Phase locking states between Fast Spiking interneurons coupled by electrical and chemical synapses

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Abstract. The synchronisation properties of a pair of Fast Spiking interneurons coupled by electrical and inhibitory synapses are investigated by using, for each of them, a two variables biophysical model. In the weak coupling condition the phase locking regimes of the network were studied theoretically. Regions in the parameter space of the duration of the synaptic current τ and stimulation current I_E exist, where bistable regimes of antiphase and inphase activity arise. Increasing both τ and I_E favours the emergence of synchrony in the network. It is also shown that the presence of the electrical coupling in a pair of inhibitory FS cells promote their synchronous discharge.

1 Introduction

The local circuits of GABAergig interneurons traditionally have been considered as modulators and regulators of principal cells. However, recent experimental findings suggest they have also an important role in detecting and promoting synchronous activity [1, 2, 3]. The relevance of these results, within the framework of the neural information processing problem, comes also from the experimental evidences that the synchronous firing of cortical neurons is a new way of neural information coding [4]. On the other side abnormal levels of synchronization among neurons are observed in a pathological condition like epilepsy [5].

A specific and open question is to understand how the coupling features determine the emergence of synchronous firing in a neural population. Experiments have shown that in neocortex networks of GABAergic inhibitory interneurons are able to generate synchronous frequency discharges in the gamma frequency range (30 – 80 Hz). Besides, both experimental and theoretical evidences relate the synchronous discharge of a population of inhibitory interneurons to some features of their coupling, like the duration and intensity of the synaptic current [6, 7, 8, 9, 10, 11].

It is well known that the neocortex contains several groups of interneurons, differing in the gross morphology, neurochemistry, the inputs they receive and their targets [12]. Recently two classes of neocortical inhibitory interneurons – Fast Spiking (FS) and Low Threshold Spiking cells (LTS) – were found to interact by electrical synapses too [1, 2]. A peculiarity of these two type of cells is that electrical synapses are prominent among members of the same group [2]. Moreover FS cells exhibit, among them, a higher level of inhibitory connections, while a lower level is found for the LTS group [1, 2]. Instead, electrical synapses between members of the two interneurons classes were found to be rare. Also, paired cell recordings of interneurons of the same group revealed synchronous discharge activities. These findings suggest that FS and LTS cells could be separated in two independent networks having different roles for the neural information coding. The importance of electrical synapses for the emergence of synchronous firing came also from recent experimental findings: that the impairing of electrical synapses between cortical interneurons disrupts the synchronous oscillations in the gamma frequency band [13, 14].

Coming to the epilepsy, it was recently suggested that electrical synapses can have a role in seizure generation [15]. How a large neural population gets such abnormal synchronization levels is still not clearly understood. Inhibitory interneurons play a critical role in modulating the discharges of targeted neurons. Thus, it was hypothesized that networks of inhibitory interneurons interacting also by electrical synapses could be critically involved in the generation of some types of seizures [15].

These results raise important questions concerning the role played by both the chemical and electrical synapses for generating coherent firing activity in networks of inhibitory interneurons. In this paper we investigate the synchronization properties of a pair of FS interneurons coupled by inhibitory and electrical synapses by using a biophysical model for each cell; in particular how the coupling features (like synaptic current duration, and chemical and electrical coupling intensities) influence and determine the emergence of a coherent activity in the network.

2 Model description and analysis method

FS interneurons do not adapt: their average firing frequency after 600 msec is ~ 97% of the initial one. The other basic properties of these cells are: a) the action potentials are shorter than those of pyramidal neurons and exhibit afterhyperpolarization; b) the mean decay time constant of the synaptic currents is ~10.5 *msec*; c) the average conductance values for electrical and inhibitory synapses are G_{El} = 0.66 *nS* and G_{Sy} = 1.7 *nS*, respectively (Galarreta and Hestrin, 1999; Gibson et al., 1999). In a previous paper [11] a H-H like model for each FS cell well accounting for those features was used; here, in order to simplify the computation, a reduction of this model will be employed. Let us begin by reporting the original model of FS cell:

$$C\frac{dV}{dt} = I_E - g_{Na}m^3h(V-V_{Na}) - g_K n^4(V-V_K) - g_L(V-V_L);$$
$$\frac{dx}{dt} = (x_\infty - x)/\tau_x; \qquad x_\infty = \alpha_x/(\alpha_x+\beta_x),\ \tau_x = 1/(\alpha_x+\beta_x),\ (x \equiv m,h,n), \tag{1a}$$

where $C = 1\mu F/cm^2$ and I_E is the external stimulation current, and

$$\alpha_m = 4.2\exp[(V+34.5)/11.57] \qquad \beta_m = 4.2\exp[-(V+34.5)/27]$$
$$\alpha_h = 0.09\exp[-(V+45)/33] \qquad \beta_h = 0.09\exp[(V+45)/12.2] \tag{1b}$$
$$\alpha_n = 0.3\exp[(V+35)/10.67] \qquad \beta_n = 0.3\exp[-(V+35)/42.68].$$

The maximal specific conductances and the reversal potentials are, respectively: $g_{Na} = 100\,mS/cm^2$, $g_K = 40\,mS/cm^2$, $g_L = 0.1\,mS/cm^2$ and $V_{Na} = 55\ mV$, $V_K = -90\ mV$ and $V_L = -68\ mV$. Now assuming that the fast gating variable *m* is set to its equilibrium value leads to a reduction of the previous model to one described by three equations. Moreover, in simulations of the complete model, we saw that the sum of the gating variables *n* and *h* is approximately constant. Then, after estimating the average value of this last quantity, we further decreased by one the number of equation by setting *h* = 0.927-*n*. So the final two dimensional model of each FS cell reads

$$C\frac{dV}{dt} = I_E - g_{Na}m_\infty^3(0.927-n)(V-V_{Na}) - g_K n^4(V-V_K) - g_L(V-V_L);$$
$$\frac{dn}{dt} = (n_\infty - n)/\tau_n. \tag{2}$$

This model retains many of the dynamical properties characterizing the complete one. For instance, the transition from rest to periodic firing was shown in [11] to occur by a saddle-node bifurcation. Consequently, the excitability property is that of class I neural model (i.e. the periodic solution originates with arbitrarily low frequency values). Now, for the reduced model, we first determine the stationary points and their stability as the parameter I_E is varied: the results are shown on the left panel of figure 1. There is a critical value of the stimulation current, $I^* \cong 0.254\ \mu A/cm^2$, above which the model generates periodic firing of arbitrarily low frequency. For $I_E < I^*$ there are three fixed points which can be characterized by inspection of the eigenvalues of the Jacobian matrix, *M*: two of them are unstable (a source and a saddle) and stable the remaining one (a sink). Moreover all eingenvalues are real. Let *Tr M* and *det M* denote the trace and the determinant of *M*, respectively. Then for a fixed value of I_E the sink and the saddle are located in the region V < -40 mV and the sink is a stable node (*Tr M* < 0, *det M* >0). The source falls in the region V > -40 mV and it is an unstable node (*Tr M* > 0, *det M* >0). As I_E approaches I^* from the left the stable node and the saddle stationary points get closer up to collide (for $I_E = I^*$) and disappear. For $I_E > I^*$ only one fixed point remains (the unstable node) and a periodic orbit or limit cycle appears. The periodic orbit arises through a saddle node bifurcation and the corresponding frequency is plotted vs. I_E in the right panel of figure 1, showing that also the reduced model is class I. Close to the bifurcation point the discharge frequency scales as $\nu = C\sqrt{I_E - I^*}$, where *C* is a constant, and the corresponding fit for $I_E > I^*$ is reported in the same panel (C = 42).

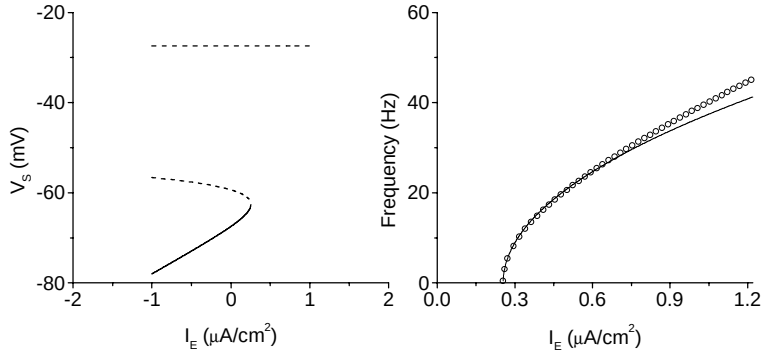

Figure 1. Left panel: stationary values of membrane voltage in the reduced model against stimulation current; stable (solid line) unstable (dashed line). Right panel: discharge frequency of the reduced model obtained by simulations (open circles) and theoretically (solid line).

The above results imply that the reduced model preserves the main qualitative and quantitative features of the complete one and so it will be used here to model the FS interneuron. The main advantage of this choice is a significant reduction of the computational effort weight.

The electrical and chemical synapses were modelled as follows. The postsynaptic current for the GABAergic synapse is given by: $I_{Sy}(t) = g_{Sy} S_{\mathrm{Pre}}(t)(V(t) - V_{\mathrm{Rev}})$, where g_{Sy} is the maximal specific conductance for the inhibitory coupling and V_{Rev}=-75 mV is the reversal potential for the neurotransmitter. The fraction of receptors in the open state on the postsynaptic neuron $S_{\mathrm{Pre}}(t)$ obeys the first order kinetics $\dot{S}_{\mathrm{Pre}} = \alpha T(V_{\mathrm{Pre}})(1 - S_{\mathrm{Pre}}) - \tau^{-1} S_{\mathrm{Pre}}$, where α is the channel opening rate, $T(V_{\mathrm{Pre}}) = 1/(1 + e^{-V_{\mathrm{Pre}}})$ represents the dependence of transmitter concentration on presynaptic voltage and τ is the time constant of the synaptic current. To derive physiological values of g_{Sy} we assume a soma radius R_{Soma} = 7.5 μm and use the experimental value G_{Sy} = 1.7 *nS*, whence the estimate $g_{Sy} = G_{Sy} / 4\pi R_{\mathrm{Soma}}^2 \cong 0.24$ mS/cm^2 follows. The electrical synapse generates the current $I_{El}(t) = g_{El}(V(t) - V_{\mathrm{Pre}})$, where g_{El} is the maximal specific conductance. Now, from G_{El} = 0.66 *nS*, we obtain $g_{El} = G_{El} / 4\pi R_{\mathrm{Soma}}^2 \cong 0.1$ mS/cm^2. In the simulations we used values for both maximal conductances lower than or equal to, the estimated ones.

Now we will outline the analytical tools that will be used, by following [16], to study the phase locking states in a pair of coupled FS cells. Let a system of two coupled identical nonlinear oscillators be described by

$$\dot{\vec{X}}_i = \vec{F}(\vec{X}_i) + \varepsilon \vec{G}_i(\vec{X}_i, \vec{X}_j), \quad \vec{X}_i \in R^n, \; i = 1,2, \; i \neq j \qquad (3)$$

where $\vec{G}_i$ and ε > 0 are, respectively, the coupling function and intensity. It is assumed that the values of control parameters are such that each unperturbed oscillator, $\dot{\vec{X}}_i = \vec{F}(\vec{X}_i)$, has a stable limit cycle $\vec{X}_0(t)$ of period *T*. Then for ε << 1, the solutions of equation (3) can be represented as $\vec{X}(t) = \vec{X}_0(\theta_i) + O_i(\varepsilon)$, where θ_i $(i = 1,2)$ are the phase of the two oscillators and obey the equations

$$\begin{aligned} \dot{\theta}_1 &= 1 + \varepsilon H_1(\theta_2 - \theta_1), \\ \dot{\theta}_2 &= 1 + \varepsilon H_2(\theta_1 - \theta_2), \end{aligned} \qquad (4)$$

H_i (i = 1,2) being *T*-periodic functions. The functions H_1, H_2 can be computed explicitly and, by setting ϕ = θ_2 - θ_1, they are defined as follows $H_1 = T^{-1} \int_0^T \vec{Y}(t) \cdot \vec{G}_1(\vec{X}_0(t), \vec{X}_0(t + \phi)) dt$ and similarly for H_2 with ϕ replaced

by -ϕ. The function $\vec{Y}(t) \in R^n$ is *T*- periodic and satisfies the adjoint equation $\dot{\vec{Y}} = -J^T(\vec{X}_0(t))\vec{Y}$, being J^T the transpose of the Jacobian matrix; moreover it is normalized ($\int_0^T \vec{Y}(t) \cdot \dot{\vec{X}}_0(t)dt = 1$). When the coupling is symmetric then $H_2(\phi) = H_1(-\phi)$ and the equation defining the time evolution of the phase difference between the two oscillators reads $\dot{\phi} = \varepsilon(H_1(-\phi) - H_1(\phi)) = \varepsilon D(\phi)$. Let ϕ_S be a fixed point of the last equation, then it will be stable or unstable according to $\dot{D}(\phi_S) < 0$ ($\dot{D}(\phi_S) > 0$), respectively. Now suppose that equation 3 represent the system of two FS cells coupled by inhibitory and electrical synapses and let $s_0(t)$ be determined from $\dot{S}_{\mathrm{Pre}} = \alpha T(V_{\mathrm{Pre}})(1 - S_{\mathrm{Pre}}) - \tau^{-1} S_{\mathrm{Pre}}$ when $V_{Pre}(t) = V_0(t)$ represents the voltage component of the unperturbed limit cycle solution of equation 2. Then for the inhibitory synapse it is $H_1(\phi) = T^{-1}\int_0^T Y_1(t)\, s_0(t+\phi)(V_{rev} - V_0(t))dt$ (with $\varepsilon = g_{Sy}$). Similarly, for the electrical synapse it is $H_1(\phi) = T^{-1}\int_0^T Y_1(t)\,(V_0(t+\phi) - V_0(t))dt$. In both cases $Y_1(t)$ is the first component of the solution of the adjoint equation and $H_2(\phi) = H_1(-\phi)$; when inhibitory and electrical synapses are present $H_1(\phi)$ is the sum of the corresponding terms. It is easy to show that for both electrical and inhibitory synapses $\phi = 0$ and $\phi = T/2$ are always fixed points of $\dot{\phi} = \varepsilon D(\phi)$.

3 Results

The left panel of figure 2 shows the stationary values of the phase difference (stable and unstable) between the two FS cells against the time constant of the inhibitory synapses when the electrical coupling is set off. For τ values lower than τ_1 = 5.68 *msec* there are only stable antyphase states, while there is a region of τ values characterized by a bistable regime (synchronous and antisynchronous). For a fixed I_E let $\tau^*(I_E)$ be the highest τ value where bistability occurs. We can see from figure 2 that in each region $\tau_1 < \tau < \tau^*(I_E)$ there are unstable phase locking states that bifurcate from $\tau^*(I_E)$. The bifurcation occurring at $\tau^*(I_E)$ is a subcritical pitchfork bifurcation. These unstable phase locking states behave as separatrices between inphase and antiphase regimes.

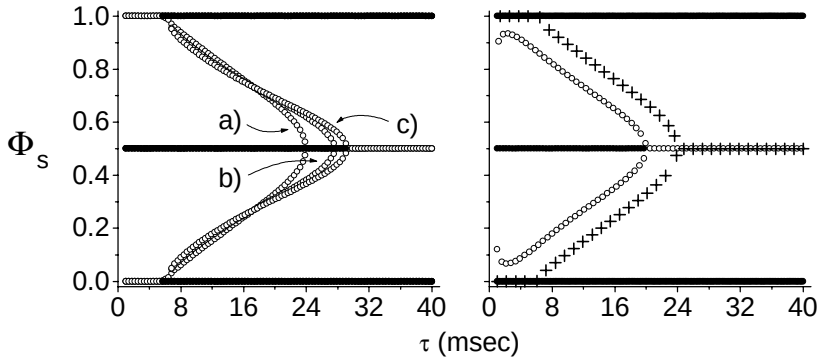

Figure 2. Stationary values of the phase difference against the time constant of the inhibitory synapses. Left panel: g_{El} =0 and a) I_E =0.5 $\mu A/cm^2$, b) I_E =0.8 $\mu A/cm^2$, c) I_E =1 $\mu A/cm^2$. Right panel: g_{El} / g_{Sy} = 0.1 and I_E =0.8 $\mu A/cm^2$; the crosses represent the unstable states corresponding to the bifurcation curve b) in the left panel. For both panels the open (solid) circles denote unstable (stable) states.

This is equivalent to say that they are the states in phase space separating the basins of attraction of the synchronous and antisynchronous states. Thus, for arbitrary initial conditions and for a fixed value of τ, their position in figure 2 can be used to estimate the probability of occurrence of a dynamical regime of complete synchrony between the two FS cells. For instance, for τ values just to the right of τ_1, these unstable state are closer to the synchronous ones and this means that for arbitrary initial conditions the probability to get an antisynchronous regime is about unity, while for τ values approaching $\tau^*(I_E)$ this probability takes values close to 0. By the way, let us remark that $\tau^*(I_E)$ is a monotonically increasing function of I_E. For $\tau > \tau^*(I_E)$ the bistable behaviour disappears (the antiphase states become unstable), as only stable synchronous states remain.

The results obtained in the presence of both type of synapse are reported in the right panel of figure 2 and, for comparison, the unstable states corresponding to the bifurcation curve b) in the left panel. When the electrical coupling is on the asynchronous unstable branches of stationary phase differences are located to the left of those corresponding to inhibitory coupling alone (crosses). The bifurcation occurs at $\tau^*(I_E) \sim 20$ *msec*, moreover synchronous discharge of the cells can also occurs for low values of τ, but the probability is low. For a fixed value of τ, in the region of bistability of both curves, the probability of occurrence of synchronous states is higher when electrical coupling is on. We found that for values of g_{El} / g_{Sy} larger than 0.1 there is a systematic reduction of the size of the bistability region; for instance when $g_{El} / g_{Sy} = 0.4$ only stable synchronous states occur. Simulations of a network of reciprocally coupled cells are in good agreement with the previous results (data not shown). In conclusion these results suggest that the presence of electrical coupling in a pair of inhibitorily coupled FS cells promotes synchrony.

Next we study how the phase locking regimes of two FS cells coupled by electrical and chemical synapses depend on the stimulation current. Figure 3 shows the bifurcation diagrams for two different values of the ratio g_{El} / g_{Sy}. For a given value of the previous ratio there is a critical value I^* of the stimulation current from which two unstable phase locking states originate through a subcritical pitchfork bifurcation. These results are similar to those obtained when the bifurcation parameter was τ, with $g_{El} = 0$. As the intensity of the electrical coupling increases (and so does the ratio g_{El} / g_{Sy}), the position of the bifurcation point I^* moves to the left, until it disappears completely. For $I_E < I^*$ there is a bistable behaviour where stable antiphase and inphase states coexist, while for $I_E > I^*$ there is only stable synchrony. An interesting result that comes out from these bifurcation diagrams is that synchrony is promoted by increasing the stimulation current. To test this conclusion we performed some numerical simulations of a pair of FS cells each described by equation 2 and coupled by electrical and chemical synapses. The results obtained are consistent with these theoretical predictions (data not shown).

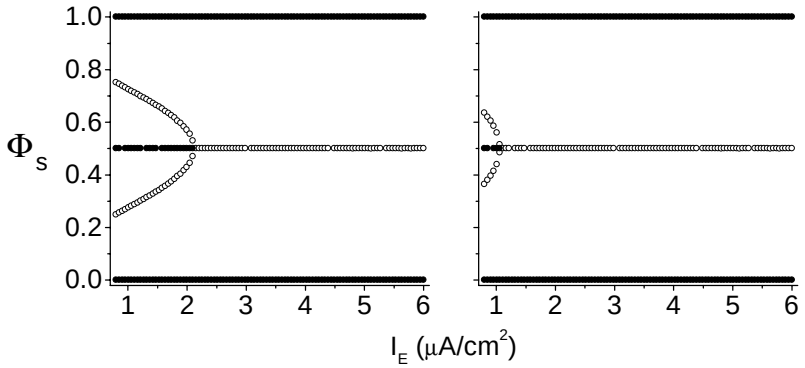

Figure 3. Stationary values of phase difference against the stimulation current duration I_E when both electrical and inhibitory synapses are on. Left panel: $g_{El} / g_{Sy} = 0.1$. Right panel: $g_{El} / g_{Sy} = 0.2$. For both panels is $\tau = 8$ *msec* and the open (solid) circles denotes unstable (stable) states.

4 Conclusions

As shown by recent experimental and theoretical studies, networks of inhibitory interneurons can synchronize their firing discharges. The coupling parameters seems to be critical for the emergence of synchronous activity. In this report we used a two variable biophysical model of the FS cells obtained by reduction derived from a four variable one used elsewhere. We show that the reduced model mimics accurately all the basic properties of the complete one. Then, by using the experimental findings concerning pairs of FS cells, we modelled satisfactorily the electrical and chemical coupling to build a network of two identical reciprocally connected interneurons. In the weak coupling condition the dynamical behaviour of the network is reduced to a pair of equations on the invariant torus. We investigated the steady state solutions of the nonlinear equation describing the time evolution of the phase difference between two units. In the case the cells interact only by inhibitory synapses we found that there exist regions of τ values where bistable dynamical regimes occur (antiphase and inphase). The increase of the synaptic current duration τ favours the

emergence of synchrony in the network. When the electrical coupling is introduced the τ - region where stable synchronous states occur, widens.
Then we studied how the phase locking regimes of coupled pairs depend on the stimulation current in the presence of both kinds of synapse. Surprisingly we found bifurcation diagrams looking like the ones obtained when only the inhibitory coupling is active. It was shown that the increasing the intensity of the stimulation current leads to the emergence of synchronous activity in the pair of FS cells.
In conclusion, we showed that the introduction of electrical coupling in a pair of coupled FS cells promotes the synchrony of their discharges.

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