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Effects of heterogeneity in synaptic conductance between weakly coupled identical neurons

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Abstract

A significant degree of heterogeneity in synaptic conductance is present in neuron to neuron connections. We study the dynamics of weakly coupled pairs of neurons with heterogeneities in synaptic conductance using Wang-Buzsaki and Hodgkin-Huxley model neurons which have Type I and Type II excitability, respectively. This type of heterogeneity breaks a symmetry in the bifurcation diagrams of equilibrium phase difference versus the synaptic rate constant when compared to the identical case. For weakly coupled neurons coupled with identical values of synaptic conductance a phase locked solution exists for all values of the synaptic rate constant, α . In particular, in-phase and anti-phase solutions are guaranteed to exist for all α . Heterogeneity in synaptic conductance results in regions where no phase locked solution exists and the general loss of the ubiquitous in-phase and anti-phase solutions of the identically coupled case. We explain these results through examination of interaction functions using the weak coupling approximation and an in depth analysis of the underlying multiple cusp bifurcation structure of the systems of coupled neurons.

Keywords

Synchrony; Weak coupling; Heterogeneity

1 Introduction

There has been a great deal of research developing a theory of weakly coupled neural oscillators. The studies have typically looked at identically coupled neurons [1-5]. Some have considered heterogeneous neurons, particularly with heterogeneities in the external, applied current [6,7]. In vivo and in vitro, significant heterogeneities in cellular properties exist [8]. Furthermore, in dynamic clamp experiments coupling two real, biological neurons or a biological neuron and a model neuron, heterogeneity is typically observed in the synaptic conductances [9]. [10] studied the effects of heterogeneous synaptic coupling on clustering in small networks, but the mutual coupling between any pair of neurons in their study was identical.

We present a detailed analysis of the effects of heterogeneous synaptic coupling between a pair of mutually coupled, identical neurons. We have chosen Hodgkin-Huxley and Wang-

Buzsaki model neurons for our study. The Hodgkin-Huxley neuron has Type II excitability and the Wang-Buzsaki Type I. The classification of Type I excitability is typically given to a neuron that enters the oscillating regime of parameter space with a zero frequency and Type II classification is typically given when a neuron begins spiking with a non-zero frequency [11,12]. In Type I neuron models the system passes through a saddle-node on an invariant circle bifurcation when moving from the resting to spiking state. For type II neurons the system passes through either a sub-critical or super-critical Andronov-Hopf bifurcation or a saddle-node off an invariant circle bifurcation during this transition [13]. It is also observed that Type I neurons have phase gradients which are almost entirely positive while Type II neurons have phase gradients which have both positive and negative regions (Fig. 1). Phase gradients show the intrinsic ways that neurons react to small perturbations. The generalized properties of phase gradients lead to generalized synchronization properties of coupled neurons still based off the classification of the individual neuron's excitability.

We model synaptic coupling between the neurons using alpha functions. We study both excitatory and inhibitory coupling for both models. The basic synchronization properties are determined by both the excitability of the neurons and the type of coupling between them.

We offer two types of analysis to explain the observed behavior. Using a phase reduction and weak coupling approximation we examine the effect heterogeneity in synaptic strength has on the interaction functions. Following this explanation we show the underlying structure of the bifurcations in the systems. The analysis of the interaction functions provides a quantitative explanation for the observed behavior, but the analysis of the bifurcation structure yields a fundamental explanation for the dynamics observed. This bifurcation structure had previously not been analyzed and explains both the identical and heterogeneous cases. Ultimately we show that the multiple pitchfork bifurcations observed for the case of identical coupling are special, symmetric cases of a more general multiple cusp bifurcation structure.

2 Weak Coupling Approximation

A weak coupling approximation can be made when an oscillator with a strongly attracting limit cycle is perturbed in a way that only advances or delays the phase of the oscillator, but the state point hardly changes from its location on the unperturbed orbit. These advances or delays in phase from the coupling can add up and result in significant deviations from the phase of the uncoupled case [14]. This situation is simplified by moving to a phase description through a variable change with each point $\mathbf{X}$ on the limit cycle described by a single phase variable $\Phi(\mathbf{X})$ [14,15]. In the case of the Hodgkin-Huxley model $\mathbf{X} = (V, m, n, h)$. The phase variable on the limit cycle increases uniformly in time

$$\frac{d\Phi}{dt} = \omega. \quad (1)$$

For a coupled pair of neurons where the coupling comes as a small perturbation to only the voltage balance equation

$$\frac{d\Phi_i}{dt} = \omega_i + \frac{\partial \Phi_i}{\partial V_i} I_{syn,i}(\Phi_i, \Phi_j). \quad (2)$$

For the Hodgkin-Huxley model the phase gradient (Fig. 1(a)) $\frac{\partial \Phi_i}{\partial V_i}$ is calculated both numerically according to the method described in [1] and using XPP [16]. Both methods

yield similar results. For the Wang-Buzsaki model the phase gradient was calculated using XPP (Fig. 1(b)). To first order, $I_{syn,i}$ can be evaluated on the unperturbed trajectories

$I_{syn,i}(\Phi_i, \Phi_j) = g_{syn,i} (V_i(\Phi_i) - E_{syn}) \sum_{spikes} F_c(\Phi_j - t_{spike})$. $F_c(\Phi_j - t_{spike})$ is the coupling function. The values chosen for E_{syn} are -77 mV (inhibitory) and 35 mV (excitatory) for the Hodgkin-Huxley Model and -90 mV (inhibitory) and 0 mV (excitatory) for the Wang-Buzsaki Model. The excitatory value of E_{syn} for the Hodgkin-Huxley model was chosen as an intermediate value between the two more physiological values of $E_{syn} = 0$ mV or $E_{syn} = E_{Na}$; however the results remain qualitatively the same in this region [1]. In this study we couple the neurons through alpha functions:

$$F_c(\Phi_j - t_{spike}) = \alpha^2 (\Phi_j - t_{spike}) \exp(-\alpha (\Phi_j - t_{spike})). \quad (3)$$

We define $\Phi = \Phi_1 - \Phi_2$ as the phase difference between the two neurons yielding:

$$\frac{d\Phi}{dt} = H_1(\Phi) - H_2(-\Phi) = G(\Phi). \quad (4)$$

If the coupling is weak, we calculate the interaction function $H_i(\Phi)$ by averaging over one period:

$$H_i(\Phi) = \int_0^T \frac{\partial \Phi_i}{\partial V_i} I_{syn}(\Phi_i, \Phi_j) dt. \quad (5)$$

The zeros of $G(\Phi)$ are the equilibrium points of the system. For identical neurons with identical coupling $G(\Phi)$ is the odd part of $H_i(\Phi) = H_j(\Phi)$. This paper deals with the case of identical neurons coupled heterogeneously. The interaction function depends linearly on $g_{syn,i}$, so heterogeneities in synaptic coupling result in heterogeneous linear scalings of $H_i(\Phi)$.

We study the Hodgkin-Huxley and Wang Buzsaki models. For the model details see the appendix. The Hodgkin-Huxley model has Type II excitability and the Wang-Buzsaki model has Type I. We study both the excitatory and inhibitory coupling cases.

2.1 The effects of heterogeneity in synaptic conductance on the calculation of $G(\Phi)$

In the previous section we described how the zeros of Eq. 4 are the fixed points of equilibrium phase difference for the system. When the coupling is identical the system is guaranteed to have zeros at $\Phi = 0, 0.5$ and 1 , representing the in-phase and anti-phase solutions (Fig. 2(a)). They can either be stable or unstable fixed points, depending on the slope of $G(\Phi)$ at the zero crossing. For the identical case $G(\Phi)$ is the odd part of the $H(\Phi)$ and the periodicity of $H(\Phi)$ guarantees $G(\Phi)$ will be zero at $F = 0$ and 1 . $F = 0.5$ is the axis about which $H(\Phi)$ is flipped so $G(\Phi = 0.5) = 0$ always. It is also possible to have other intermediate values of phase difference for fixed points with identical coupling, but these are always in addition to $\Phi = 0, 0.5$ and 1 . In the case of identical neurons coupled with heterogeneous values of synaptic conductance, in-phase and anti-phase are in general not solutions (Fig. 2(b)). In the weak coupling approximation heterogeneous values of g_{syn} result in differences in scaling of $H(\Phi)$ for the respective neurons. Graphically the differences between the identical and heterogeneous cases are easily seen by noting how the intersections of $H_1(\Phi)$ and $H_2(-\Phi)$ change with heterogeneity. These intersections are the fixed points of the system. Heterogeneous values of synaptic conductance also can cause the

appearance of regions of α where no fixed points exist. If the heterogeneous, linear scalings by $g_{syn,i}$ result in $H_1(\Phi)$ never intersecting $H_2(-\Phi)$ then $G(\Phi)$ will have no zeros over the entire period (Fig. 2(c)-(d)). When examining $G(\Phi)$ for different amounts of heterogeneity but the same value of α the effects are seen as a smooth "sliding" of the zeros of the function and thereby the fixed points for the system (Fig. 3). We see how even a slight amount of heterogeneity in synaptic coupling removes the ubiquitous in-phase and anti-phase solutions.

The details about fixed points of the phase difference of any one value of the synaptic rate constant, α , can be found by examining $G(\Phi)$. We will next analyze the full bifurcation diagrams of equilibrium phase difference versus the synaptic rate constant which are created by tracking the zeros of $G(\Phi)$ while α is changed and noting the sign of the slope of $G(\Phi)$ at the zero crossings to mark the stability of the fixed points.

2.2 Hodgkin-Huxley

We study both excitatory and inhibitory coupled, identical Hodgkin-Huxley neurons with heterogeneous values of g_{syn} . We observe the introduction of heterogeneity in synaptic conductance to result in the general loss of in-phase and anti-phase synchronous solutions (Fig. 4). As we make α small the heterogeneous cases produce a near anti-phase solution, but this arises as a gradual change from the near in-phase solution which occurs for large values of α . A continuous branch of solutions connects the near in-phase and near anti-phase solutions for the heterogeneously coupled cases. We observe the analogous result for the inhibitory coupled cases (Fig. 4(b)). In the inhibitory coupled cases we see another qualitative change when compared to the identical case; one that we did not observe in the excitatory case. Our results show a region of α where no phase locked solutions exist. When

$\frac{g_{syn,1}}{g_{syn,2}} = 1/3$ the region of no phase locked solution is $0.198 \leq \alpha \leq 0.342$. When $\frac{g_{syn,1}}{g_{syn,2}} = 0.1$ the region of no phase locked solution is $0.112 \leq \alpha \leq 0.382$. The predictions for the identical case show phase locking for all values of α .

We observe an interesting similarity between the bifurcation diagrams of the excitatory and inhibitory cases. The diagrams are qualitatively symmetric under an exchange of stabilities. The symmetry is not perfect, but we observe it at all values of heterogeneity and nearly all values of α .

2.3 Wang-Buzsaki

For pairs of weakly coupled Wang-Buzsaki neurons we observe that they have a greater sensitivity to heterogeneity in synaptic conductance than Hodgkin-Huxley neurons (Fig. 5). Both the excitatory and inhibitory cases have regions of α where no phase locked solution exists. For the Hodgkin-Huxley excitatory coupling case, at least one stable phase-locked solution exists over the entire parameter space studied. However, for Wang-Buzsaki neurons

with excitatory coupling, when $\frac{g_{syn,1}}{g_{syn,2}} = 0.1$ we see no phase locked solutions over the range of α we studied. As with the Hodgkin-Huxley results, we observe a general loss of in-phase and anti-phase synchronous solutions at all values of heterogeneity studied.

A surprising observation we make is that there is also a symmetry between the bifurcation diagrams of the Hodgkin-Huxley neurons compared with the Wang-Buzsaki neurons. This symmetry is quite striking for the identical cases. The excitatory (inhibitory) coupled Wang-Buzsaki bifurcation diagram is qualitatively very similar to the inhibitory (excitatory) coupled Hodgkin-Huxley case. Since this is true, there exists a symmetry under the exchange of stabilities between the identically, excitatory coupled cases of the Wang-Buzsaki and Hodgkin-Huxley neurons as well as the inhibitory cases. In fact, all 4 identical

cases are largely comprised of a triple pitchfork bifurcation structure with different criticalities. From this symmetry we conclude that it is not enough to only identify the type of coupling when stating that for slow enough synapses inhibition not excitation leads to in-phase synchrony [2]. We see now that the type of neuron must also be given to make this type of prediction. Although further investigation must be made into this topic, we believe that the symmetries we see between the Wang-Buzsaki and Hodgkin-Huxley bifurcation diagrams exist between Type I and Type II neurons in general.

3 Bifurcation Analysis

In a one dimensional system

$$\frac{d\Phi}{dt} = G(\Phi, \alpha) \quad (6)$$

a saddle-node bifurcation occurs at Φ_b when $G(\Phi_b, \alpha) = 0$, $\frac{dG(\Phi_b, \alpha)}{d\Phi} = 0$, $\frac{dG(\Phi_b, \alpha)}{d\alpha} \neq 0$ and $\frac{d^2G(\Phi_b, \alpha)}{d\Phi^2} \neq 0$ [17]. If the second derivative is also zero at the bifurcation point then the system is at a cusp bifurcation. The cusp bifurcation is a codimension 2 bifurcation and occurs when two branches of saddle-node bifurcations meet. The pitchfork bifurcation which appears multiple times in the identical coupling case is a special, symmetric case of the cusp bifurcation.

The pitchfork bifurcation is a codimension 2 bifurcation indicating that there are more details in the dynamics of the system than can be observed by changing any single parameter. In this study we are varying two parameters, the synaptic rate constant a and the

heterogeneity in synaptic conductance $h = \frac{g_{syn,1}}{g_{syn,2}}$.

We have shown only results for $h \leq 1$ thus far. Because the neurons are identical there is still a symmetry present in our system. The bifurcation diagram of any value of h is a reflection about the $\Phi = 0.5$ axis of the bifurcation diagram for $1/h$ (Fig. 6). In order to understand the cusp bifurcation we now examine both $h < 1$ and $h > 1$ to track both branches of saddle-node bifurcations which coalesce as a cusp bifurcation.

Plotting both branches of the saddle-node points (one branch for $h \leq 1$ and the second for $h \geq 1$), they intersect at the point in phase space where the pitchfork bifurcation occurred ($h = 1$) (Fig. 7). This provides a qualitative description of the role of heterogeneity in the bifurcation structure, the viewer need not be concerned with the exact value of heterogeneity but more importantly the direction on each branch which heterogeneity is increasing and decreasing. The different bifurcation diagrams observed for individual values of h (Fig. 4, 5) occur because the branches of saddle-node points are crossed at distinct locations (Fig. 8) in the phase space (h, α) . The special case where $h = 1$ passes, symmetrically through all the cusp points of the system. Any value of $h \neq 1$ will not intersect any cusp point, and will intersect branches of saddle-node points individually.

In all four of the cases with identical coupling we study there is a similar bifurcation structure, all having three pitchfork bifurcations (Fig. 4, 5). The pitchfork bifurcations occur at values of $\Phi = 0.5$, 1 or 0, and 0.5 again as α is increased. When the coupling is identical varying α passes the system through the different cusp points in a symmetric way with respect to the branches of saddle-node points which converge at the cusp, producing the series of pitchfork bifurcations observed. When there are heterogeneities in g_{syn} varying α

no longer moves the system over the cusp points and the two branches of saddle-node points can be observed separately by varying heterogeneity. By tracking the branches of saddle-node points and noting their intersections we show the more general form of the cusp bifurcations in our systems. This bifurcation diagram enables consideration of both the identically and heterogeneously coupled cases.

The most significant change to the dynamics that we observe with heterogeneity in synaptic coupling is the loss of any phase locked solution in some regions of parameter space. For the Wang-Buzsaki model these regions come as a result of the cusp points being very close together. Usually a pitchfork bifurcation will split into a saddle node bifurcation and a branch of fixed points for any given value of h . Because of the close proximity the branch of fixed points from one cusp bifurcation intersects the branch of fixed points from the second cusp yielding another saddle-node bifurcation. For a given value of h , this produces a region of parameter space between the saddle-node points where no fixed point exists. The inhibitory coupled Hodgkin-Huxley case has another mechanism leading to a region of parameter space with no fixed points. In this case two saddle node bifurcations intersect at a transcritical bifurcation (Fig. 9). The transcritical bifurcation is different from a saddle-node or pitchfork bifurcations as fixed points are neither created nor destroyed [18]. They can be thought of as a point where branches of solutions exchange stability. If we think of the actual transcritical bifurcation as an 'X' where two curves cross, varying h splits the 'X' either horizontally ($h = 2/3$ curve in Fig. 9) or vertically ($h = 1/3$ curve in Fig. 9).

We previously discussed the observed symmetry between the bifurcation diagrams for the identically coupled cases of the Hodgkin-Huxley and Wang-Buzsaki systems. This symmetry is much less apparent when heterogeneity is introduced. Future studies of the interactions between the various cusp surfaces is needed to understand why we see the symmetry is largely lost when heterogeneity is introduced.

4 Numerical Results

We sought verification of the results of the weak coupling approximation by solving the full equations numerically in the Matlab environment. Our algorithm began by solving the system of equations with Matlab's ode45 integrator, a Runge-Kutta integrator. The equations were integrated until a voltage threshold (10 mV) was reached by one of the neurons. The corresponding α -function was then initialized and integration was restarted at that point in phase space. This process continued until a stable orbit was achieved, the phase difference was then numerically calculated. Our criteria for having found a stable point was that the phase difference (Φ) changed by less than a factor of 10^{-10} , period to period. In this way we verified the stable fixed points of equilibrium phase difference predicted by the weak coupling approximation. Far more complex methods would need to be employed to verify the weak coupling approximation predictions of the unstable states. Verification of the regions where the weak coupling approximation predicted no phase-locking to occur was accomplished using the same method as described to verify the stable fixed points. No predictions about the behaviour of the system in these regions was made other than that of no phase-locking. We allowed the algorithm to run for many periods. We used a two part criteria for concluding that there was no stable, phase-locked state: the phase difference changed by more than a factor of 10^{-10} from period to period and the phase difference was not steadily decreasing from period to period. We chose different example parameter sets in these regions and examined the voltage traces to get some qualitative idea of the behaviour (Fig. 10). We observed regions where there was no phase-locking but there were distinct regions of parameter space where the period to period change in phase difference always slowed down. In the regions where the change in phase slowed, the trajectory is passing through the "ghost of the attractor" from a fixed point that exists nearby in parameter space

[13]. A fixed point is where the rate of change of phase difference in time is zero. In a region of parameter space near the fixed point, the rate of change is going to be small. We do not suggest that all the behaviour in regions with no phase-locking is captured by this description, this is meant to be an example. A more complete, future study should be undertaken to understand the dynamics.

In general we found qualitative agreement between the weak coupling approximation and the results from the full numerical simulations (Fig. 11, 12, 13, 14). The predicted locations of bifurcations are somewhat different when compared to the weak coupling approximation results. However, qualitatively the numerical results and the weak coupling results are quite similar. When heterogeneity is introduced, the loss of in-phase and anti-phase solutions and the regions of no phase locking occurs in the same manner in the numerical simulations as predicted by the weak coupling approximation.

The numerical simulations were calculated with $g_{syn} \leq 0.1 \frac{mS}{cm^2}$. These values of synaptic conductance remain within the valid region of weak coupling as shown in [1] where network frequency as a function of synaptic conductance predicted by the weak coupling approximation was compared to the frequency observed in full numerical simulations. This range of synaptic conductance also corresponds with the experimentally observed range where the phase response curve depends *linearly* on the synaptic conductance [19].

5 Discussion

We have shown that there are qualitative changes to the dynamics of coupled neurons when heterogeneity in synaptic conductance is present when compared to the identical case. Heterogeneity introduces regions where no phase-locked solutions exist and even a modest amount of heterogeneity results in phase-locked solutions that are neither in-phase nor anti-phase. Surprisingly, there is a general duality to the types of solutions (generally in-phase, generally anti-phase) that exist between the type I excitatory coupled neurons and the type II inhibitory coupled neurons for similar ranges of α and g_{syn} . We show that the ways in which heterogeneity alter the symmetric/homogeneous case are generic to the class of model and coupling and rely upon a multiple cusp mechanism. Finally, these analyses show that heterogeneity introduces regions of parameter space where no phase-locked solution exists, and numerical verification of this phenomena reveals that there is nevertheless a preferred range of phases that are more attractive near where the stable phase-locked solution existed at nearby regions of parameter space.

When considering excitatory coupled type II neurons as α is increased, we observed that the firing order changed. While firing order of the two neurons is interchangeable for identically coupled neurons, the introduction of heterogeneity implicitly includes information about the firing order when using the weak coupling approximation. Bifurcation diagrams for the identically coupled case are symmetric under an exchange of neurons. For this reason every branch of fixed points has a corresponding branch reflected about the anti-phase ($\Phi = 0.5$) axis for the identical case. The symmetry breaking effects to the bifurcation diagrams occur immediately when any heterogeneity is introduced. This loss of symmetry caused by heterogeneous coupling allows an additional prediction, that of firing order, to be made. When heterogeneity in synaptic conductance is present solutions are no longer found as symmetric pairs reflected about the anti-phase axis, only a single solution which specifies a firing order is found. For example, $\Phi(\alpha) = \Phi_1(\alpha) - \Phi_2(\alpha) = 0.1$ is a prediction of nearly in-phase synchrony with neuron 1 is firing at $0.1T$ ms before neuron 2 where T is the period. Since there is no symmetric solution, a phase difference along with a firing order is predicted from the weak coupling approximation. Obviously no multi-period behavior, such

as alternating firing order from one period to the next, will be captured by a straight forward application of this weak coupling technique.

We have performed a similar analysis with weakly coupled Morris-Lecar neurons with both Type I and Type II parameters and inhibitory and excitatory coupling(not shown), and all show the multiple pitchfork bifurcation structure for the case of identical synaptic conductance. This is a special case of a multiple cusp bifurcation [20]. We speculate that multiple cusp bifurcations maybe the fundamental bifurcation structure of the dynamics of weakly coupled neurons. A second, related observation we have made is that qualitatively there is little difference between excitatory (inhibitory) coupled Hodgkin-Huxley neurons and inhibitory (excitatory) coupled Wang-Buzsaki neurons for the identical case. For the cases that are qualitatively different, the difference is simply a swapping of the stable and unstable fixed points. For the heterogeneous cases, the Type I Wang-Buzsaki neuron system shows a greater sensitivity to heterogeneity in conductance strength then the Type II Hodgkin-Huxley neuron system. We suspect that this sensitivity, particularly the region of no-phase locking, occurs because of the close proximity of the cusp bifurcations on the a axis (Fig. 8(a)).

This analysis was motivated by studies of interacting regions of the brain stem underlying respiration that possess intrinsic excitatory coupling, such as the pre-Botzinger Complex [21,22] and the parafacial Respiratory Group [23]. Activity within each region is largely synchronous, but the details of this synchronization and the impact of this synchrony on how the regions interact is a future mode of investigation. We intend to apply these methods to studies of synchrony within inter-neuron and motor neuron populations in these regions which underly the generation of respiratory rhythms (e.g. synchrony in hypoglossal pools) [24].

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Appendix

Appendix A: Hodgkin-Huxley Model

The equations for the Hodgkin-Huxley Model are:

$$C_m \frac{dV}{dt} = -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) + I_{stim} \quad (A1)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \quad (A2)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (A3)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \quad (\text{A4})$$

$$\alpha_n = 0.01 \frac{V+55}{1 - \exp \frac{-(V+55)}{10}} \quad (\text{A5})$$

$$\beta_n = 0.125 \exp \frac{-(V+65)}{80} \quad (\text{A6})$$

$$\alpha_m = 0.1 \frac{V+40}{1 - \exp \frac{-(V+40)}{10}} \quad (\text{A7})$$

$$\beta_m = 4.0 \exp \frac{-(V+65)}{18} \quad (\text{A8})$$

$$\alpha_h = 0.07 \exp \frac{-(V+65)}{20} \quad (\text{A9})$$

$$\beta_h = \frac{1}{1 - \exp \frac{-(V+35)}{10}} \quad (\text{A10})$$

$$\text{With } g_{Na} = 120 \frac{mS}{cm^2}, g_K = 36 \frac{mS}{cm^2}, g_L = 0.3 \frac{mS}{cm^2}, E_{Na} = 50 \text{ mV}, E_K = -77 \text{ mV}, V_L = -54.6 \text{ mV}, \\ C_m = 1 \frac{\mu F}{cm^2}, I_{stim} = 10 \frac{\mu A}{cm^2}$$

Appendix B: Wang-Buzsaki Model

The equations for the Wang-Buzsaki Model are:

$$C_m \frac{dV}{dt} = -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) + I_{stim} \quad (\text{B1})$$

$$\frac{dn}{dt} = \phi (\alpha_n (1 - n) - \beta_n n) \quad (\text{B2})$$

$$\frac{dh}{dt} = \phi(\alpha_h(1-h) - \beta_h h) \quad (\text{B3})$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \quad (\text{B4})$$

$$\alpha_m = \frac{-0.1(V+35)}{\exp - 0.1(V+35) - 1} \quad (\text{B5})$$

$$\beta_m = 4 \exp - (V+60) / 18 \quad (\text{B6})$$

$$\alpha_h = 0.07 \exp - (V+58) / 20 \quad (\text{B7})$$

$$\beta_h = \frac{1}{\exp - 0.1(V+28) + 1} \quad (\text{B8})$$

$$\alpha_n = \frac{-0.1(V+34)}{\exp - 0.1(V+34) - 1} \quad (\text{B9})$$

$$\beta_n = 0.125 \exp - (V+44) / 80 \quad (\text{B10})$$

$$\text{With } g_{Na} = 35 \frac{mS}{cm^2}, g_K = 9 \frac{mS}{cm^2}, g_L = 0.1 \frac{mS}{cm^2}, E_{Na} = 55 \text{ mV}, E_K = -90 \text{ mV}, V_L = -65 \text{ mV}, \\ C_m = 1 \frac{\mu F}{cm^2}, I_{stim} = 10 \frac{\mu A}{cm^2}$$

References

1. Hansel D, Mato G, Meunier C. Phase dynamics for weakly coupled hodgekin-huxley neurons. *Europhys. Lett.* 1993; 23:367–372.
2. Van Vreeswijk C, Abbott L, Ermentrout GB. When inhibition not excitation synchronizes neural firing. *J. Comput. Neurosci.* 1994; 1:313–321. [PubMed: 8792237]
3. Hansel D, Mato G, Meunier C. Synchrony in excitatory neural networks. *Neural Computation.* 1995; 7:307–337. [PubMed: 8974733]
4. Terman D, Kopell N, Bose A. Dynamics of two mutually coupled slow inhibitory neurons. *Physica D.* 1998; 117:241–275.
5. Bose A, Kopell N, Terman D. Almost-synchronous solutions for mutually coupled excitatory neurons. *Physica D.* 2000:69–94.

6. Hansel D, Mato G. Patterns of synchrony in a heterogeneous Hodgkin-Huxley neural network with weak coupling. *Physica A*. 1993;662–669.
7. White J, Chow C, Ritt J, Soto-Tervino C, Kopell N. Synchronization and oscillatory dynamics in heterogeneous, mutually inhibited neurons. *J. Comput. Neurosci.* 1998; 5:5–16. [PubMed: 9580271]
8. Song S, Sjöström PJ, Reigl M, Nelson S, Chklovskii D. Highly nonrandom features of synaptic connectivity in local cortical circuits. *PLoS Biology*. 2005; 3(3):e68. [PubMed: 15737062]
9. Sieling F, Canavier C, Prinz A. Predictions of phase-locking in excitatory hybrid networks: excitation does not promote phase-locking in pattern-generating networks as reliably as inhibition. *Journal of Neurophysiology*. 2009; 102:69–84. [PubMed: 19357337]
10. Li Y, Wang Y, Miura R. Clustering in small networks of excitatory neurons with heterogeneous coupling strengths. *J. Comput. Neurosci.* 2003; 14:139–159. [PubMed: 12567014]
11. Prescott S, Koninck Y, Sejnowski T. Mechanisms of action potential initiation. *PLoS Biology*. 2008; 4(10)
12. Rinzel, J.; Ermentrout, GB. *Methods in neuronal modeling*. MIT Press; 1989. p. 135-169.
13. Izhikevich, E. *Dynamical Systems in Neuroscience*. The MIT Press; 2007.
14. Kuramoto, Y. *Chemical Oscillations, Waves and Turbulence*. Springer; New York: 1984.
15. Ermentrout GB, Kopell N. Oscillator death in systems of coupled neural oscillators. *SIAM J. Appl. Math.* 1990; 50(1):125–146.
16. Ermentrout GB. *Simulating, Analyzing, and Animating Dynamical systems: A guide to XPPAUT for Researchers and Students*. SIAM. 2002
17. Izhikevich, E.; Hoppensteadt, F. *Weakly connected neural networks*. Springer; 1997.
18. Crawford JD. Introduction to bifurcation theory. *Rev. Mod. Phys.* 1991; 63(4):991–1037.
19. Preyer A, Butera RJ. Neuronal oscillators in *Aplysia californica* that demonstrate weak coupling *In Vitro*. *Physical Review Letters*. 2005; 95:138103. [PubMed: 16197185]
20. Izhikevich E. Multiple cusp bifurcations. *Neural Networks*. 1998; 11:495–508. [PubMed: 12662825]
21. Smith JC, Ellenberger HH, Ballanyi K, Richter DW, Feldman JL. Pre-bötzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science*. 1991; 254:726–729. [PubMed: 1683005]
22. Smith JC, Koizumi H, Butera RJ. Bursters increase the robustness of rhythm generation in an excitatory network. *Journal of Neurophysiology*. 2007; 97:1515–1526. [PubMed: 17167061]
23. Mellen N, Janczewski W, Bocchiaro C, Feldman JL. Opioid induced quantal slowing reveals dual networks for respiratory rhythm generation. *Neuron*. 2003; 37:821–826. [PubMed: 12628172]
24. Bou-Flores C, Berger AJ. Gap junctions and inhibitory synapses modulate inspiratory motoneuron synchronization. *Journal of Neurophysiology*. 2001; 85:1543–1551. [PubMed: 11287478]

Fig. 1.

(a) The numerically calculated phase gradient for the Hodgkin-Huxley neuron. (Subplot) Voltage trajectory as a function of Φ . (b) The phase gradient for the Wang-Buzsaki neuron calculated using the adjoint procedure in XPP. (Subplot) Voltage trajectory as a function of Φ .

Fig. 2.

(a) $G(\Phi)$ with identical values of g_{syn} and excitatory coupling and $\alpha = 0.1 \text{ ms}^{-1}$. In this case $H_1(\Phi) = H_2(\Phi)$ so we need only calculate $H(\Phi)$ once. $G(\Phi) = H(\Phi) - H(-\Phi)$ which is simply the ‘odd part’ of $H(\Phi)$. For identical coupling at least 3 solutions are guaranteed, $\Phi = 0, 0.5$ and 1 . (b) $G(\Phi)$ calculated from $H_1(\Phi)$ and $H_2(-\Phi)$ with heterogeneous synaptic

conductance, $g_{syn,1} = 0.1 \frac{\text{mS}}{\text{cm}^2}$ and $g_{syn,2} = 0.3 \frac{\text{mS}}{\text{cm}^2}$, and excitatory coupling with $\alpha = 0.1 \text{ ms}^{-1}$. When the coupling is not identical in-phase and anti-phase are no longer general solutions. The solutions occur when $H_1(\Phi) = H_2(-\Phi)$. (c) $G(\Phi)$ with identical values of g_{syn} and excitatory coupling with $\alpha = 0.28 \text{ ms}^{-1}$. (d) $G(\Phi)$ calculated from $H_1(\Phi)$ and $H_2(-\Phi)$ with

heterogeneous synaptic conductance, $g_{syn,1} = 0.1 \frac{\text{mS}}{\text{cm}^2}$ and $g_{syn,2} = 0.3 \frac{\text{mS}}{\text{cm}^2}$, and excitatory coupling with $\alpha = 0.28 \text{ ms}^{-1}$. The heterogeneous values of synaptic conductance scale $H_1(\Phi)$ and $H_2(\Phi)$ so that $G(\Phi)$ does not equal zero for the entire period, predicting no fixed points for equilibrium phase at these parameters.

Fig. 3. The effect of various amounts of heterogeneity on the function $G(\Phi)$ with $\alpha = 0.1 \text{ ms}^{-1}$, calculated for the Hodgkin-Huxley model with excitatory coupling.

Fig. 4.

(a) Bifurcation diagram of equilibrium phase difference versus the synaptic rate constant for excitatory coupled Hodgkin-Huxley neurons. As heterogeneity is introduced immediately it is seen that the in-phase solution ($\Phi = 0, 1$) only occurs for a single value of α and the anti-phase solution ($\Phi = 0.5$) is completely lost. For larger amounts of heterogeneity the pitchfork bifurcation at about $\alpha = 0.12 \text{ ms}^{-1}$ has completely disappeared and its remnants can only be seen as changes in curvature in stable line in that region. (b) Inhibitory coupled Hodgkin-Huxley neurons.

Fig. 5.

(a) Bifurcation diagram of equilibrium phase difference versus the synaptic rate constant for excitatory coupled Wang-Buzsaki neurons, calculated using the weak coupling approximation. (b) Bifurcation diagram of equilibrium phase difference versus the synaptic rate constant for inhibitory coupled Wang-Buzsaki neurons, calculated using the weak coupling approximation. The color coding is consistent with Fig. 4. Solid lines indicate stable solutions and dashed lines unstable solutions.

Fig. 6.

There is a symmetry between heterogeneities of h and $1/h$. (a) Bifurcation diagram of excitatory coupled Wang-Buzsaki neurons with $h \leq 1$. (b) Bifurcation diagram of excitatory coupled Wang-Buzsaki neurons with $h \geq 1$. Both figures have the same color coding referring to heterogeneity consistent with the rest of the paper. The black triangles indicate saddle-node points, with the vertex that points in the x -direction indicating the direction of increasing heterogeneity.

Fig. 7.

Bifurcation diagram of excitatory coupled Wang-Buzsaki neurons with several branches of saddle-node bifurcation points highlighted. We have combined the cases with $h > 1$ and $h < 1$ on a single plot to illustrate the interaction of the branches of saddle-node points. The black triangles numerically track the branches of saddle-node points as h is varied. Heterogeneity is being varied to create the saddle-node branches and the vertex of the triangles point in the direction of increasing heterogeneity. In this plot the black curve is the identically coupled case, blue curves are both the $h = 2/3$ and $h = 3/2$ cases and green curves are both the $h = 1/3$ and $h = 3/1$ cases.

Fig. 8.

Bifurcation points plotted as a function of α and h for the same system as Fig. 7. The dotted lines show two possible paths, the first path is when $h = 1$ or the identical case. When $h = 1$ the system passes symmetrically through all the cusp points as α is varied. When only plotting α vs. Φ this would appear as a series of pitchfork bifurcations. The other path is an example heterogeneous path where neither cusp point is encountered, a series of saddle-node bifurcations occur as α is varied.

Fig. 9.

Transcritical bifurcation leading to the loss of phase locking for the inhibitory coupled Hodgkin-Huxley case. The black triangles are tracking the two branches of saddle-node bifurcations which intersect at $\alpha \approx 0.28 \text{ ms}^{-1}$. The horizontal vertexes of the triangles indicate the direction of increasing heterogeneity. We plotted additional curves for values of heterogeneity with $1.1 \leq g_{\text{syn},1}/g_{\text{syn},2} \leq 1.2$ (dark gray). These additional curves show more clearly how the two saddle-node bifurcations converge and then split as a stable and unstable pair of trajectories.

Fig. 10.

Panels (a) and (b) show the phase difference, Φ , vs. time for inhibitory coupled Hodgkin-Huxley neurons with $\alpha = 0.25 \text{ ms}^{-1}$. (a) In-phase synchrony with identical values of synaptic

conductance, $g_{syn,1} = g_{syn,2} = 0.1 \frac{mS}{cm^2}$ (b) A region of phase space where no phase locking

occurs with heterogeneous values of synaptic conductance, $g_{syn,1} = 0.01 \frac{mS}{cm^2}$ and

$g_{syn,2} = 0.1 \frac{mS}{cm^2}$. (c) Voltage trace for same coupling as panel (a) showing in-phase synchrony. (d) Voltage trace for the same coupling as panel (b) showing no phase locking. In panels (c) and (d) solid lines are the voltage traces for neuron 1 and dashed lines are the voltage traces for neuron 2.

Fig. 11. Bifurcation diagrams of equilibrium phase difference versus synaptic rate constant for excitatory coupled Hodgkin-Huxley neurons calculated (a) using the weak coupling approximation and (b) by solving the full set of equations numerically. Only stable fixed points are plotted.

Fig. 12.

Bifurcation diagrams of equilibrium phase difference versus synaptic rate constant for inhibitory coupled Hodgkin-Huxley neurons calculated (a) using the weak coupling approximation and (b) by solving the full set of equations numerically. Only stable fixed points are plotted.

Fig. 13. Bifurcation diagrams of equilibrium phase difference versus synaptic rate constant for excitatory coupled Wang-Buzsaki neurons calculated (a) using the weak coupling approximation and (b) by solving the full set of equations numerically. Only stable fixed points are plotted.

Fig. 14.

Bifurcation diagrams of equilibrium phase difference versus synaptic rate constant for inhibitory coupled Wang-Buzsaki neurons calculated (a) using the weak coupling approximation and (b) by solving the full set of equations numerically. Only stable fixed points are plotted.