CLUSTERING AND SYNCHRONIZATION IN A ONE-DIMENSIONAL MODEL FOR THE CA3 REGION OF THE HIPPOCAMPUS

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The behavior of a system of coupled ordinary differential equations is studied in order to characterize the CA3 region of the hippocampus. Clustering and synchronization behavior in a one-dimensional array of cells modeled by a modified Morris–Lecar model is analyzed in terms of a time delay included in the model. The random formation of phase dislocations whose number increases with the time delay seems to be responsible for complex spatiotemporal patterns that have been observed. Alterations to the transmission time between cells have been simulated by adding some noise to the system.

Keywords: Chaos; neural networks; synchronization; clusters.

1. Introduction

Theoretical analysis and computational modeling are important tools for characterizing what nervous systems do, determining how they function, and understanding why they operate in a particular way. Different models try to characterize the complex behavior of the brain. The brain is essentially a system of interacting neural networks. The study of many brain regions has shown patterns of oscillatory activity in these neural networks, for example, neurons of the cerebral cortex are characterized by a marked tendency to participate in coherent oscillatory behavior of several frequencies [Freeman, 1992].

The mechanisms to generate oscillatory activity are twofold: The oscillations can arise as an intrinsic property of individual neurons, or alternatively, from the synaptic interactions between neurons that would not oscillate otherwise. We examine oscillatory phenomena of the latter kind, that is, oscillations arise from the interplay of excitatory and inhibitory feedback provided by synaptic connections. Such pairs of interacting populations of neurons, excitatory and inhibitory, will receive the name of neural oscillators. The neural networks, which are formed for these neural oscillators, display a rich variety of oscillatory and complex phenomena which will result in different dynamical properties of the network and consequently in different functions.

Clustering and synchronization behavior have devoted a great deal of interest in the past years as such studies could be used to understand

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complex biological dynamical networks [Kaneko, 1994]. In neural systems, Walter Freeman has noticed the importance of the change of the degree of coherence of neural activities [Freeman & Skarda, 1985; Freeman, 1994]. In the epilepsy, an ensemble of neurons exhibits a large spike due to the coherent oscillation of neural activities. Epileptic seizures are thought to originate from an area of focal abnormality in the brain, usually in the hippocampal portion of the temporal lobe [Jeffreys, 1990; Jensen & Yaari, 1997]. The abnormal firing patterns exhibited by this focal region spread throughout surrounding normal brain tissue synchronizing all neurons to the same stationary or periodic behavior. In this sense, it has been suggested that a healthy brain should display chaotic activity [Wilson & Cowan, 1972; Freeman, 1994; Kelso & Fuchs, 1995] whereas lower-dimensional chaos or periodicity is an indicator of disease [Belair et al., 1995]. From this perspective, the epileptic seizure with its massive rhythmic depolarization may be considered as the expression of pathological corrective mechanisms.

The large body of evidence available today supports the hypothesis that correlated firing between neurons may be functionally relevant in the brain, for the binding of distributed neurons into coherently active assemblies, and the dynamic selection of their responses for joint processing [Singer & Gray, 1995; Engel et al., 1997]. Moreover, synchronization with prevalence of the gamma frequency range is well known to occur in the olfactory bulb and entorhinal cortex of various species, where these phenomena have been related to the integration of odor information [Freeman, 1988]. In the auditory cortex, synchronized gamma oscillations have been described by several groups [Galambos et al., 1981; Eggermont, 1992]. In the somatosensory system, interactions in this frequency range have also recently been described in the awake monkey [Murthy & Fetz, 1992]. Similar evidence is available for the motor system where neural synchronization has been discovered in monkeys [Murthy & Fetz, 1992] and in humans [Kristeva-Feige et al., 1993]. These findings can be related to the dynamics of the so-called central pattern generators (CPGs), i.e. networks of coupled oscillators found in the spinal cord of vertebrates and in the nervous system of invertebrates which are involved in the execution of basic motor programs [Grillner et al., 1991].

In the current paper, we use a recently introduced three-variable ordinary differential model [Larter et al., 1999] for the region CA3 of the hippocampus believed to be of importance in the generation of focal, or complex partial, seizures. The variables in this model correspond to membrane potentials for prototypical pyramidal cells and inhibitory interneurons in the CA3 region of the hippocampus, the most likely location of the focus. This model is constituted by local populations of excitatory and inhibitory neurons which have extensive and strong synaptic connections between them. The excitatory cells of the hippocampus correspond to pyramidal cells whose mathematical model was initially proposed by Morris and Lecar in 1981. This model encloses important features of pyramidal cells such as burst morphology, dependence of bursting behavior on the resting potential and summation of spikes among others [Traub & Miles, 1991]. By simplicity, the inhibitory neurons can be simulated by a single equation [Terman & Lee, 1997; Destexhe, 1994]. To simulate the effect of a population of inhibitory interneurons synapsing on the pyramidal cells, Raima Larter and coworkers recently included a third differential equation to the previous Morris–Lecar model to simulate this effect [Larter et al., 1999].

Finally, coupling between cells in a lattice is modeled by a system of N excitatory and inhibitory cells, constituted by N neural oscillators with connections between excitatory cells which mimic chemical synapses [Destexhe, 1994]. This connectivity is defined using the input–output channels of potassium, i.e. in terms of potassium diffusion. Only local connectivity is assumed here, which is closer to the connectivity of cerebral cortical neurons.

The modified Morris–Lecar model includes an effective time delay which accounts for the time each of the cells in the lattice evolves autonomously before coupling to the nearest neighbors. Models of neural networks with time-delayed interactions have been proposed in the past years to account for synchronized oscillations in the cerebral cortex [Singer, 1993]. In this paper, we will study the influence of the time delay on clustering and synchronization behavior on a one-dimensional array. We will show the formation of clusters of synchronized cells separated by phase dislocations. The influence of some tolerance on the parameters of the model is also discussed.
2. Model and Analyzing Tools

The one-dimensional array consists of cells of the modified Morris–Lecar type [Larter et al., 1999] which is constituted by two neurons: excitatory and inhibitory ones. This descriptive model corresponds to the CA3 region in the hippocampus. Then, the dynamic of the network is described by the next set of coupled differential equations

\[
\frac{dV_i}{dt} = -g_{Ca}m_\infty(V_i - 1) - g_K W_i(V_i - V_i^K) - g_L (V_i - V^L) + I - \alpha_{inh} Z_i; \\
\frac{dW_i}{dt} = \frac{\phi(w_\infty - W_i)}{\tau_w}; \\
\frac{dZ_i}{dt} = b(cI + \alpha_{exc} V_i),
\]

with

\[
m_\infty = 0.5 \left[ 1 + \tanh \left( \frac{V_i - v_1}{v_2} \right) \right], \\
w_\infty = 0.5 \left[ 1 + \tanh \left( \frac{V_i - v_3}{v_4} \right) \right], \\
\alpha_{exc} = a_{exc} \left[ 1 + \tanh \left( \frac{V_i - v_5}{v_6} \right) \right], \\
\alpha_{inh} = a_{inh} \left[ 1 + \tanh \left( \frac{Z_i - v_7}{v_6} \right) \right], \\
\tau_w = \cosh^{-1} \left( \frac{V_i - v_3}{2v_4} \right)
\]

where \(V_i\) and \(Z_i\) are the membrane potentials of the pyramidal and inhibitory cells, respectively, while \(W_i\) is a relaxation factor which is essentially the fraction of open potassium channels in the population of pyramidal cells, for the node \(i = 1, \ldots, N\). The third equation corresponds to the effect of inhibitory neurons, while the first two equations, without the last term in the first equation, correspond to the Morris–Lecar model [Morris & Lecar, 1981]. The parameters \(g_{Ca}, g_K\) and \(g_L\) are the conductances for Ca, K and leakage channels, respectively. \(V_i^K\) is the Nernst potential for potassium in node \(i\). \(V^L\) is a leak potential, \(\tau_w\) is a voltage dependent time constant for \(W_i\), \(I\) is the applied current, and \(\phi\) and \(b\) are temperature scaling factors. The parameter \(c\) modifies the current input to the inhibitory neuron. The functions \(w_\infty\) and \(m_\infty\) correspond to the voltage-regulated Ca\(^{2+}\) channels in the cell membrane. The functions \(\alpha_{exc}\) and \(\alpha_{inh}\) are dimensionless parameters, describing the synaptic, either excitatory or inhibitory, strengths.\(^1\)

The parameter \(V_i^K\) encloses the coupling among the oscillators of the network as a function of the average membrane potential of the neighbors, following the equation

\[
V_i^K = \left( \sum_{j=1}^{n} \frac{V_j}{n} \right) - \frac{1}{2}
\]

with \(n = 2\); number of neighbors

\[
\overline{V}_j = \frac{1}{T} \int_{t_{int}/6}^{t_{int}} V_j(t) dt, \quad \text{and} \quad T = t_{int} - t_{int}/6
\]

The parameter \(t_{int}\) is a measure of the speed of communication between nodes, that means, the time during which the node \(i\) is coupled to its neighbors, and it controls both input and output of the potassium. This value can be considered a time delay because this is the time needed to update potassium ion potential which is used in the next iteration.

Equations (1)–(3) were numerically integrated using an explicit Euler method with a time step of 0.05 time units (t.u.) per iteration. Free ends were considered at the boundaries. Random initial conditions for all the variables were assigned to each cell in the array.

The behavior of an isolated oscillator of the network can present simple limit cycles as well as complex periodic oscillations and aperiodic behavior, in our case, with the chosen parameters the time series for the three variables, \(V\), \(W\) and \(Z\), as well as the three-dimensional phase portrait are shown in Fig. 1. Figure 2 shows the bifurcation diagram in which the maxima values of the \(V\) time series are plotted against the bifurcation parameter \(c\), which represents the current strength of input to inhibitory neuron. Note the large variety of states among regions of possible chaotic behavior.

In order to characterize the degree of synchronization between cells of the array we introduced the following space-time averaged quantity

\[
K = \lim_{T \to \infty} \frac{1}{T} \sum_{t=1}^{T} \left( \frac{1}{n(N-1)} \sum_{j=2}^{N} \sum_{i=1}^{n} ||x_j(t) - x_i(t)|| \right)
\]

\(^1\)A more detailed description of all the parameters concerning the modified Morris–Lecar model, Eqs. (1)–(3), can be found in [Larter et al., 1999].
Fig. 1. Temporal evolution of the dynamical variables, \( V, W, Z \) and three-dimensional phase portrait of a single oscillator. Parameter values are \( v_1 = -0.01, v_2 = 0.15, v_3 = 0.0, v_4 = 0.3, v_5 = 0.0, v_6 = 0.6, v_7 = 0.0, V^L = -0.5, V^k = -0.7, g_{Ca} = 1.1, g_K = 2.0, g_L = 0.5, I = 0.3, \alpha_{exc} = 0.5, \phi = 0.7, \alpha_{inh} = 0.5, b = 0.1 \) and \( c = 0.165 \).

Fig. 2. Bifurcation diagram of a single oscillator showing the behavior of the maxima of \( V \) as a function of the bifurcation parameter \( c \). Note that in general, the dynamics is less complex for smaller values of \( c \). Parameters as in Fig. 1.
with \( \mathbf{x} = (V, W, Z) \) and \( \| : \| \) represents the Euclidean distance. This function is positive definite and vanishes when all the cells in the array are globally synchronized. Numerical simulations were run until \( K \) varied less than 5\%. Here \( N \) corresponds to the number of elements of the array and \( n \) represents the neighbors of each cell. An other way to measure the synchronization between cells, most relevant in models of biological excitable media where the distance between spike times is considered to be more interesting than the full synchronization, is in terms of phase synchronization. Recently, in the context of Rössler oscillators we have shown that similar results could be obtained by using \( K \) or the phase synchronization method, so to avoid redundancy we focus here only on the first measure [Lorenzo & Pérez-Muñozuri, 2001].

Nevertheless, we will use, when appropriate, the phase of the signal to analyze the synchronization of a variable of the system, e.g. the membrane potential, \( V_i \). Then, we use the method of analytic signal, where the phase \( \Phi \) is estimated using the Hilbert transform [Dabrowski et al., 2000].

Following previous works, we noticed that the onset of full synchronization is preceded by clustering. In this regime, some of the cells form synchronous clusters, while others may be still nonentrained [Zanette & Mikhailov, 2000]. So, to characterize more precisely the state of the lattice, the number of clusters can be identified through the examination of the distribution of instantaneous pair distances \( d_{ij}(t) \) between elements, which are defined as

\[
d_{ij}(t) = \|x_j(t) - x_i(t)\|.
\]

To measure the extent of clustering two order parameters can be introduced.

\[
r(t) = \frac{1}{N(N-1)} \sum_{i=1}^{N} \sum_{j=1}^{N} \Theta[\delta - d_{ij}(t)],
\]

\[
s(t) = 1 - \frac{1}{N} \sum_{i=1}^{N} \prod_{j=1, j \neq i}^{N} \Theta[d_{ij}(t) - \delta],
\]

where \( \Theta(x) \) is the Heaviside function. The first function, \( r(t) \), is given by the fraction of pairs of elements \( (i, j) \) which are found at time \( t \) separated by a distance \( d_{ij}(t) < \delta \). On the other hand, \( s(t) \), is the fraction of elements \( i \) which at time \( t \) have at least one other element \( j \) located at a distance \( d_{ij} < \delta \). The time-averaged number of clusters will be estimated as [Zanette & Mikhailov, 1998]

\[
M = \lim_{T \to \infty} \frac{1}{T} \int_{0}^{T} \frac{s(t)^2}{r(t)} dt.
\]

3. Results

Figure 3 shows the influence of the parameter \( t_{\text{int}} \) on the spatiotemporal behavior of the system. Two well differentiated behaviors can be observed; (i) the presence of dislocations whose number increases with \( t_{\text{int}} \) (see for example, \( t_{\text{int}} = 10, 20, 30 \)); between two neighboring dislocations, cells oscillate in phase with no signal propagation across the array, and (ii) for certain values of \( t_{\text{int}} \), cells among the dislocations are not synchronized but give rise to signal propagation (\( t_{\text{int}} = 0, 5, 17, 27, 50 \)), which is easily observed by following the signal maxima through the spatiotemporal patterns. In a few words, the number of dislocations increases with \( t_{\text{int}} \) giving rise to a spatiotemporal disordered behavior which periodically becomes ordered to repeat the process again. Dislocations occur randomly in the array, depending its location only on the initial conditions for Eqs. (1)–(3). By choosing a different set of initial conditions the dislocations appear in different places, although in average their number remains approximately the same, increasing as well as \( t_{\text{int}} \) does. By dynamical selection, synchronized cells organize themselves in clusters separated by cells not synchronized with any of the neighboring clusters which we call a phase dislocation. Finally, for \( t_{\text{int}} \to \infty \) cells are no longer connected among them and cells are not synchronized. Next Figs. 4 to 7, try to characterize in more detail the behaviors described above.

For \( t_{\text{int}} = 10 \), Figs. 4(a)–4(h) show a phase portrait mosaic for the behavior of the system. In this, phase diagram points corresponding to the phase of two cells near one of the dislocations shown above are plotted. A phase dislocation takes place at cells \( i = 106 \) and \( i = 107 \) (later this fact will be clearly shown) which are mutually synchronized (red line at 45° shown in panel (e)). To the left of a dislocation, consecutive cells are not synchronized (a) while alternate cells synchronize perfectly (b, c), i.e. even cells synchronize each other as well as odd cells do. On the other hand, to the right of the phase dislocation a similar behavior is observed (f, g), but in this case the behavior of the even (odd) cells commute with the behavior of the odd (even) cells on the left side of the phase dislocation. This is observed in
panel (h) where the phase of cell $i = 86$ is represented as a function of phase of cell $i = 116$ and no synchronization is observed. Moreover, the cells corresponding to the dislocation do not synchronize with the cells outside the phase dislocation (d).

Dislocations are clearly visible in Fig. 5 for two different values of $t_{\text{int}}$ when the time average value of $\Delta \Phi = |\Phi_i - \Phi_{i+1}|$ is plotted for each cell. Note clearly the four phase dislocations, also seen in Fig. 3, for $t_{\text{int}} = 10$, while for $t_{\text{int}} = 17$ cells are

Fig. 3. Spatiotemporal patterns of the neural network activity for different values of $t_{\text{int}}$. Only the variable $V_i$ is shown here with the same color scale for all graphs. The system was iterated 1800 t.u. to allow for the decay of transients. $N = 200$. Rest of parameters as in Fig. 1.
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Fig. 4. Space-time phase portrait mosaic for the behavior of the preceding figure for \( t_{\text{int}} = 10 \). 200 time units are overlaid in each figure and points show the phase of the \( V_i \) variable. Parameters as in Fig. 3.

Fig. 5. Time-average value of the phase difference (calculated through the Hilbert transform) of the \( V_i \) signals for (a) \( t_{\text{int}} = 10 \) and (b) \( t_{\text{int}} = 17 \). Note clearly the phase dislocations shown in panel (a). Parameters as in Fig. 3.
uncorrelated. Figures 6(a)–6(d) show the temporal evolution of three oscillators, \( i = 20, 21, 46 \) with \( i = 46 \) located at one of the phase dislocations for \( t_{\text{int}} = 10 \). Note the different oscillatory behavior of the cell at the dislocation in comparison to the other pair of cells. For \( i = 46 \) the cell oscillates as in Fig. 1 when uncoupled, while the remaining cells oscillate periodically.

The degree of synchronization among the cells of the array was measured and analyzed both with the function \( K \), Eq. (4), and the number of clusters in the array, Eq. (8), as a function of the bifurcation parameter \( t_{\text{int}} \). Obviously, both methods must be related as the number of clusters should increase if the synchronization among cells is poor, i.e. \( K \) attains big values. On the other hand, it is interesting to know for low values of \( K \) the way cells are organized, in terms of cluster formation. In order to test the robustness of the method and since alterations in the transmission time between cells could be accepted to occur in the neuronal field, we have simulated this effect by introducing some noise inherent to the neurons. In this sense, the value of \( t_{\text{int}} \) for each cell within the array was initially chosen randomly between \( (t_{\text{int}}) \pm \text{Tol} \), where \( \text{Tol} \) is some tolerance which was here fixed to 1\%.
Figures 7(a) and 7(b) show the behavior of the function $K$ and the time-averaged number of clusters $M$, as a function of $\langle t_{\text{int}} \rangle$. When no tolerance is considered, $K$ shows an irregular behavior, although several local minima can be observed that correspond to an improvement of the synchronization between cells as it was shown in Fig. 3, for example, for $t_{\text{int}} = 10$. On the other hand, for $\text{Tol} = 1\%$ the complex behavior of the function $K$ has been completely smoothed now and it only shows a minimum for $t_{\text{int}} = 2$. Besides, for $\langle t_{\text{int}} \rangle \to \infty$, in both cases $K \to 0.15$, as nearly all cells become completely unsynchronized, and they are no longer coupled.

The time-averaged number of clusters $M$ [Fig. 7(b)] also shows a similar behavior as that
shown by $K$. Moreover, at the local minima shown by $K$, the number of clusters diminishes to nearly zero since most cells are now synchronized. Local minima occur at some periodicity nearly equal to the oscillation period of a single oscillator ($T \approx 10.3$ t.u.). As well as above for $K$, considering some tolerance the dependence of $M$ as a function of $t_{int}$ is smoothed. For $\langle t_{int} \rangle \rightarrow \infty$, $M$ tends to different constant values depending on the value of the tolerance. In average, the value of $M$ is smaller for the case of Tol = 1% than without tolerance, in fact as we will show later, the disorder increases both temporally and spatially, but the averaging method used to calculate $M$ smoothes the results giving rise to an apparent better synchronization.

By varying the bifurcation parameter $c$, the number of clusters continue to have consecutive abrupt falls [blue stripes in Fig. 8(a)] as the time delay $t_{int}$ increases. In fact, the stripes position is only slightly curved towards higher values of $t_{int}$ as $c$ increases. Note as well, the narrow blue band (small values of $M$, nearly equal to zero) at the left side of the figure, for $t_{int} \rightarrow 0$. On the other hand, for large values of $t_{int}$ the number of clusters $M$ remains constant for all values of $c$ and equal to some intermediate value. The observed oscillation of the number of clusters with $t_{int}$, independently of the local dynamics (controlled by $c$), depends only on the oscillation period of the cells which is approximately 10.3 t.u. Figures 8(b)–8(d) show the temporal evolution of the $V$ variable for the middle cell of the chain. Note that the mean period is rather similar, independently of the different observed dynamics.

The influence of the bifurcation parameter $t_{int}$ on the spatiotemporal behavior of the system when some tolerance is considered (Tol = 1%) is shown in
Fig. 9. Spatiotemporal patterns of the neural network activity for different values of \( t_{\text{int}} \) when some tolerance Tol = 1% is considered. Only the variable \( V_i \) is shown here with the same color scale for all graphs. Parameters as in Fig. 3.

Fig. 9. Clearly, the disorder increases, signal propagation is observed in all directions, and the mean number of clusters remains approximately the same independently of the specific value of \( t_{\text{int}} \). Collapse of fronts propagating in opposite directions is also observed.

4. Conclusions

The behavior of a one-dimensional array of cells described by a modified version of the Morris–Lecar model [Larter et al., 1999] has been analyzed in this paper. This array simulates a network of neurons
where at each node a population of pyramidal cells and inhibitory interneurons, both of which are fed by an external current, is considered. The study has been carried out in terms of the time delay \( t_{\text{int}} \) which accounts for the amount of time that each of the nodes in the array evolves autonomously before a given node undergoes a discrete change of the parameter \( V_{\text{k}}^n \), Eq. (3).

As the time delay \( (t_{\text{int}}) \) is increased, random phase dislocations occur at the one-dimensional array which do not evolve on space. The random position of these dislocations depends only on the ray which do not evolve on space. The random phase dislocations occur at the one-dimensional array [Terman & Lee, 1997].

References


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References

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