The engram formation and the global oscillations of CA3

Francesco Ventriglia

Received: 12 March 2008 / Revised: 19 August 2008 / Accepted: 19 August 2008 / Published online: 19 September 2008
© Springer Science+Business Media B.V. 2008

Abstract The investigation on the conditions which cause global population oscillatory activities in neural fields, originated some years ago with reference to a kinetic theory of neural systems, as been further deepened in this paper. In particular, the genesis of sharp waves and of some rhythmic activities, such as theta and gamma rhythms, of the hippocampal CA3 field, behaviorally important for their links to learning and memory, has been analyzed with more details. To this aim, the modeling-computational framework previously devised for the study of activities in large neural fields, has been enhanced in such a way that a greater number of biological features, extended dendritic trees—in particular, could be taken into account. By using that methodology, a two-dimensional model of the entire CA3 field has been described and its activity, as it results from the several external inputs impinging on it, has been simulated. As a consequence of these investigations, some hypotheses have been elaborated about the possible function of global oscillatory activities of neural populations of Hippocampus in the engram formation.

Keywords Engram formation ·
Global population oscillations · Kinetic model ·
CA3 · Power spectral densities

Introduction

The Hippocampus is a fundamental station in the chain of neural structures along which the neural information flows

in brain, going from the primary (sensorial) cortices to superior areas and back. The information reaching the Hippocampus from polymodal cortical areas through Entorhinal Cortex (EC) is processed in subsequent steps by its sub-fields: Dentate Gyrus (DG) (or Fascia Dentata), hippocampus proper [hilus, CA3, CA1] and subicular complex, and is returned to the same polymodal regions of cortex via the EC. In fact, several lines of evidence remark the great importance of this structure for learning and memory in rat, monkey and man (Scoville and Milner 1957; Milner 1972; Mishkin 1982; Squire et al. 1989; Wilson and McNaughton 1993). The modality according which the information is coded within the activities of the neural fields of Hippocampus and the way with which they produce the memory traces, or *engrams*, specifically related to the sensory events of brain, constitute a very elusive problem and no clear elucidation about its nature exists still now.

Some hypotheses on the possible processes governing the production of engrams are presented in this article. They take into account both the sharp waves and the global oscillatory activities of neural populations of Hippocampus as a possible base of engram formation. In fact, the synchronous oscillatory activity constitutes one of the most characteristic aspects of brain activity and is associated closely to fundamental behavioral states. In Hippocampus, rhythmic oscillations in the theta (4–15 Hz) and in the gamma (20–80 Hz) ranges are among the most prominent patterns of activity (Buzsaki and Chrobak 1995) and the neuroscientists believe that both rhythms reflect essential aspects of the hippocampal functions, mainly related to learning and memory (Traub et al. 2003; Cohen and Eichenbaum 1993). It is commonly supposed that activity coming from Medial Septum and entorhinal cortex are needed to induce the theta rhythm in Hippocampus. Vice versa, the hypothesis that the gamma rhythm is generated

F. Ventriglia (✉)
Istituto di Cibernetica “E.Caianiello” del CNR, Via Campi
Flegrei 34, 80078 Pozzuoli (NA), Italy
e-mail: franco@ulisse.cib.na.cnr.it

intrinsically by the network of inhibitory interneurons in Hippocampus is supported by recent experimental and theoretical articles. Both rhythms are present during the exploratory activity in awake animals. Some fast (80–200 Hz) (Draguhn et al. 2000) and ultra-fast (200–500 Hz) (Kandel and Buzsaki 1997) oscillations have been also recorded in the hippocampus (and cortex) of several animals and in man. Also sharp waves were related to learning (Buzsaki 1986; Molter et al. 2007).

The importance of CA3 field in this setting springs from several elements. CA3 is the main source of rhythmic activity in the Hippocampus. It has a pyramidal axonic structure with one of the highest levels of reentry among all the other structures of brain (1.9% of probability of coupling between two pyramidal neurons) (Amaral et al. 1990). At CA3, not only mossy fibers from granular neurons of DG arrive, but also fibers directly from EC (III layer) and from sub-cortical nuclei, among which the most important are Medial Septum (MS) and Diagonal Band, Raphe and Corpus Coeruleus (Vertes 1986). They are linked to attention, to overt behavior, to stress. Also the results of evolutionary studies, assigning to CA3 a progression index of 1.04, assert the necessity to preserve such a structure during the evolution without changes, as a basic one. As a comparison, the progression index of CA1 is 9.65 (West 1990).

We used the CA3 field of the Hippocampus to evaluate the new hypotheses about the global oscillatory activity of neural populations as base of engrams. To this aim, the global reactions of CA3 to its main inputs and the precise spatio-temporal behavior of excitatory and inhibitory waves invading the CA3 field as a consequence of the triggering by such inputs have been carefully investigated.

The kinetic model

The kinetic theory of neural systems, formulated several years ago (Ventriglia 1994, 1974) to describe the activity of large neural fields, has been utilized here for the description of the activity of the CA3 field. The most original aspect of such a theory is the statistical description of the neuronal interaction. In fact, the action potentials traveling along the axonic branches are represented as massless particles with a volume, the *impulses*, having only statistical links to the axonic structure. The impulses move freely in the neural space until they collide with a neuron. The collision can possibly result in the absorption of an impulse by a neuron and, in this circumstance, the membrane potential of the neuron increases or decreases in time according to the excitatory or inhibitory nature of the absorbed impulse. If in its wandering the membrane

potential goes over a characteristic value, i.e. the neuronal threshold, the neuron *fires* a stream of new impulses within the neural field. In general, the impulses are short-range with a span of about 300–400 μm , but the CA3 pyramidal neurons can emit also long-range impulses which can reach distant zones in CA3, also some millimeters far from the emitting neuron. After the firing the neuron goes in a refractoriness state, for a period of time τ . Vice versa, in the event that the subthreshold potential, due to an excessive inhibition, reaches values well under the resting value, the neuron passes in the so called hyperpolarized state, where it remains until the excitation changes sign.

We associate the variables $\mathbf{r}$, $\mathbf{v}$, e and t to position, velocity, subthreshold membrane potential and time, respectively. Since our model of the field CA3 is based on a projection to a two-dimensional surface, both vectors $\mathbf{r}$ and $\mathbf{v}$ have two dimensions. The different impulses traveling within CA3 are denoted by an index s and an index s' is associated to the different families of neurons in CA3. Moreover, s_{ex} denotes a generic impulse coming from sources external to CA3 and s_{in} denotes a generic impulse generated by neurons within CA3. The velocity spectra of the different type of impulses emitted in CA3 have been represented by the following functions related to the neural structure: $f^s(\mathbf{r}, \mathbf{v})$ and $f^{s'}(\mathbf{v})$ denote structural velocity distribution functions for short range and long range impulses, while $\xi_{s's}(\mathbf{r}, \mathbf{r}')$ is an origin/destination matrix for long-range impulses, and the velocity distribution along long-range paths is denoted by $f^s(\mathbf{v})$.

The functions $f_s(\mathbf{r}, \mathbf{v}, t)$ and $g_{s'}(\mathbf{r}, e, t)$ are used to express the dynamic activity of the neural field and describe, respectively, the velocity distribution of impulses and the distribution of the subthreshold neuronal excitation within the neural field. The function $\psi_{s'}(\mathbf{r})$ denotes the local density of neurons of a specific type s' and it is related to $g_{s'}(\mathbf{r}, e, t)$ via integration on e .

It is necessary to note that the set of equations, reported in previous articles (Ventriglia 1974, 1990, 1994, 1998, 2005, 2006) do not describe accurately the dynamics of the neuronal interaction. In fact, by considering only local absorptions (restricted to elemental space $(\mathbf{r}, d\mathbf{r})$ where impulses collide with neurons—somata) these equations handle too grossly the process of absorption and, as a consequence, the activity of the neural field could not be adequately described. In cerebral structures, indeed, the span of the mean dendritic arborization of the neurons (about 300–400 μm), is much larger than the diameter of the neuronal somata and probably this is an important element to take into account. In a new setting, still based on the methods of the kinetic theory of neural systems, the mean number of impulses of type s absorbed in $\mathbf{r}$ at time t from neurons s' can be described by the following function:

$$I_{s's}(\mathbf{r}, t) = \int_{D(\mathbf{r})} \int f_s(\mathbf{r}', \mathbf{v}, t) d\mathbf{r}' \psi_{s'}(\mathbf{r}) \sigma_{s's} |\mathbf{v}| d\mathbf{v} \quad (1)$$

where $\sigma_{s's}$ —the absorption coefficient—corresponds to the collision kernel as defined in the transport theory, and $D(\mathbf{r})$ denotes the region of extension of the dendritic arborization of neurons located in $\mathbf{r}$. As it appear evident from this equation, the absorption of impulses is no more a local process, as in equations of earlier articles, but it interests a larger extension of the neural field from which the impulses can be absorbed. Accordingly, the previous set of equations will be denoted *local absorption model*, while the actual set will be denoted *non-local absorption model*.

By using this function, the mean number of impulses of type s absorbed from each neuron in $\mathbf{r}$ at time t is given by:

$$i_{s's}(\mathbf{r}, t) = \frac{I_{s's}(\mathbf{r}, t)}{\psi_{s'}(\mathbf{r})}. \quad (2)$$

To compute the time course of the net excitatory effect on subthreshold neurons s' in $\mathbf{r}$ at time t , induced by all the absorbed impulses, a new function was introduced. It is denoted by $E_s(t)$ and describes the time course of the mean post synaptic potential associated to the absorption of an impulse of type s —a positive function for excitatory impulses, negative for inhibitory ones. Based on this function, the net excitatory effect, $\epsilon_{s'}(\mathbf{r}, t)$, is given by the following convolution equation:

$$\epsilon_{s'}(\mathbf{r}, t) = \sum_{s=1}^n \int_0^t E_s(t) \cdot i_{s's}(\mathbf{r}, t - t') dt'. \quad (3)$$

Finally, this function allows the computation of the probable number of neurons in $\mathbf{r}$ which are in a firing state at time t :

$$N_{s'}(\mathbf{r}, t) = \int_{1-\epsilon(\mathbf{r}, t)}^1 g_{s'}(\mathbf{r}, e, t) de \quad (4)$$

While, the probable number of neurons in hyperpolarized state are described by the equation:

$$\nabla_t M_{s'}(\mathbf{r}, t) = \int_0^{-\epsilon(\mathbf{r}, t)} g_{s'}(\mathbf{r}, e, t) de - M_{s'}(\mathbf{r}, t) \theta(\epsilon) \quad (5)$$

where $M_{s'}(\mathbf{r}, t)$ denotes the probable number of neurons in $\mathbf{r}$ which stay in maximum hyperpolarization level at time t . In the above equations, use is made of the conditions that the function $g_{s'}(\mathbf{r}, e, t) = 0$ if $e \leq 0$ or if $e > 1$, and 0 and 1 represent the normalized maximum hyperpolarization level and neuronal threshold, respectively. The function $\theta(\cdot)$ denotes the step function.

Based on these preliminary definitions and equations, we could compute that the time evolution of the two distribution functions $f_s(\mathbf{r}, \mathbf{v}, t)$ and $g_{s'}(\mathbf{r}, e, t)$ is governed by the following set of coupled differential equations:

$$\begin{aligned} \nabla_t f_s(\mathbf{r}, \mathbf{v}, t) + \mathbf{v} \cdot \nabla_{\mathbf{r}} f_s(\mathbf{r}, \mathbf{v}, t) + f_s(\mathbf{r}, \mathbf{v}, t) \\ \left(\sum_{s'} \int_{D(\mathbf{r})} \psi_{s'}(\mathbf{r}') |\mathbf{v}| \sigma_{s's} d\mathbf{r}' \right) \\ = S_s(\mathbf{r}, \mathbf{v}, t) \delta(s - s_{\text{ex}}) + f_s^s(\mathbf{r}, \mathbf{v}) N_{s'}(\mathbf{r}, t) \delta(s - s_{\text{in}}) \end{aligned} \quad (6)$$

$$\begin{aligned} + f_s^l(\mathbf{v}) \int_A \zeta_{s's}(\mathbf{r}, \mathbf{r}') d\mathbf{r}' \int f'(\mathbf{v}) N_{s'} \\ \left(\mathbf{r}', t - \frac{|\mathbf{r} - \mathbf{r}'|}{v} \right) dv \delta(s - s_{\text{in}}) \\ \nabla_t g_{s'}(\mathbf{r}, e, t) + \mu(e_r - e) \nabla_e g_{s'}(\mathbf{r}, e, t) \\ = [g_{s'}(\mathbf{r}, e - \epsilon, t) - g_{s'}(\mathbf{r}, e, t)] (1 - \delta(\epsilon)) \\ + N_{s'}(\mathbf{r}, t - \tau_{s'}) \delta(e - e_r) \\ + M_{s'}(\mathbf{r}, t) \theta(\epsilon) \delta(e - e_0) \end{aligned} \quad (7)$$

where $\delta(\cdot)$ denotes the Dirac function. A not standard use of the Dirac function is done in equation 6. In this case, the Dirac function has been utilized to obtain a more compact presentation of the set of equations related to different type of impulses propagating in CA3. In particular, the factor $\delta(s - s_{\text{ex}})$ in Eq. 6 means that the source term $S_s(\mathbf{r}, \mathbf{v}, t)$ is present only for the specific subset of the impulses coming from external sources. When this term is present, the other two terms on the right side of the equation, which are multiplied by the factor $\delta(s - s_{\text{in}})$ are lacking, and vice versa. Moreover, also the short-range and the long-range terms (the second and the third terms on the right member in Eq. 6) are mutually exclusive. In the above equations, ϵ stands for $\epsilon_{s'}(\mathbf{r}, t)$, and e_r and e_0 denote the resting potential and the maximum hyperpolarization level (this last was assumed as normalized to 0), μ is the decay constant of the subthreshold excitation, and A is the surface occupied by CA3.

The third term on left member of Eq. 6, i.e. $f_s(\mathbf{r}, \mathbf{v}, t) (\sum_{s'} \int_{D(\mathbf{r})} \psi_{s'}(\mathbf{r}') |\mathbf{v}| \sigma_{s's} d\mathbf{r}')$, is the other distinguishing element of the non-local model. It describes the fact that the impulses present at time t in $(\mathbf{r}, d\mathbf{r})$ are absorbed not only by neurons lying there, but by the entire set of neurons which, having somata occupying the space $D(\mathbf{r})$, extend their dendrites till to the position $\mathbf{r}$.

The impulses conveyed by the Mossy fibers, which terminate on the base of the shaft of the dendritic tree (*stratum lucidum*), can be still described by the non-local equations. In this case, the absorption space is very close to the pyramidal soma, and strictly confined within the soma boundary. For the description of Mossy impulses absorption we use the equation:

$$I_{s's}(\mathbf{r}, t) = \int \int_{D(\mathbf{r})} f_s(\mathbf{r}', \mathbf{v}, t) \delta(\mathbf{r} - \mathbf{r}') d\mathbf{r}' \psi_{s'}(\mathbf{r}) \sigma_{s's} |\mathbf{v}| d\mathbf{v}. \quad (8)$$

which is equivalent to the corresponding equation of the local model.

Discretized model

Both the local and the non-local versions of this mathematical model have been utilized to carry out several series of computational experiments. The space-time course of some macroscopic parameters (local frequency of spikes, local mean sub-threshold excitation, number of firing neurons), which have close analogy with the in vivo recorded activity of the hippocampal CA3 field (i.e., population spike trains, local field potentials—*LFPs*), has been analyzed to obtain information on their ability to simulate oscillating hippocampal activity. The results about the activity of this field, investigated by the local absorption model, have been reported in previous articles (Ventriclia 2005, 2006). The activity of CA3, analyzed by using the non-local absorption equation set, is presented here. The integro-differential equations of the non-local model are transformed in the following discrete-difference equations, according to a procedure based on the suggestions of Angel and Bellman (1972), Chap. 9, for equations related to the theory of invariant embedding:

$$\begin{aligned} f_s(\mathbf{r} + \mathbf{v}\Delta, \mathbf{v}, t + \Delta) = & f_s(\mathbf{r}, \mathbf{v}, t) - f_s(\mathbf{r}, \mathbf{v}, t) \\ & \left(\sum_{s'} \int_{D(\mathbf{r})} \psi_{s'}(\mathbf{r}') |\mathbf{v}| \sigma_{s's} d\mathbf{r}' \right) \Delta \\ & + f_s^s(\mathbf{r}, \mathbf{v}) N_{s'}(\mathbf{r}, t) \Delta \delta(s - s_{in}) \\ & + f_s^l(\mathbf{v}) \int_A \xi_{s's}(\mathbf{r}, \mathbf{r}') d\mathbf{r}' \\ & \times \int f'(v') N_{s'}\left(\mathbf{r}', t - \frac{|\mathbf{r} - \mathbf{r}'|}{v'}\right) dv' \\ & \Delta \delta(s - s_{in}) + S_s(\mathbf{r}, \mathbf{v}, t) \Delta \delta(s - s_{ex}) \end{aligned} \quad (9)$$

$$\begin{aligned} g_{s'}(\mathbf{r}, e + \mu(e_r - e), t + \Delta) = & g_{s'}(\mathbf{r}, e, t) [g_{s'}(\mathbf{r}, e - \epsilon, t) \\ & - g_{s'}(\mathbf{r}, e, t)] (1 - \delta(\epsilon)) \Delta \\ & + \delta(e - (e_{rs'} + e_{ts'})) \\ & N_{s'}(\mathbf{r}, t - \tau_{s'}) \Delta + \theta(\epsilon) \\ & \delta(e - (e_{rs'} + e_{ts'})) M_{s'}(\mathbf{r}, t) \Delta \end{aligned} \quad (10)$$

$$\begin{aligned} M_{s'}(\mathbf{r}, t + \Delta) = & M_{s'}(\mathbf{r}, t) + \int_0^{-\epsilon(\mathbf{r}, t)} g_{s'}(\mathbf{r}, e, t) de \Delta \\ & + \theta(-\epsilon) \{ \theta[(-(e_{rs'} + e_{ts'}))] N_{s'}(\mathbf{r}, t - \tau_{s'}) \} \Delta. \end{aligned} \quad (11)$$

The activity of the entire CA3 field of the rat, having dimensions of 8.4 mm long (septo-temporal axis) and 3 mm large (transverse axis) as reported in the Atlas of Rat Brain (Paxinos and Watson 1986), has been simulated. The neuronal densities and parameters of connectivity have been computed by values from literature (see Ventriglia 1998, where some structural values are reported). According to those values, about 300.000 pyramidal neurons and 30.000 fast and 10.000 slow inhibitory neurons constituted the three neuronal families of the simulated CA3 field. Having assumed a space step: $\delta x = \delta y = 50 \mu\text{m}$, each grid point was representative of a small square of neural matter, with a side length equal to the space step, in which 30 excitatory neurons, 3 fast and 1 slow inhibitory neurons, in mean, were contained and the entire model was composed of 60×160 points (10,080 modules).

As regards to the inputs, excitatory stimuli originated from Entorhinal Cortex both via Dentate Gyrus (through the Mossy Fibers) and by a direct path have been simulated. Also, the effects of inhibitory afferences from Medial Septum have been investigated. In summary, seven different families of impulses have been used in the description [i.e. CA3 pyramidal impulses with short range effects, CA3 pyramidal with long range effects—related to Schaffer collaterals, CA3 inhibitory impulses with fast time-course and CA3 inhibitory impulses with slow time-course, Entorhinal Cortex pyramidal impulses, Mossy Fibers impulses from Dentate Gyrus, Medial Septum (inhibitory) impulses], and three families of neurons: pyramidal, inhibitory fast and inhibitory slow.

Moreover, to compute $E_s(t)$, the time-course of the mean post synaptic potential produced at the axon hillock by absorption of the different impulses impinging on pyramidal neurons, information on the synaptic structure of hippocampal pyramidal neurons has been considered. As it is well known from literature, the synapses on pyramidal neurons in CA3 field of Hippocampus are parceled in four main layers: *Oriens*, *Lucidum*—formed by the mossy synapses of axons coming from granular neurons in *Dentate Gyrus*, *Radiatum*, and *Lacunosum-moleculare*. Another layer, the *stratum Pyramidal* containing the somata of pyramidal neurons, is the place of arrival of several inhibitory terminals. As regards the origin zones of the axons whose terminals distribute in different layers of

Fig. 1 Time-courses of the mean post synaptic potential produced at the axon hillock by absorption of the different impulses considered in the simulation. The time is in seconds

CA3, we know from Ishizuka et al. (1990) that Entorhinal Cortex neurons send axons in *Lacunosum-moleculare* layer, some of the pyramidal Schaffer's collaterals from CA3 terminate in *Oriens* and *Radiatum* layers, and Medial Septum neurons excite synapses in *Oriens* and, at a minor extent, synapses in *Radiatum*. Due to the passive propagation along the dendritic trees, the distance between the synapses and the axon hillock produces a widening and weakening of the synaptic effect at the axon hillock. By using the results of Ventriglia and Di Maio (2005), the time-course of $E_s(t)$ produced by input in *Lacunosum-moleculare* layer (EC input) was considered maximally widened and weakened, whereas the input in *Oriens* and *Radiatum* layers (MS and pyramidal short and long range impulses) had a mean widening and weakening time-course, and the input in *Lucidum* and *Pyramidal* layers was only slightly widened and weakened (see Fig. 1). Dentate Gyrus input, conveyed by layered mossy fibers in stratum lucidum, was assumed to be distributed along parallel strips of pyramidal neurons, each strip being 3 mm long and 50 μm large and containing about 6.250 mossy fibers and 87.500 mossy synapses. The amplitude of the strip (50 μm) being imposed by the space step.

Ca3 global activity

The genesis of sharp waves and rhythmic oscillations in gamma and theta ranges mentioned in Introduction has been investigated by computational experiments which simulated the reaction of the CA3 model to external stimuli. In general, each simulation had a duration of 2 s, requiring 16,000 time steps ($\delta t = 0.125$ ms).

In all the experiments, the main stimuli came from Dentate Gyrus, Entorhinal Cortex, and Medial Septum.

In the simulations described here, an inhibitory input from MS has been simulated which inhibited selectively the inhibitory neural populations of CA3 (Gulyas et al. 1991). The Dentate Gyrus input to each neural strip was constituted by random volleys of impulses, whose arrival times were distributed according to a Poisson distribution, while the amplitudes were Gaussian. Once a volley arrived to a strip, it traveled through all the transverse length of CA3 (3 mm), impulses being absorbed along the route. In some cases the volleys along the different strips were correlated. The CA3 field was also reached by Poissonian inputs originating from a direct Entorhinal Cortex path. The Entorhinal Cortex inputs had Gaussian distributed amplitudes. A Poisson distribution was assumed also for the inhibitory input coming from MS, but the amplitude was modulated by a square wave at different frequencies in different simulations (see Fig. 2).

The main aim of the simulations was the investigation of the effect of the inhibitory input from Medial Septum on the activity of CA3. To study the activity of this field, a meaningful parameter was considered to be the summed potentials at the axon hillock of neurons, averaged on all the modules (10,080) of the CA3 model. This parameter is a nice representation of the *LFP* recorded by micro-electrodes in electrophysiological experiments.

At first, to bring forth a CA3 global activity to use as basic reference, we considered a low and ineffective MS inhibition, lasting for all the duration of the simulation. Some results are reported in Fig. 3. Here, the *LFPs*, separated for the three different neural populations (pyramidal,

Fig. 2 First 3 ms of CA3 input from EC, MS, DG. Each single frame represents the entire CA3 field, stretched on the plain, and each frame row shows the time evolution of a specific input. The time arrow is from left to right. The three frames in the first column all represent CA3 at time $t = 0$. Those of the subsequent 8 columns have an inter-frame time of 0.125 ms, i.e. the time-step of the simulation ($\delta t = 0.125$ ms). Whereas, the last two columns are at time 2 ms and 3 ms. About the orientation of the single frames we have: the left side faces DG, while the right side faces CA1, the upper side is in the septal direction, while the inferior side is in the temporal direction

Fig. 3 Time course of the global input at axon hillock of the average neuron of the average modulus (*local field potentials, LFPs*) in CA3 under constant, but not effective, inhibitory MS input. The time course is shown for pyramidal, inhibitory fast and inhibitory slow neurons. The total time displayed is 2 s

inhibitory—fast and slow), are shown. Five volleys (or complex waves) are evident in the activity of the pyramidal population, with a global frequency of 2.5 Hz, each volley being composed by three or four waves at about 25 Hz, at the lower edge of the gamma range. But, differently from the results obtained in electrophysiological experiments, the model can provide not only this data, but a complete information about the CA3 activity. We can know both the firing space–time course of all the populations of neurons and the impulse density behavior, in space and time, for all the different impulses. The course in space and time of the absorption of different families of impulses by different families of neurons can also be recorded. Of course, this complete space–time information cannot be presented in an article, since it would require a very large number of pictures, each composed of long series of sub-frames, for each simulation. But, it seems interesting to show some important elements of the behavior of CA3 when observed by the propagation of short-range and long-range pyramidal impulses and of fast inhibitory impulses. In particular, in Fig. 4a, b, the propagation of these impulses can be observed during some of the volleys of Fig. 3. From this figure we can describe a typical CA3 activity, when the inhibitory input from Medial Septum is absent or not meaningful. At the starting time all the activity parameters are set to null (all the neurons are at the resting level and no impulse is flowing in the system), then the simulated input from DG and EC begin to influence the pyramidal neural population. At some times, depending on the characteristics of the Poisson distributions governing the DG input and the EC input, the first volleys of impulses begin to propagate in one or more strips, for DG input, or to hit some moduli, for the EC input. The absorption of impulses

Fig. 4 CA3 global activity linked to the *LFPs* shown in Fig. 3. In each sub-figure the upper frames show the course of long-range pyramidal impulses, the medial ones that of short-range pyramidal impulses, whereas the bottom frames are related to impulses emitted by fast inhibitory neurons. **(a)** Activity linked to the first wave in Fig. 3. Starting time at 27 ms and endingtime at 44 ms, the inter-frame time step is 1 ms. **(b)** Activity linked to the third wave in Fig. 3. Starting time at 820 ms and endingtime at 835 ms, the inter-frame time step is 1 ms

triggers some pyramidal neurons to fire action potentials. This induces firing in other pyramidal cells and also in fast and slow inhibitory neurons. In some milliseconds a patterned, self-organized activity begin to appear in the neuronal firing, which stabilizes and propagates throughout the entire CA3 field, involving both the pyramidal and the inhibitory neurons. The induced firing of fast and slow inhibitory neurons produces a level of inhibition sufficient to reduce to a silent state the pyramidal neurons. In such a way they remain unable to react to new inputs originating from the simulated external sources. The patterned activity of the inhibitory neural population remains active for several periods of time, as long as they have sufficient drive from their excitatory synapses. After some time, the decaying of the residual excitation on inhibitory neurons reduced gradually their firing. This permits the inputs from EC and DG to ignite again some of the neurons of the pyramidal population of CA3. A new cycle begins with a patterned activity that could be slightly or strongly different from the previous one. In fact, in Fig. 4b a new cycle, related to the third volley of Fig. 3, is reported having a quite different course with respect to Fig. 4a. In a new simulation a 20 Hz inhibitory activity, coming from MS, and inhibiting both inhibitory populations, fast and slow, of

Fig. 5 Time course of *LFPs* of pyramidal, inhibitory fast and inhibitory slow neurons in CA3 under a inhibitory MS input at 20 Hz frequency. The total time displayed is 2 s

Fig. 6 CA3 global activity linked to the 11th wave of the *LFPs* shown in Fig. 5. The starting time is at 499 ms and the ending time is at 533 ms, the inter-frame time step is 2 ms

CA3 was investigated. The results of the global parameter used for observation are reported in Fig. 5. From this figure we can note that the CA3 field reacts to MS input producing an activity with the same frequency of the MS input. In Fig. 6 the local density of impulses, for some characteristic elements of Fig. 5, are presented. Also a 10 Hz inhibitory MS activity was investigated. The results as manifested by the usual global parameter are reported in Fig. 7. Also in this case, CA3 reacts to the MS input by assuming its same frequency. But, now the behavior of the single waves tends to be more jagged. In Fig. 8 the space-time behavior of the local density of the previously selected families of impulses is presented, near one oscillation of the *LFPs*. To study the reaction of CA3 to a MS inhibition at a lower frequency, a 5 Hz input was utilized. The results, as expressed by the usual *LFP* parameter, are reported in Fig. 9. In this case CA3 is unable to follow the input with a 1:1 regime. Vice versa, some complex waves are produced, each wave showing a time-course with different frequency contents. A two way course is shown in each wave, a sharp wave followed by some oscillations in the gamma range (from 21 to 35 Hz). In Fig. 10 the local density of impulses

Fig. 7 Time course of *LFPs* of pyramidal, inhibitory fast and inhibitory slow neurons in CA3 under a 10 Hz inhibitory MS input. The total time displayed is 2 s

Fig. 8 CA3 global activity linked to the sixth wave of the *LFPs* shown in Fig. 7. The starting time is at 549 ms and the ending time is at 583 ms, the inter-frame time step is 2 ms

Fig. 9 Time course of *LFPs* of pyramidal, inhibitory fast and inhibitory slow neurons in CA3 under 5 Hz inhibitory MS input. The total time displayed is 2 s

are represented. In this case, the three families of impulses show different propagation behaviors during the gamma and the sharp waves courses.

Fig. 10 CA3 global activity linked to the transition phase in the second wave of Fig. 9. Two time periods are shown. The first nine frames—from 0.560 to 0.576 s—frame step 2 ms, fall in a *sharp wave*. The last nine frames—from 0.648 to 0.664 s—frame step 2 ms, belong to a period of *gamma waves*

To observe the results of the MS inhibition when its frequency is very low, a 1 Hz input was investigated. The results, as expressed by the usual *LFPs*, are reported in Fig. 11. In this case CA3 reacts to the MS inhibition yet in a different way. Some, few (three) complex waves are produced in 2 s, some not fully displayed during this time. The structure of these waves are different from those of the previous simulation at low frequency. The most representative complex wave, i.e. the second, shows a time-course with different frequency contents: the wave starts with some oscillations in the lower gamma range (about 25 Hz), then passes to a kind of sharp wave with a long gamma queue at higher frequency (about 68 Hz), and terminates with oscillations in the lower gamma range (about 15–20 Hz). In Fig. 12 the local density of impulses are presented, near one characteristic moment, the transition from a gamma wave course to a sharp wave behavior. Two, quite different kind of propagation behaviors are presented by the three families of impulses, during the gamma and the sharp waves courses. To get more information about the relationship between the CA3 global activity and the frequency of the MS input, the

Fig. 11 Time course of *LFPs* of pyramidal, inhibitory fast and inhibitory slow neurons in CA3 under 1 Hz inhibitory MS input. The total time displayed is 2 s

Fig. 12 CA3 global activity linked to the transition phase in the third wave of Fig. 11. Two time periods are shown. The first nine frames—from 1.380 to 1.396 s—frame step 2 ms, are from a period of *gamma waves*. The last nine frames—from 1.590 to 1.606 s—frame step 2 ms, belong to a period of *sharp wave*

power spectral density (*PSDs*) of the pyramidal activity, as expressed by the *LFPs*, has been computed. In Fig. 13 the power spectra of 7 *LFPs* are presented, they are related to MS input at 0, 1, 5, 6.6, 8, 10, 20 Hz frequency. Let us note, that to investigate more thoroughly a possible singularity point in the CA3 activity, two new simulations, with respect to those discussed above, were carried out: they are related to MS input at 6.6 and 8 Hz. Their *PSDs* have been computed and shown in Fig. 13, along with the other power spectra. In fact, from that figure we can observe that whereas the maximum peaks of the *PSDs* shift towards lower frequency values going from 0 to 5 Hz MS input, at this last value the left shifting is halted, and then the maximum peak begins to move towards higher values, following the input in a one to one manner.

To deepen further the analysis, we carried out some more computer simulations, where the time-course of the postsynaptic response, $E_s(t)$, of the GABA_B receptors was modified. A longer time for the slow inhibition—reported

Fig. 13 Power spectral density computed on pyramidal *LFPs* of CA3. The power spectra are related to simulations where MS inhibitory input on inhibitory neurons of CA3 had 0, 1, 5, 6.6, 8, 10, 20 Hz periodic time-course. The amplitude of the spectrum, computed for simulation related to 20 Hz MS input, has been reduced by a factor 2 to show a not too squashed view of the others spectra

Fig. 14 Comparison of the power spectral densities for MS input to 5 and 8 Hz with the lengthening of the slow inhibition duration

as InSIlonger in Fig. 1—was used. For this case, the CA3 model was stimulated by MS input at 5 and at 8 Hz, the DG and EC inputs being as usual. A comparison among the changes induced on the global CA3 reaction as a consequence of the variation of the slow inhibitory parameter is shown in Fig. 14. There, for the two different MS input, the power spectra computed on the pyramidal LFPs are presented. From this figure, one can note that, while for the 8 Hz MS input, the lengthening of the slow inhibition produces only a change in the relative amplitudes of the peaks of the two power spectra, the global shape of the spectra being unaffected, for the case of the 5 Hz MS input, it is the global shape that changes: the more prominent peak shifts from about 6 Hz to about 22 Hz. This result stress the greater importance of the duration of the slow inhibitory effects on the CA3 global reaction at low stimulation frequency.

Discussion

The study by computer simulation of the neural activity of the CA3 field of Hippocampus shed light on some remarkable features of the neural dynamics. Under appropriate driving inputs, some self-organized activity within the pyramidal neuronal population spread to the entire CA3 region. In the wake of the excitatory activity, stable and well-organized oscillatory activities occurred within the inhibitory neural population. They presented a sort of complex and persistent remnant, or trace, of the spatio-temporal behavior of the vanished pyramidal activity. The oscillations of the inhibitory neural population activity lasted for periods of time much longer than those of the activity in driving pyramidal neurons. During this time, the pyramidal neurons could not generate new activities, being very efficiently inhibited.

The inhibition of fast and slow inhibitory neurons could modulate the duration of such inhibitory periods. This possibility was investigated by simulating an oscillating, inhibitory input originating from Medial Septum. The four computer simulations discussed here, besides that related to the basic activity, enlightened the processing ability of the CA3 field. It can be described as follows.

When reached by an inhibitory input from Medial Septum at 10 Hz frequency and higher (simulations related to Figs. 5, 6, 7, 8)—but also as low as 6.6 Hz—results not shown, the CA3 field is able to produce oscillating activity at the same frequency of the driving input. But the time course of the single waves tends to be more and more jagged with the decreasing of the frequency, or, if we consider the time, with the increasing of the periods of inhibitory drive on inhibitory neurons of CA3. If the frequency of the inhibitory input from MS continues to decrease, as in simulations with 5 Hz or lower frequency, a different behavior is manifested. In the simulation with 5 Hz input, we observe (Figs. 9, 10) 5 complex waves in 2 s. Leaving out the first one, each wave starts with a kind of *sharp wave* with a duration going from 80 to 50 ms, followed by 3–4 waves at about 30 Hz—falling in the range of the gamma waves. In the simulation with 1 Hz input, we observe (Figs. 11, 12) 3 complex waves in 2 s, which, leaving out the first one, starts with a kind of gamma waves, passes to a *sharp wave* with a much longer duration with respect to previous one, about 400 ms, in which fast oscillations at about 68 Hz are produced, and terminates again with some gamma waves. This case represents a kind of perturbation of that shown in Figs. 3, 4, related to a constant and low MS inhibition. From the 5 Hz and, more clearly, from the 1 Hz case it appears evident that the increasing of the duration of the inhibition period from Medial Septum on inhibitory neurons of CA3 stimulates the generation of sharp waves and/or high frequency activity in CA3.

Hence, the global processing structure of CA3 seems to be organized in such a way to present specific time windows for the generation of excitatory activities by pyramidal neurons. These activities are very characteristic, as we have observed above, and depend strictly by the input from Medial Septum. In general, they are separated by short or long periods of patterned inhibition. This suggests that a sort of temporal coding—with a meaning quite different from the common view—is associated to the function of the entire CA3 field, that seems to operate as follows. Among all the inputs from cortical regions arriving to CA3, only those which reach it in appropriate time intervals are able to trigger specific, global activities (as those shown in Figs. 4, 6, 8, 10, 12) and can produce effects on the brain regions driven by CA3. These time intervals can be also under the control of activities in

behavior-linked sub-cortical nuclei (like locus coeruleus and median raphe), that we have not simulated here. Other volleys, which arrive out of phase with the winning activity, cannot filter through the inhibitory barrage, and are unable to stimulate reactions in CA3. Hence, the information they convey is not allowed to pass to other brain stages. In such a way, some free periods of time with a variable duration are reserved to the successful inputs, during which they can drive specific activities in cortical regions, reflecting the global reaction of CA3, without interferences by competing inputs. These activities may result in learning, memory and other cognitive effects.

Based on a long experimental activity also Vinogradova hypothesized a link between the theta rhythm and the attention mechanism (Vinogradova 2001). A weaker, but similar hypothesis has been proposed in (Csicsvari et al. 1999) on the coding ability of the inhibitory activity in Hippocampus. These authors suggest that oscillating inhibitory networks may provide temporal windows for single cells to suppress or facilitate their synaptic inputs in a coordinated manner. In the last years, the effects of the septo-hippocampal pathway on the genesis of theta and gamma rhythm has been investigated also by Erdi and his group from a computational point of view, but they focused on the hippocampal CA1 field in their studies (Orbán et al. 2006). Moreover, without specific references to biological neural structures, a proposal about the coding possibilities of the oscillatory neural activity has been advanced by Borisyuk and Borisyuk (1997). In a recent review article, some theoretical results about neural dynamics of CA3 (but also of the EC—Hippocampus system, in general) related to theta phase coding are discussed in the ambit of place cells. This approach, which considers also the synaptic plasticity, allowed the investigation of encoding, updating, and retrieval of behavioral sequences in the hippocampus. It has been considered by the authors as a cue for the grasping of the episodic memory function in human hippocampus (Wagatsuma and Yamaguchi 2007). In the framework of the hippocampal functions, another case where time among events is important, i.e. the learning of the trace interval—a classical conditioning process, has been investigated by the use of a simpler model of CA3 field (Howe and Levy 2007). But, in both the above two cases no attentional mechanism has been taken into consideration.

Appendix

The following values have been utilized for the basic neuronal parameters in the above reported computer simulations. The resting levels $e_{rs'}$ of different neurons were: $e_{rp} = 0.34$ (corresponding to -75 mV)—pyramidal neurons,

$e_{rf} = 0.67$ (corresponding to -62.5 mV)—fast inhibitory neurons, $e_{rs} = 0.34$ (corresponding to -75 mV)—slow inhibitory neurons. The periods of absolute refractoriness and the synaptic delays were: $\tau_p = 15$ ms, $\tau_f = \tau_s = 1.75$ ms and $t_{op} = t_{of} = t_{os} = 0.5$ ms, respectively. The slow-IPSP onset time had value $\bar{t}_s = 30$ ms. The long-distance impulses in the absorption-free zone assumed a constant velocity $v' = 60$ cm/s.

References

- Amaral DG, Ishizuka N, Claiborne B (1990) Neurons, number and the hippocampal network. In: Storm-Mathisen J, Zimmer J, Otterson OP (eds) Progress in brain research, vol 83. Elsevier, Amsterdam, pp 1–11
- Angel E, Bellman R (1972) Dynamic programming and partial differential equations. Academic Press, New York
- Borisyuk RM, Borisyuk GN (1997) Information coding on the basis of synchronization of neuronal activity. Biosystems 40:3–10
- Buzsaki G (1986) Hippocampal sharp waves: their origin and significance. Brain Res 398:242–252
- Buzsaki G, Chrobak JJ (1995) Temporal structure in spatially organized neuronal ensembles: a role for interneuronal networks. Curr Opin Neurobiol 5:504–510
- Cohen NJ, Eichenbaum H (1993) Memory, amnesia, and the hippocampal system. The MIT Press, Cambridge
- Csicsvari J, Hirase H, Czurko A, Mamiya A, Buzsaki G (1999) Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. J Neurosci 19:274–287
- Draguhn A, Traub RD, Bibbig A, Schmitz D (2000) Ripple (approximately 200-Hz) oscillations in temporal structures. J Clin Neurophysiol 17:361–376
- Gulyas AI, Seress L, Toth K, Acsady L, Antal M, Freund TF (1991) Septal gabaergic neurons innervate inhibitory interneurons in the hippocampus of the macaque monkey. Neurosci 41:381–390
- Howe AG, Levy WB (2007) A hippocampal model predicts a fluctuating phase transition when learning certain trace conditioning paradigms. Cogn Neurodyn 1:143–155
- Ishizuka N, Weber J, Amaral DG (1990) Organization of intra-hippocampal projections originating from CA3 pyramidal cells in the rat. J Comp Neurol 295:580–623
- Kandel A, Buzsaki G (1997) Cellular-synaptic generation of sleep spindles, spike-and-wave discharges, and evoked thalamocortical responses in the neocortex of the rat. J Neurosci 17:6783–6797
- Milner B (1972) Disorders of learning and memory after temporal lobe lesions in man. Clinical Neurosurg 19:421–446
- Mishkin M (1982) A memory system in the monkey. Philos Trans R Soc Lond B298:85–95
- Molter C, Sato N, Yamaguchi Y (2007) Reactivation of behavioral activity during Sharp Waves: a computational model for two stage hippocampal dynamics. Hippocampus 17:201–209
- Orbán G, Kiss T, Erdi P (2006) Intrinsic and synaptic mechanisms determining the timing of neuron population activity during hippocampal theta oscillation. J Neurophysiol 96:2889–2904
- Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates. Academic Press, San Diego
- Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Psychiatry 20:11–21
- Squire LR, Shimamura AP, Amaral DG (1989) Memory and the hippocampus. In: Byrne JH, Berry WO (eds) Neural models of plasticity. Academic Press, San Diego, pp 208–239

- Traub RD, Cunningham MO, Gloveli T, LeBeau FE, Bibbig A, Buhl EH, Whittington MA (2003) GABA-enhanced collective behavior in neuronal axons underlies persistent gamma-frequency oscillations. *Proc Natl Acad Sci USA* 100:11047–11052
- Ventriglia F (1974) Kinetic approach to neural systems. I. *Bull Math Biol* 36:534–544
- Ventriglia F (1990) Activity in cortical-like neural systems: short-range effects and attention phenomena. *Bull Math Biol* 52:397–429
- Ventriglia F (1994) Towards a kinetic theory of cortical-like neural fields. In: Ventriglia F (eds) *Neural modeling and neural networks*. Pergamon Press, Oxford, pp 217–249
- Ventriglia F (1998) Computational experiments support a competitive function in the CA3 region of the hippocampus. *Bull Math Biol* 60:373–407
- Ventriglia F (2005) Coding by neural population oscillations? In: De Gregorio M, Di Maio V, Frucci M, Musio C (eds) *Brain, vision and artificial intelligence*. LNCS 3704. Springer, Berlin, pp 78–88
- Ventriglia F (2006) Global rhythmic activities in hippocampal fields and neural coding. *BioSystems* 86:38–45
- Ventriglia F, Di Maio V (2005) Neural code and irregular spike trains. In: De Gregorio M, Di Maio V, Frucci M, Musio C (eds) *Brain, vision and artificial intelligence*. LNCS 3704. Springer, Berlin, pp 89–98
- Vertes RP (1986) Brainstem modulations of hippocampus: anatomy, physiology, and significance. In: Isaacson RL, Pribram KL (eds) *The hippocampus*, vol 4. Plenum Press, New York, pp 41–75
- Wagatsuma H, Yamaguchi Y (2007) Neural dynamics of the cognitive map in the hippocampus. *Cogn Neurodyn* 1:119–141
- West MJ (1990) Stereological studies of the hippocampus: a comparison of the hippocampal subdivisions of diverse species including hedgehogs, laboratory rodents, wild mice and men. In: Storm-Mathisen J, Zimmer J, Otterson OP (eds) *Progress in brain research*, vol 83. Elsevier, Amsterdam, pp 13–36
- Vinogradova OS (2001) Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus* 11:578–598
- Wilson MA, McNaughton B (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261:1055–1058