
n_{22}	=	$4 \left(a_3^{'} \left(-8 T^2 +21 T W-8 W^2\right)+8 T^2-24 T W+10 W^2\right)$
n_{23}	=	$4Wa'_3+2T-5W$

Region (o)

$$\begin{array}{rcl}
o_{11} &= & T\left(-4T\,a'_{3}+3T+W\right)\\
o_{12} &= & 16Ta'_{3}-16T-W\\
o_{13} &= & 18-16a'_{3}\\
o_{20} &= & -T\left(4a'_{3}\left(T^{2}-2TW+4W^{2}\right)-5T^{2}+16\,TW-20W^{2}\right)\\
o_{21} &= & 8a'_{3}\left(2T^{2}-TW+2W^{2}\right)-15T^{2}+16\,TW-20W^{2}\\
o_{22} &= & T\left(15-16a'_{3}\right)
\end{array}$$

Region (p)

$$\begin{array}{rcl} p_{11} & = & (2T-5W) \, (2T-W) \\ p_{12} & = & 10W-4T \\ p_{20} & = & (2T-5W) \, (T^2+8\,TW-4W^2) - 4W \, a_3^{'} \, (3T^2-10\,TW+4W^2) \\ p_{21} & = & 8W \, a_3^{'} \, (T-4W) - 6T^2 - \,TW + 40W^2 \\ p_{22} & = & 4W \, a_3^{'} + 2T - 5W \end{array}$$

Region (q)

$$\begin{array}{rcl} q_{11} & = & W - 2T \\ q_{12} & = & 2 \\ q_{20} & = & 4W \left(2a'_3(T - 2W) - 4T + 5W \right) \\ q_{21} & = & 5T \end{array}$$

References

- Abramovich-Sivan S, Akselrod S. A pacemaker cell pair model based on the phase response curve. Biol Cybern. 1998; 79:77–86. [PubMed: 9742680]
- Achuthan S, Canavier CC. Phase-resetting curves determine synchronization, phase locking, and clustering in networks of neural oscillators. J Neurosci. 2009; 29:5218–5233. [PubMed: 19386918]
- Bem T, Le Feuvre Y, Rinzel J, Meyrand P. Electrical coupling induces bistability of rhythms in networks of inhibitory spiking neurons. Eur J Neurosci. 2005; 22:2661–2668. [PubMed: 16307609]
- Bou-Flores C, Berger AJ. Gap junctions and inhibitory synapses modulate inspiratory motoneuron synchronization. J Neurophysiol. 2001; 85:1543–1551. [PubMed: 11287478]
- Brown E, Moehlis J, Holmes P. On the phase reduction and response dynamics of neural oscillator populations. Neural Comput. 2004; 16:673–715. [PubMed: 15025826]
- Carlen PL, Skinner F, Zhang L, Naus C, Kushnir M, Perez Velazquez JL. The role of gap junctions in seizures. Brain Res Rev. 2000; 32:235–241. [PubMed: 10751673]
- Chow CC, Kopell N. Dynamics of spiking neurons with electrical coupling. Neural Comput. 2000; 12:1643–1678. [PubMed: 10935921]
- Cui J, Carmen CC, Butera Robert J. Functional phase response curves: A method for understanding synchronization of adapting neurons. J Neurophysiol. 2009; 102:387–398. [PubMed: 19420126]
- Demir SS, Clark JW, Giles WR. Parasympathetic modulation of sinoatrial node pacemaker activity in rabbit heart: a unifying model. Am J Physiol. 1999; 276:H2221–H2244. [PubMed: 10362707]
- Devlin PF, Kay SA. Circadian photoperception. Annu Rev Physiol. 2001; 63:677–694. [PubMed: 11181972]
- Erisir A, Lau D, Rudy B, Leonard CS. Function of specific K⁺ channels in sustained high-frequency firing of fast-spiking neocortical interneurons. J Neurophysiol. 1999; 82:2476–2489. [PubMed: 10561420]
- Ermentrout B. Type I membranes, phase resetting curves, and synchrony. Neural Comput. 1996; 8:979. [PubMed: 8697231]
- Ermentrout B, Pascal M, Gutkin B. The effects of spike frequency adaptation and negative feedback on the synchronization of neural oscillators. Neural Comput. 2001; 13:1285–1310. [PubMed: 11387047]
- Ermentrout GB, Galán RF, Urban NN. Relating neural dynamics to neural coding. Phys Rev Lett. 2007; 99:248103. [PubMed: 18233494]
- Ermentrout GB, Kopell B. Multiple pulse interactions and averaging in systems of coupled neural oscillators. J Math Biol. 1991; 29:195–217.

- Ermentrout GB, Kopell N. Parabolic bursting in an excitable system coupled with a slow oscillation. SIAM J Appl Math. 1986; 46:233–253.
- Fuentealba P, Crochet S, Timofeev I, Bazhenov M, Sejnowski TJ, Steriade M. Experimental evidence and modeling studies support a synchronizing role for electrical coupling in the cat thalamic reticular neurons *in vivo*. Eur J Neurosci. 2004; 20:111–119. [PubMed: 15245484]
- Galán RF, Ermentrout GB, Urban NN. Efficient estimation of phase-resetting curves in real neurons and its significance for neural-network modeling. Phys Rev Lett. 2005; 94:158101. [PubMed: 15904191]
- Galarreta M, Hestrin S. A network of fast-spiking cells in the neocortex connected by electrical synapses. Nature. 1999; 402:72–75. [PubMed: 10573418]
- Gao J, Holmes P. On the dynamics of electrically-coupled neurons with inhibitory synapses. J Comput Neurosci. 2007; 22:39–61. [PubMed: 16998640]
- Gibson JR, Beierlein M, Connors BW. Two networks of electrically coupled inhibitory neurons in neocortex. Nature. 1999; 402:75–79. [PubMed: 10573419]
- Goel P, Ermentrout B. Synchrony, stability, and firing patterns in pulse-coupled oscillators. Physica D. 2002; 163:191–216.
- Hansel D, Mato G, Meunier C. Synchrony in excitatory neural networks. Neural Comput. 1995; 7:307–337. [PubMed: 8974733]
- Hansel, D.; Mato, G.; Pfeuty, B. The role of intrinsic cell properties in synchrony of neurons interacting via electrical synapses. In: Schultheiss, N.; Prinz, A.; Butera, R., editors. Phase response curves in neuroscience: Theory, experiment, and analysis. Springer; 2012.
- Hestrin S, Galarreta M. Electrical synapses define networks of neocortical gabaergic neurons. Trends Neurosci. 2005; 28:304–309. [PubMed: 15927686]
- Hoppensteadt, FC.; Izhikevich, EM. Weakly connected neural networks. Springer; New York, NY 10013, USA: 1997.
- Izhikevich, EM. Dynamical systems in neuroscience: The geometry of excitability and bursting. The MIT Press; 2007.
- Jalife J. Mutual entrainment and electrical coupling as mechanisms for synchronous firing of rabbit sino-atrial pace-maker cells. J Physiol. 1984; 356:221–243. [PubMed: 6097670]
- Kepler TB, Marder E, Abbott LF. The effect of electrical coupling on the frequency of model neuronal oscillators. Science. 1990; 248:83–85. [PubMed: 2321028]
- Klaus A, Planert H, Hjorth JJ, Berke JD, Silberberg G, Kotaleski JH. Striatal fast-spiking interneurons: from firing patterns to postsynaptic impact. Front Syst Neurosci. 2011; 5:57. [PubMed: 21808608]
- Koos T, Tepper JM. Inhibitory control of neostriatal projection neurons by gabaergic interneurons. Nat Neurosci. 1999; 2:467–472. [PubMed: 10321252]
- Kuramoto, Y. Chemical oscillations, waves, and turbulence. Springer-Verlag; Berlin: 1984.
- Landisman CE, Long MA, Beierlein M, Deans MR, Paul DL, Connors BW. Electrical synapses in the thalamic reticular nucleus. J Neurosci. 2002; 22:1002–1009. [PubMed: 11826128]
- Lee SC, Cruikshank SJ, Connors BW. Electrical and chemical synapses between relay neurons in developing thalamus. J Physiol. 2010; 588:2403–2415. [PubMed: 20457735]
- Lewis TJ, Rinzel J. Self-organized synchronous oscillations in a network of excitable cells coupled by gap junctions. Network. 2000; 11:299–320. [PubMed: 11128169]
- Lewis TJ, Rinzel J. Dynamics of spiking neurons connected by both inhibitory and electrical coupling. J Comput Neurosci. 2003; 14:283–309. [PubMed: 12766429]
- Lewis, TJ.; Skinner, FK. Understanding activity in electrically coupled networks using prcs and the theory of weakly coupled oscillators. In: Schultheiss, N.; Prinz, A.; Butera, R., editors. Phase response curves in neuroscience: Theory, experiment, and analysis. Springer; 2012.
- Mancilla JG, Lewis TJ, Pinto DJ, Rinzel J, Connors BW. Synchronization of electrically coupled pairs of inhibitory interneurons in neocortex. J Neurosci. 2007; 27:2058–2073. [PubMed: 17314301]
- Mirollo RE, Strogatz SH. Synchronization of pulse-coupled biological oscillators. SIAM J Appl Math. 1990; 50:1645–1662.

- Netoff TI, Banks MI, Dorval AD, Acker CD, Haas JS, Kopell N, White JA. Synchronization in hybrid neuronal networks of the hippocampal formation. J Neurophysiol. 2005; 93:1197–1208. [PubMed: 15525802]
- Neu JC. Chemical waves and the diffusive coupling of limit cycle oscilltors. SIAM J Appl Math. 1979a; 36:509–515.

Neu JC. Coupled chemical oscillators. SIAM J Appl Math. 1979b; 37:307-315.

- Nomura M, Fukai T, Aoyagi T. Synchrony of fast-spiking interneurons interconnected by gabaergic and electrical synapses. Neural Comput. 2003; 15:2179–2198. [PubMed: 12959671]
- Ostojic S, Brunel N, Hakim V. Synchronization properties of networks of electrically coupled neurons in the presence of noise and heterogeneities. J Comput Neurosci. 2009; 26:369–392. [PubMed: 19034642]
- Perez Velazquez JL, Galán RF, Garcia Dominguez L, Leshchenko Y, Lo S, Belkas J, Erra RG. Phase response curves in the characterization of epileptiform activity. Phys Rev E. 2007; 76:061912.
- Pfeuty B, Mato G, Golomb D, Hansel D. Electrical synapses and synchrony: the role of intrinsic currents. J Neurosci. 2003; 23:6280–6294. [PubMed: 12867513]
- Preyer AJ, Butera RJ. Neuronal oscillators in *Aplysia californica* that demonstrate weak coupling *in vitro*. Phys Rev Lett. 2005; 95:138103. [PubMed: 16197185]
- Smeal RM, Ermentrout GB, White JA. Phase-response curves and synchronized neural networks. Phil Trans R Soc Lond B Biol Sci. 2010; 365:2407–2422. [PubMed: 20603361]
- Tateno T, Robinson HP. Phase resetting curves and oscillatory stability in interneurons of rat somatosensory cortex. Biophys J. 2007; 92:683–695. [PubMed: 17192317]
- Traub RD, Pais I, Bibbig A, LeBeau FE, Buhl EH, Hormuzdi SG, Whittington MA, et al. Contrasting roles of axonal (pyramidal cell) and dendritic (interneuron) electrical coupling in the generation of neuronal network oscillations. Proc Nat Acad Sci USA. 2003; 100:1370–1374. [PubMed: 12525690]
- Tsubo Y, Teramae JN, Fukai T. Synchronization of excitatory neurons with strongly heterogeneous phase responses. Phys Rev Lett. 2007; 99:228101. [PubMed: 18233330]
- Valiante TA, Perez Velazquez JL, Jahromi SS, Carlen PL. Coupling potentials in cal neurons during calcium-free-induced field burst activity. J Neurosci. 1995; 15:6946–6956. [PubMed: 7472451]
- Van Vreeswijk C, Abbott LF, Ermentrout GB. When inhibition not excitation synchronizes neural firing. J Comput Neurosci. 1994; 1:313–321. [PubMed: 8792237]
- Verheijck EE, Wilders R, Joyner RW, Golod DA, Kumar R, Jongsma HJ, van Ginneken AC, et al. Pacemaker synchronization of electrically coupled rabbit sinoatrial node cells. J Gen Physiol. 1998; 111:95. [PubMed: 9417138]
- Winfree AT. Biological rhythms and the behavior of populations of coupled oscillators. J Theor Biol. 1967; 16:15–42. [PubMed: 6035757]



Figure 1.

Parameterizing the voltage and the PRC shapes. (a) Model piecewise linear voltage (thick) and (b) phase response curve, PRC (thick) shapes employed in the current study. The voltage time course gives one time parameter (*W/T*, normalized spike width parameter), and three amplitude parameters, V_p , V_{th} , and V_m , which can be cast in terms of a_1 , a_2 , and a_3 . The ratio a_3/a_2 will be used as a useful parameter in the bifurcation diagrams. The PRC, Z(t) gives just one time parameter, the PRC skewness, A, and one amplitude parameter B which is the maximum delay. The maximum advancement C(> 0) can be used to normalize B. The thin overlaid curves are the model curves of the standard Hodgkin-Huxley equations with an applied current of 10μ A/cm². The model can be fit with the parameters: A/T = 0.567, W/T = 0.075, B/C = -0.5, and $a_3/a_2 = 0.2234$. These are the only four independent parameters that the stability boundaries of synchrony and antisynchrony depend on. (c) Comparison of the interaction function and (d) the growth function computed from the HH model (thin) and the piecewise linear model (thick). The piecewise model predicted the stability of the synchrony (slope of *G* at spike time difference 0) and antisynchrony (slope of *G* at spike time difference 0) and antisynchrony (slope of *G* at spike time difference 0).

(A) Determining eigenvalues for synchronous state:



(B) Determining eigenvalues for antisynchronous state:



Figure 2.

Segmenting the parameter space and finding the stability. (A) Left: (W, A) space for studying synchrony. Right: The arrangement of Z(t) and V(t) for determining the stability of synchrony. Cases (a), (b), (c), and (d) depict the parameter regimes that have different expressions for the eigenvalue and thus different stability criteria. The destabilizing segments of Z(t) and V(t) are gray-shaded in the plots for type-1 and type-2 PRCs in each of the four cases. The six eigenvalue segments $_{1a}$, ..., $_{6a}$ (and likewise $_{1b}$, etc.) together contribute to the total eigenvalue. (B) Left: (W, A) space for studying antisynchrony. Right: Illustration of the arrangement of Z(t) and V(t) for determining the stability of antisynchrony in four out of seventeen regimes. As in (A), the shaded portions of the segments contribute to instability. Parameters for a few models and experiments are marked in the (W, A) planes: Hodgkin-Huxley (HH) model depicted in Fig. 1, Morris-Lecar model (ML) at an applied current of 0.11 μ A/cm², Erisir et al.'s model at low (E-1) and high (E-2) frequencies (discussed in Fig. 12), and Mancill et al.'s experimental recordings at low (M-1) and high (M-2) frequencies (see Fig. 12).



Figure 3.

When spike width is zero, large skewness in type-1 PRCs could (1) make antisynchronous state stable and (2) cause bistability between synchronous and antisynchronous states. (a) Voltage time course from Eq. 7 at W/T = 0. (b) Z(t) from Eq. 14 when B/C = 0. Eigenvalue for the synchronous state (c) and the antisynchronous state (d) as the PRC skewness is increased. (T = 1, C = 1, $a_3 = 24$ mV, = 1.) (e) Numerical bifurcation diagram showing stable (solid lines) and unstable (dashed lines) phase-locked states with skewness. Synchronous state (phase-locked state at T/2) acquires stability for large skewness. Other phase-locked states exist at large skewness, but are unstable. (f) Stable and unstable regions along skewness.

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Figure 4.

When spike width is zero, large skewness in type-2 PRCs can (1) destabilize synchronous state, (2) still cause bistability between synchronous and antisynchronous states, and (3) destabilize both synchronous and antisynchronous states. (a) Voltage time course from Eq. 7 at W/T = 0. (b) PRC profiles from Eq. 14 when B/C = -0.5. The eigenvalue and the different components that make up the eigenvalue which determine the stability of synchronous (c) and antisynchronous (d) states. Bifurcation diagram (e) showing stable (solid curves) and unstable (dashed curves) phaselocked states as the skewness is increased. Different stable regimes are marked pictorially in (f).

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Figure 5.

Stability diagram and its verification in the absence of spike width. (a) Stability regions in (A/T, B/C) plane for zero spike width. (At zero spike width a_3/a_2 does not affect the stability boundaries.) The diagram does not include the edge effects at A = 0. Synchrony is stable for all type-1 PRCs, and for type-2 PRCs if the type-parameter B/C > 1. The antisynchrony is mostly confined to large skewness, but is also possible for very large positive B/C with small skewness. The circled numbers mark parameter values which are used to compute numerically the growth function $[G(\phi)]$ from the voltage and PRC profiles. (b,c,d) The growth functions computed from the Z(t) and V(t) profiles for the parameters marked in (a).

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Figure 6.

Effect of non-zero spike width on type-1 PRC neurons illustrated when B/C = 0 and W/T = 0.15. For this choice, antisynchrony rather than synchrony could become stable for very small skewness. (a) Voltage time course from Eq. 7. (b) Z(t) from Eq. 14 when B/C = 0. The eigenvalue (thick curves) and their components (thin curves) that determine the stability of synchrony (c) and antisynchrony (d) are plotted as the skewness is increased. $_{3a}$ is the result of spike downstroke and causes the synchrony to become unstable. The sharp upstroke contributes to $_{4a}$ that stabilizes the antisynchrony, but $_{5a}$ and $_{6a}$ which are the result of the spike downstroke cause instability of antisynchronous state as the skewness is increased. (e) One-parameter bifurcation diagram showing the stable (solid curves), and unstable (dashed curves) phase-locked solutions. (f) Stable synchrony and antisynchrony are pictorially depicted as skewness is increased. The white space holds other stable phase-locked solutions as seen in (e). $a_3/a_2 = 0.2234$.



Figure 7.

Effect of non-zero spike width on type-2 PRC neurons illustrated when B/C = -0.5 and W/T = 0.15. For this choice, antisynchrony could become stable in two ranges: at small and large skewness levels. Boundaries of synchrony are moderately sensitive to decreasing B/C. (a) Voltage time course from Eq. 7. (b) Z(t) from Eq. 14 when B/C = -0.5. Total eigenvalue (thick curve) and its components (thin curves) that determine the stability of synchrony (c) and antisynchrony (d) are shown as a function of skewness. (e) One-parameter bifurcation diagram showing stable (solid curves) and unstable (dashed curves) phase-locked solutions as a function of A/T. (f) The stability regions are shown pictorially as a function of skewness. $a_3/a_2 = 0.2234$.



Figure 8.

At moderate skewness (here A/T = 0.2 which is less than that of the HH model) the parameter regime where synchronous state is stable expands to larger values of W/T. The antisynchronous state is not accessible for small W/T. The eigenvalue components (thin curves) and the total eigenvalue (thick curve) that determine the stability of the antisynchronous state as W/T is increased are shown in (a) for a type-1 PRC (at B/C = 0.2). The stability diagram in (W/T, a_3/a_2) plane is plotted in (b). The interaction and growth functions for a parameter point that supports only other phase-locked states are shown in (c), and a one-parameter bifurcation diagram is shown (d) at $a_3/a_2 = 0.2234$. Similar to (b) and (d), the results obtained for a type-2 PRC (B/C = -0.25) are shown in (e) and (f). In (d) and (f) solid lines are stable branches, and dashed unstable.



Figure 9.

Large skewness (A/T = 0.6 here) can make the antisynchronous state accessible for a range of W/T values starting at zero. Such regime is thinner in type-1 than in type-2 PRCs. (a) Stability regions in $(W/T, a_3/a_2)$ space for B/C = 0.2, 0, -0.25. The curves $_a$ and $_b$ are the boundaries for synchrony. The curves $_d$ and $_e$ are the boundaries for the antisynchrony. (b) One-parameter bifurcation diagram showing stable (solid) and unstable (dashed) states as a function of W/T at $a_3/a_2 = 0.22$ that shows bistability of synchronous (phase-locked state at 0) and antisynchronous state (phase-locked state at T/2) at small W/T. (c) The eigenvalue components (thin curves) and the total eigenvalue (thick curve) that determine the stability of antisynchronous state as a function of W/T at $a_3/a_2 = 0.22$. (d) Growth functions at $a_3/a_2 =$ 0.22 at a few values of W/T depicting how antisynchronous state becomes unstable at large W/T.



Figure 10.

Exploring all the PRC parameter space: Stability regions of both synchrony and antisynchrony in the PRC skewness vs. its type parameter space at W/T = 0.02 (a), 0.05 (b), 0.15 (c), and 0.3 (d) when $a_3/a_2 = 0.2234$. The HH model discussed in Fig. 1 (with $I_{app} = 10\mu A/cm^2$ resulting in W/T = 0.075, B/C = -0.5 and A/T = 0.567) lies in a stability diagram that is nearly identical to (b) in the bistability region above the curve $_c$ and slightly to the right of $_d$. The unmarked white space to the right of the vertical dashed line is the forbidden parameter space by the condition in Eq. 15. But the white space regions to the left of the vertical dashed line that are interspersed between synchronous and antisynchronous states hold other non-zero phase-locked states. While a number of models display a wide range of PRC skewness levels, the type parameter (B/C) for many neuronal models is above -1.



Figure 11.

Exploring the spike width and the PRC type parameters: Stability of the synchronous and antisynchronous states at A/T = 0.25 (a, c, e), and 0.6 (b, d, f) in (B/C, W/T) plane. The voltage profile for panels in each column is illustrated at the top. Panels (a) and (b) depict the effect of skewness at very small spike threshold (i.e. the case of tall spike). Panels (c) and (d) are for the HH model parameter of $a_3/a_2 = 0.2234$ that is depicted in Fig. 1. The panels (e) and (f) are for very high spike threshold (i.e. the case of a short spike). The white space holds other non-zero phase-locked states. While synchronous state may occur for small W/T, the occurrence of antisynchronous state at either small or large W/T depends on the level of PRC skewness.



Figure 12.

Demonstrating piecewise linear formulation for Erisir et al. (Erisir et al., 1999) model (a-f) and Mancilla et al. (Mancilla et al., 2007) experiments (g-i). (a-f) The voltage, PRC, and the resultant growth functions computed from the original models are shown as thin lines, and the corresponding computations with PWL approximation are shown in thick lines. (g-i) Mancilla et al.'s neocortical recordings for the voltage and the PRC and the resultant growth functions are shown at two different frequencies: open circles at low frequency, and filled circles at high frequency. (Data was kindly provided by Jaime G. Mancilla, and the data displayed is the average of multiple trials). The PWL approximation for the experimental voltage and PRC traces and the resultant growth functions predicted stability of synchrony and instability of antisynchrony agreeing with those computed experimentally.