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Information Transfer Between Rhythmically Coupled Networks: Reading the Hippocampal Phase Code

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There are numerous reports on rhythmic coupling between separate brain networks. It has been proposed that this rhythmic coupling indicates exchange of information. So far, few computational models have been proposed that explore this principle and its potential computational benefits. Recent results on hippocampal place cells of the rat provide new insight; it has been shown that information about space is encoded by the firing of place cells with respect to the phase of the ongoing theta rhythm. This principle is termed *phase coding* and suggests that upcoming locations (predicted by the hippocampus) are encoded by cells firing late in the theta cycle, whereas current location is encoded by early firing in the theta cycle. A network reading the hippocampal output must inevitably also receive an oscillatory theta input in order to decipher the phase-coded firing patterns. In this article, I propose a simple physiologically plausible mechanism implemented as an oscillatory network that can decode the hippocampal output. By changing only the phase of the theta input to the decoder, qualitatively different information is transferred: the theta phase determines whether representations of current or upcoming locations are read by the decoder. The proposed mechanism provides a computational principle for information transfer between oscillatory networks and might generalize to brain networks beyond the hippocampal region.

1 Introduction

Occasional frequency locking is often observed between two or more brain regions (for an extensive review see Varela, Lachaux, Rodriguez, & Martinerie, 2001). This coherent oscillatory activity could indicate exchange and manipulation of information between networks. For instance, whisker twitching in the rat synchronizes the neural activity in the brain stem, thalamus, and primary somatosensory cortex at a 7–12 Hz rhythm (Nicolelis, Baccala, Lin, & Chapin, 1995). The olfactory system provides numerous examples of rhythmic coupling. In the cat, synchronized oscillations in the 35–50 Hz band were measured between the entorhinal cortex, posterior periform cortex, and olfactory bulb during odor sampling (Boeijinga & Lopes

da Silva, 1989). In the salamander, the presentation of odors elicits 10–20 Hz synchronized oscillations in the olfactory epithelium and olfactory bulb (Dorries & Kauer, 2000). When rats are performing demanding olfactory memory tasks (reversal learning), the hippocampal theta rhythm occasionally couples to the sniffing rhythm (Macrides, Eichenbaum, & Forbes, 1982). In humans, long-range oscillatory synchrony has been reported. An electroencephalogram (EEG) study demonstrated coherence in the 4–7 Hz band between frontal and posterior regions in a working memory task (Sarnthein, Petsche, Rappelsberger, Shaw, & von Stein, 1998).

Beyond the work of Ahissar, Haidarliu, and Zacksenhouse (1997) and Ahissar, Sosnik, and Haidarliu (2000) on somatosensory processing, little theoretical work has been done to explore the potential computational advantages of information exchange between oscillatory brain networks. The rat hippocampus and regions to which it projects provide an excellent system for exploring theoretical ideas on oscillatory coupled networks. Of particular interest are the firing properties of hippocampal place cells (O'Keefe & Dostrovsky, 1971; Olton, Branch, & Best, 1978), which are strongly modulated by the theta rhythm: as a rat enters a place field, place cells fire late in the theta cycle. As the rat passes through the place field, the phase of firing advances systematically (O'Keefe & Recce, 1993; Skaggs, McNaughton, Wilson, & Barnes, 1996; Shen, Barnes, McNaughton, Skaggs, & Weaver, 1997). This effect is termed the theta phase precession or phase advance. Recently it was demonstrated that when reconstructing a rat's location from an ensemble of place cells, the error of reconstruction is significantly reduced when the theta phase of firing is taken into account (Jensen & Lisman, 2000). This result supports the case that information is encoded by the theta phase of firing: phase coding. A network receiving the hippocampal firing pattern, for example, the entorhinal and cingulate cortex, can by phase decoding extract information beyond what is encoded in the firing rates. The decoding network must necessarily also receive information about the theta rhythm. Hence, if one accepts the principle of phase coding, there might be an advantage to oscillatory coupling between networks. To explore this idea, I will suggest a physiologically plausible oscillatory network that can read the hippocampal phase code.

Section 2 is devoted to an improved implementation of the Jensen and Lisman oscillatory network model (Jensen & Lisman, 1996a), which, by sequence readout, can account for the theta phase precession and thereby the generation of phase-coded information (the phase encoder). The output produced by this network is then used to test the network receiving the hippocampal phase code (the phase decoder). By numerical simulations, I will demonstrate how qualitatively different information is transferred from one network to the other, depending on only the phase lag between the networks. I then discuss the brain regions that might perform the phase decoding and different principles according to which the phase decoding might work. The model framework results in a set of testable predictions.

2 Methods

The model presented in this article consists of two networks—one representing the hippocampal phase encoder (CA3) and the other the phase decoder. I describe each network individually. A diagram of the network model is shown in Figure 1.

2.1 The Hippocampal Phase Encoder. This network is an improved version of a previously proposed network model (Jensen & Lisman, 1996a),

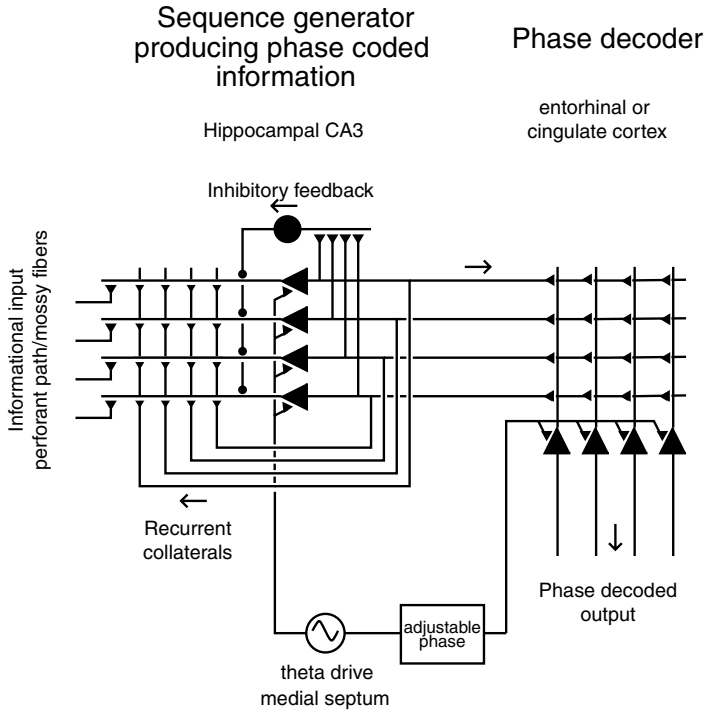


Figure 1: A schematic illustration of the oscillatory networks responsible for performing the phase encoding and decoding. The pyramidal neurons of the CA3 region (left) receive informational input from the perforant path or the mossy fibers. The synchronized activity of the inhibitory network is represented by a single interneuron providing local GABAergic feedback. The theta drive is imposed externally on all pyramidal neurons. Sequence representations are encoded by the synapses of the recurrent CA3 collaterals. The pyramidal cells of the phase decoder (right) receive excitatory input from a subset of the pyramidal neurons and the theta input.

which can account for the phase precession by repeated sequence readout. In the original network, the model neurons were implemented without a membrane capacitance. This has been improved by implementing each neuron with a membrane capacitance so they function as leaky integrate-and-fire units (Koch & Segev, 1998). The advantage of integrate-and-fire units is that they are computationally inexpensive since the sodium, potassium, and calcium currents producing a spike are not modeled explicitly. The simplicity of the integrate-and-fire units is mainly justified by the inhibitory feedback from the interneurons. This feedback hyperpolarizes the cells in the network well below firing threshold after a subset of pyramidal neurons has fired. Thus, the detailed membrane dynamics following an action potential is of less importance. The representation of the interneuronal network responsible for generating the GABAergic feedback has also been improved. The interneuronal network is represented by an inhibitory integrate-and-fire unit rather than just as a function of the spike times of the pyramidal neurons. In the original model, representations of locations were modeled by only a single cell per location (Jensen & Lisman, 1996a). To simulate a location which is represented by the simultaneous firing of a group of neurons, five cells firing in synchrony will represent a location. The full hippocampal network has 45 pyramidal neurons and one inhibitory interneuron.

The membrane potential of each pyramidal neuron is modeled by the equation:

$$-C\frac{dV}{dt} = I_L + I_{AHP} + I_{\Theta,hippo} + I_{syn,GABA_A} + I_{syn,AMPA} + I_{syn,RC} + I_{noise}. \tag{2.1}$$

The membrane potential is reset to $V_{rest} = -65$ mV when it reaches the threshold $V_{threshold} = -55$ mV. This event represents a spike or a short burst. The membrane capacitance is $C = 0.5\ \mu\text{F/cm}^2$. The leakage current is defined as $I_L = g_L(V - E_L)$ with the reversal potential $E_L = -65$ mV and conductance $g_L = 0.03\ \text{mS/cm}^2$. The conductance of the slow afterhyperpolarization (AHP) current is modeled by a decreasing exponential function: $g_{AHP}(t) = g'_{AHP}\exp(-\frac{t-t_{spike}}{\tau_{AHP}})$, where t_{spike} is the time when the cell spikes and $g'_{AHP} = 0.06\ \text{mS/cm}^2$ and $\tau_{AHP} = 40$ ms. The AHP current is defined as $I_{AHP} = g_{AHP}(t)(V - E_{AHP})$, where $E_{AHP} = -70$ mV. The slow AHP current makes it less likely for a pyramidal cell to fire multiple times within a theta cycle.

The septal input to the hippocampus that provides the drive at theta frequency is modeled as $I_{\Theta,hippo} = I'_{\Theta}cos(2\pi f_{\Theta}t)$, where the theta frequency is $f_{\Theta} = 7$ Hz and $I'_{\Theta} = 0.18\ \mu\text{A/cm}^2$.

The informational input to the CA3 (from the perforant path or the mossy fibers) excites the pyramidal neurons synaptically by AMPA-receptor-mediated currents. The AMPA receptor conductances are modeled by α-functions, $g_{AMPA}(t) = g'_{AMPA}\frac{t-t_{input}}{\tau_{AMPA}}\exp(-\frac{t-t_{input}}{\tau_{AMPA}})$, and the excitatory postsynaptic currents (EPSCs) are $I_{AMPA} = g_{AMPA}(t)(V - E_{AMPA})$. The constants are $\tau_{AMPA} = 3$ ms, $E_{AMPA} = 0$ mV, and $g'_{AMPA} = 0.13$ mS/cm^2.

The conductance of the GABAergic input is implemented by an α-function: $g_{GABA}(t) = g'_{GABA}\frac{t-t_{spike,inh}}{\tau_{GABA}}\exp(-\frac{t-t_{spike,inh}}{\tau_{GABA}})$, where $t_{spike,inh}$ denotes the time of spiking of the neuron representing the interneuronal network. The inhibitory postsynaptic current (IPSC) is expressed as $I_{GABA} = g_{GABA}(t)(V - E_{GABA})$, where $\tau_{GABA} = 5$ ms, $E_{GABA} = -70$ mV, and $g'_{GABA} = 0.15$ mS/cm^2. The neuron representing the inhibitory network is modeled by a leaky integrate-and-fire unit:

$$-C\frac{dV}{dt} = I_L + I_{AHP} + I_{syn,AMPA} + I_{noise}. \tag{2.2}$$

The parameters that are different from those of the excitatory neurons (see equation 2.1) are $C = 0.25$ μF/cm^2, $g'_{AHP} = 0.60$ mS/cm^2, and $\tau_{AHP} = 5$ ms. All the pyramidal neurons are connected to the inhibitory neuron with AMPA synapses, $g'_{AMPA} = 0.026$ mS/cm^2. With these settings, the interneuron will fire after four to five pyramidal cells fire synchronously. For a justification of the time constants and reversal potentials, see Jensen, Idiart, and Lisman (1996) and Jensen and Lisman (1996b).

The excitatory feedback of the CA3 recurrent collaterals produces the sequence readout creating the phase code. Since the excitatory feedback has to outlast at least the interval of the inhibitory feedback (one gamma cycle, 20–30 ms), it was suggested that NMDA receptors with a decay time of approximately 100 ms mediate the excitation (Jensen & Lisman, 1996a, 1996b). This hypothesis has become less plausible in the light of recent results demonstrating that place fields of well-learned environments are relatively unaffected by the NMDA antagonist CPP (Kentros et al., 1998). Several alternatives exist. One possibility is that the firing of CA3 pyramidal cells is sustained by reciprocal connections between the dentate and CA3 during each gamma cycle (Lisman, 1999). Another solution is that kainate receptors mediate the slow excitatory feedback. Kainate receptors are found postsynaptically at CA3 neurons and have a decay time of 50–100 ms (Castillo, Malenka, & Nicoll, 1997; Yamamoto, Sawada, & Ohno-Shosaku, 1998). Although most research has concentrated on kainate receptors at mossy fiber terminals, it is possible that they also are involved in mediating recurrent CA3 excitation. Further research is required to identify the details of the recurrent excitation creating the sequence readout. In this work, I assume that kainate receptors are responsible. Thus, the time-dependent conduc-

tance of the synapses of the CA3 recurrent collaterals (RC) at cell i from cell j (spiking at time t^j_{spike}) is modeled by a double exponential function:

$$g^{ij}_{RC}(t) = g'_{RC} W^{ij}_{CA3} \exp\left(-\frac{t - t^j_{spike}}{\tau_{RC,decay}}\right)\left(1 - \exp\left(-\frac{t - t^j_{spike}}{\tau_{RC,rise}}\right)\right), \quad (2.3)$$

where W^{ij}_{CA3} is the synaptic weight from cell j to cell i and the common scaling constant is $g'_{RC} = 0.0061\ \mathrm{mS/cm^2}$. The rise and decay times at room temperature of the kainate receptors have, respectively, been estimated to $\tau_{rise} \approx 7$ ms and $\tau_{decay} = 60$–100 ms. Since the kinetics is faster at body temperature, the constants are set to $\tau_{RC,rise} = 5$ ms and $\tau_{RC,decay} = 40$ ms. The model is fairly robust with respect to variations of these time constants. The total current to cell i from the recurrent collaterals is $I_{syn,RC} = \sum_j g^{ij}_{RC}(t)(V^i - E_{RC})$ where $E_{RC} = 0$ mV. The sequence of locations is encoded in the asymmetric weight matrix W^{ij}_{CA3}. The synaptic strengths for representation N (cell $j = 1+5(N-1)$ to $5N$) to representation $N+K$ (cell $i = 1+5(N+K-1)$ to $5(N+K)$) are $W^{ij}_{CA3} = \exp(-\frac{KT_\gamma}{\tau_{decay}})(1 - \exp(-\frac{KT_\gamma}{\tau_{rise}}))$. The time $T_\gamma = 30$ ms is approximately the period of a gamma cycle. As a result, representation A ($N = 1$) is connected most strongly to representation B ($N = 2$), with weaker connections to representation C ($N = 3$), and so on. It has previously been demonstrated how an asymmetric synaptic weight matrix could emerge in a model with NMDA-dependent long-term potentiation (LTP) (Blum & Abbott, 1996; Jensen & Lisman, 1996b).

2.2 The Phase Decoder. This network receives an afferent input from the CA3 network (see Figure 1). The membrane potential of each of the nine cells in the decoder is defined as

$$-C\frac{dV}{dt} = I_L + I_{syn,AMPA} + I_{\Theta,decoder} + I_{noise}. \quad (2.4)$$

The theta drive takes the form $I_{\Theta,decoder} = I'_\Theta \cos(2\pi f_\Theta t + \phi)$ where ϕ defines the phase lag with respect to the hippocampal theta rhythm. The synaptic AMPA conductances to cell k from hippocampal cell i are defined as

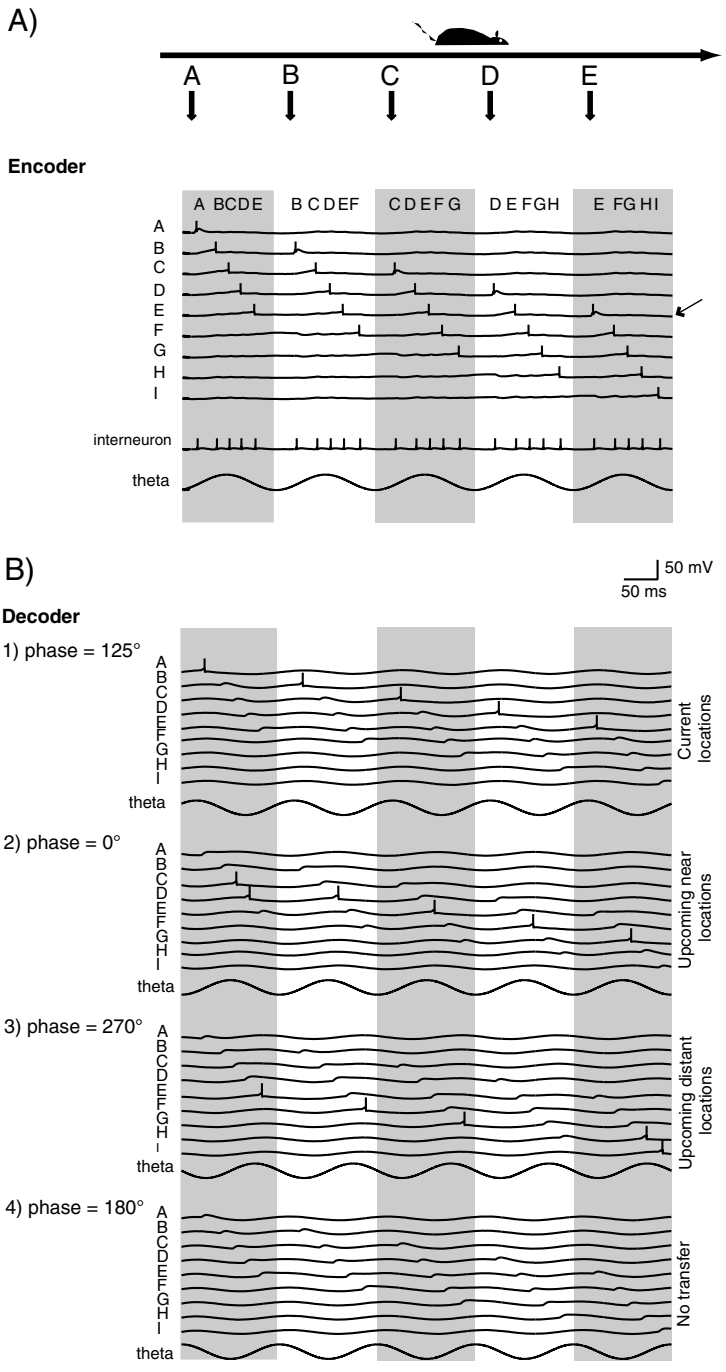
$$g^{ik}_{syn,AMPA} = W^{ik}_{decoder} \frac{t - t^i_{spike}}{\tau_{AMPA}} \exp\left(-\frac{t - t^i_{spike}}{\tau_{AMPA}}\right), \quad (2.5)$$

where the matrix $W^{ik}_{decoder}$ defines the connectivity from the hippocampus to the decoder. The first five cells in the hippocampal network are connected to the first cell of the decoder: $W^{i1}_{decoder} = 0.006\ \mu\mathrm{S/cm^2}$ for $i = 1, \ldots, 5$.

Cells 6 to 10 are connected to the second cell of the decoder: $W^{i2}_{decoder} = 0.006\ \mu S/cm^2$ and so on. For the other connections, $W^{ik}_{decoder} = 0$. Cells in the decoder will fire when they receive sufficiently strong synaptic input coinciding with a depolarizing theta drive. Constants that are different from those of the pyramidal neurons in the encoder are $I'_{\Theta} = 0.18\ \mu A/cm^2$ and $g'_{AMPA} = 0.006\ mS/cm^2$. In the simulations, gaussian distributed noise, I_{noise}, with a mean of 0 and a standard deviation of $0.1\ \mu A/cm^2$ was applied to all the neurons in the two networks. The differential equations defining the networks were numerically integrated with the time step $\Delta t = 0.1$ ms.

3 Results

Several groups have suggested that the theta phase precession is produced by repeated readouts of time-compressed sequences (Jensen & Lisman, 1996a; Skaggs et al., 1996; Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996; Wallenstein & Hasselmo, 1997). Figure 2A illustrates this principle. Assume that each location from A to I has a neuronal representation in the hippocampus. These representations are linked synaptically as a sequence in the CA3 region as a result of the temporal asymmetry in NMDA-dependent long-term potentiation (LTP) (Blum & Abbott, 1996; Jensen & Lisman, 1996b). When the rat arrives at location A, the sequence from B to E is recalled within a theta cycle. In the next theta cycle, the rat has advanced to location B, and the sequence from C to F is recalled. When recording from a place cell participating in the representation of location E, one observes a systematic advance in the theta phase of firing as the rat traverses through the place field: theta phase precession. A consequence of this model is that qualitatively different information is encoded in the phases of the theta cycle: predicted upcoming locations are represented by firing in the late phase of the theta cycle, whereas current locations are represented by early-phase firing. It is problematic to make the sequence models recall the individual representations at a sufficiently slow rate (about seven representations per theta cycle). Jensen and Lisman (1996a, 1997) proposed a solution in which the gamma rhythm (30–80 Hz) clocks the sequence readout: within a theta cycle, each of the recalled representations is separated in time by a hyperpolarizing GABAergic drive from the interneuronal network. This principle is in agreement with experimental work showing that the gamma and theta rhythms coexist in the rat hippocampus with a frequency ratio of about 5 to 10 (Soltesz & Deschenes, 1993; Bragin et al., 1995). Thus, the theta phase of place cell firing advances about one gamma period per theta period. As shown by Jensen and Lisman (1997) this scheme is in accordance with the experimental values for the phase precession and the observation that a place cell is active for about 5 to 10 theta cycles as a rat crosses a place field (Skaggs et al., 1996). Another finding consistent with the sequence readout models is that the theta phase of firing advances as a function of location rather


A)
A
B
C
D
E
Encoder
A BCDE
B CDEF
CDEFG
DEFGH
E FGHI
A
B
C
D
E
F
G
H
I
interneuron
theta
B)
50 mV
50 ms
Decoder
1) phase = 125°
2) phase = 0°
3) phase = 270°
4) phase = 180°
Current locations
Upcoming near locations
Upcoming distant locations
No transfer

than time (O'Keefe & Recce, 1993). This is a consequence of the sequence recall being probed by the rat's location. Finally, it was demonstrated that if the synaptic strength of the encoded sequences increases with number of presentations (Jensen & Lisman, 1996a), the sequence model can account for the systematic expansion of place cells after multiple traversals of the same path as observed experimentally (Mehta, Barnes, & McNaughton, 1997). Since the theta-gamma model is consistent with these experimental findings, it is a qualified candidate for a biophysically realistic mechanism that can produce phase-coded information.

3.1 Simulation of the Hippocampal Phase Encoder. The model of the hippocampal CA3 network (see Figure 1) is an improved version of a previously proposed model (Jensen & Lisman, 1996a). (For details on the improvements and implementation, see section 2.) The network has 45 pyramidal cells. The synchronous firing of 5 cells represents a location, allowing the network to represent up to nine different locations. Only voltage traces of 1 cell per representation are shown in Figure 2A (traces A–I). The last trace illustrates the theta drive. When the rat arrives at location A, the first 5 pyramidal neurons of the CA3 are excited by inputs from the dentate gyrus or by direct input from the entorhinal cortex (trace 1; only one neuron shown). The firing of these 5 cells activates the next representation (B, trace 2) by the CA3 recurrent collaterals. The firing pattern of representation B then activates representation C, and so forth. The inhibition from the interneuron (second to the last trace) serves to keep the representations in the sequence separate in time. Simulations demonstrated that in the

Figure 2: *Facing page.* Simulations demonstrating information transfer by the principle of phase encoding and decoding. (A) Hippocampal phase encoding by sequence readout. The top panel illustrates a rat traversing a path from left to right. Neuronal representations of locations A to E are received by the hippocampus as the rat advances. At each location, a time-compressed sequence of upcoming locations is recalled. In the simulations, each location is represented by the synchronous firing of five cells, but only the voltage trace of one cell per representation is shown (traces A–I). The second to the last trace is the voltage trace of the inhibitory interneuron, and the last trace is the hippocampal theta drive. (B) The voltage traces of the cells in the decoder and the theta inputs. The only parameter varied in the simulations is the phase ϕ of the theta drive. In panel 1, the decoder receives an input at 125 degrees, resulting in a transfer of representations from the early phases of the hippocampal theta rhythm, that is, the rat's current location. In panel 2, the encoder receives a theta input in phase (0 degree) with the hippocampus; thus upcoming near locations are transferred. In panel 3, where the phase is 270 degrees, representations from the late theta phase of the encoder are read out (i.e., upcoming distant locations). In panel 4, the decoder receives a theta input in anti-phase with the input of the encoder, and the information transfer is blocked.

presence of noise, the sequences were recalled with few errors. About 5% of the recalled patterns were represented by only 4 instead of 5 cells' firing simultaneously. The incomplete representations were due to cells' failing to fire or firing a gamma cycle too early or too late. Due to the redundancy of the representations, these errors did not prevent a correct recall of the following representations or errors in the phase decoding. Further simulations (not shown) demonstrated that the model can tolerate at least a 20% overlap between neighboring representations.

As an example of theta phase precession, consider the voltage trace of a pyramidal cell participating in the representation of pattern E (marked by the arrow). As the rat runs through the linear maze, the firing occurs earlier and earlier in the theta cycle. It is the spatiotemporal firing pattern that carries the phase-coded information.

3.2 Simulation of the Phase Decoder. The oscillatory network model reading the hippocampal phase code is illustrated in the right-hand portion of Figure 1. The hippocampal output of the CA3 region might pass several structures, among others the CA1, before arriving at a network that can perform the phase decoding. This work is not directly concerned with the processing in these intermediate regions. (For a discussion on how other hippocampal regions besides the CA3 might be involved in sequence readout, see Lisman, 1999.) Each of the 9 pyramidal cells in the decoder represents one of the locations from A to I. The first cell is synaptically connected to pyramidal cells 1 to 5 (representation A) of the CA3 network. The next cell is synaptically connected to cells 6 to 10 (representation B), and so on. Cells in the decoder fire if they receive sufficiently strong synaptic excitation coinciding with a depolarizing theta drive. The only parameter varied in the numerical simulations, Figure 2B, is the phase of the theta drive. The top panel represents the phase-coded input from the hippocampus. In panel 1, the phase decoder receives a theta input shifted 125 degrees from the hippocampal theta rhythm. The result is that representations from the early part of the hippocampal theta cycle activate cells in the decoder. For instance, the decoder cell representing location A fires shortly after representation A activates in the CA3 network. By this principle, information about current location is transferred to the decoder. If the decoder receives a theta input that is in phase with the hippocampal theta drive (panel 2), upcoming nearby locations about two to three theta cycles ahead in time (about 8–13 cm ahead of the rat with running speed of 30 cm/s) are activated in the decoder. In panel 3, the decoder receives a theta input shifted 270 degrees from the hippocampus. In this case, firing patterns from the very late phase of the hippocampus are transferred. Hence, upcoming distant locations about four theta cycles ahead in time (about 17–18 cm ahead of the rat with a running speed of 30 cm/s) are represented in the decoder. If the theta input to the decoder is in antiphase (panel 4) with the hippocampal CA3 input, the cells in the decoder will not fire; no information is transferred. Nor will cells in

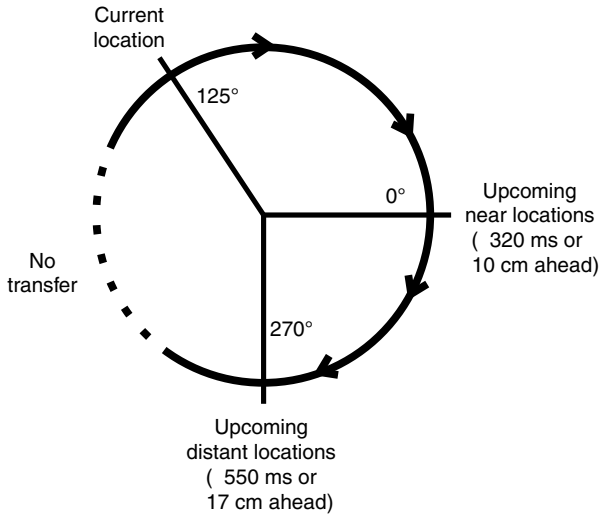


Figure 3: Qualitatively different information is decoded depending on the theta phase lag (angle in the circle map) between the hippocampus and the decoding network.

the decoder fire if the amplitude of the theta input is zero (data not shown). Notice that in panels 2 and 3, the phase decoder makes a few errors. For instance, the cell representing D, panel 2, fires twice. These errors are due to the noise added in the simulations and would be of less importance if the decoding network included more cells per representation. When adjusting the parameters of the neurons in the decoding network, it is crucial that the sum of the synaptic input currents and the maximum current of the theta input is strong enough to bring the pyramidal cells just above firing threshold. When this condition is fulfilled, the model is relatively insensitive to the ratio of the synaptic current compared to the theta current. For instance, the results in Figure 2B are reproduced when the synaptic input conductance is decreased from $g'_{AMPA} = 0.006$ mS/cm^2 to 0.0034 mS/cm^2 while the theta current is increased from $I'_{\Theta} = 0.18$ μA/cm^2 to 0.27 μA/cm^2.

The results of the simulations are summarized in the circle map (see Figure 3). The phase values in degrees denote the phase lag between the hippocampal network and the phase decoder. At phase lags of 125 degrees, current locations are decoded. As the phase difference is decreased, more and more distant locations are represented in the decoder. At phase lags of 270 degrees (= -90 degrees), the most distant locations are represented. At the portion where the theta drives are in antiphase (broken line), no information is transferred.

4 Discussion

I have proposed a simple but biophysically plausible mechanism for information transfer between rhythmically coupled networks. The mechanism was tested on a model for the CA3 region of the hippocampus, which can produce phase-coded spatial information by repeated readout of spatiotemporal firing patterns. By varying the phase of the rhythmic theta drive to the network receiving the phase-coded firing pattern, qualitatively different information is transferred. The phase difference determines if representations of the current location or predicted upcoming representations are transfered to the decoder. Information transfer is blocked if the theta inputs to the two networks are in antiphase. A network receiving the hippocampal firing pattern, but not the theta input, would only be able to decipher the firing rates and extract less detailed information. Hence, the rhythmic coupling is computationally advantageous since it allows transfer and decoding of phase-coded representations.

Which firing properties would be expected of the cells in regions performing the phase decoding of the hippocampal firing patterns? The summed activity of a large number of decoding cells, measured by field recordings, for instance, would produce a rhythmic theta signal. This signal would be coherent but not necessarily in phase with the hippocampal theta rhythm. The firing of the individual cells would correlate with the theta rhythm but not show phase precession since the cells in the decoder fire at a fixed phase with respect to the theta rhythm (see Figure 2B). Like the firing of place cells, the firing of the decoding cells would be correlated with the position of the rat. However, the spatial extent of the place fields would be five to seven times smaller compared to the place fields of the hippocampal place cells (see Figure 2B).

What brain areas could possibly make use of the hippocampal phase code? One candidate is the entorhinal cortex. This structure has abundant connections both to and from the hippocampal areas through the perforant path. The firing of some entorhinal cells is strongly modulated by a theta rhythm, possibly paced by the medial septum. Recently the existence of an entorhinal theta generator relatively independent of the hippocampal CA3 theta generator was established (Kocsis, Bragin, & Buzsaki, 1999). The phase relationship between the two generators was not reported. The firing of entorhinal cells is correlated with the location of the rat. Contradicting the predictions of the model, the entorhinal place fields are larger than hippocampal place fields (Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990). However, one cannot exclude the possibility that entorhinal place cells with small fields do exist but have not yet been identified. Another possibility is that the phase-coded information passes through the entorhinal cortex to the cingulate cortex. In this area, cells that fire rhythmically at the theta frequency have been identified in both urethane-anesthetized rats (Holsheimer, 1982) and freely moving rats (Borst, Leung, & MacFabe, 1987).

In an in vivo study, the activity of some cingulate cells was shown to be coherent with the hippocampal theta rhythm (Holsheimer, 1982). No consistent phase lag between pairs of coherent cells in the hippocampus and the cingulate cortex was found. As for the hippocampus, the theta activity of the cingulate cortex is thought to be modulated by input from the medial septum (Bland & Oddie, 1998). Interestingly, one study demonstrated cases in which the cingulate theta rhythm persists, whereas the hippocampal theta rhythm is abolished following lesions of the medial septum (Borst et al., 1987). Also, the cingulate cortex is well connected to many cortical areas (Vogt & Miller, 1983). Thus, both the entorhinal and the cingulate cortex are candidates for networks that can use the hippocampal phase code. A recent study in which the firing of prefrontal cortical neurons was phase-locked to the hippocampal theta rhythm opens the possibility that the prefrontal cortex makes use of the phase code (Siapas, Lee, Lubenov, & Wilson, 2000). Further research is required to characterize the prefrontal cells with respect to the rat's position and phase precession.

The regions reading the hippocampal phase code can work according to at least two different principles, as illustrated in Figure 4. According to the first principle, different regions of the phase decoder receive theta inputs at different phases. An example is shown in Figure 4A. The left-hand part of the phase decoder receives a theta input at 125 degrees phase relative to that of the hippocampus, corresponding to panel 1 in Figure 2B. The activity in this region will represent information about the current location of the rat. The right-most region of the phase decoder receives a theta input at 270 degrees, corresponding to panel 3 of Figure 2B. This region represents upcoming distant locations. By this principle, phase-coded firing patterns are spatially segregated into different regions. The maximum number of regions required to represent the degrees of predictions is determined by the phase resolution of the hippocampal code. Since the theta phase of firing advances about one gamma cycle per theta cycle, it is the number of gamma cycles per theta cycle that determines the degrees of predictions. Thus, a maximum of about 5 to 10 subregions in the decoder is sufficient for extracting the complete information of the phase code. The proposed scheme requires that theta inputs with different phases are available at different subregions of the decoder. The septum could potentially provide drives at different theta phases since different cells in the septum fire at different phases of the theta rhythm (Brazhnik & Fox, 1997; King, Recce, & O'Keefe, 1998). Thus, the proposed mechanism provides a purpose for septal cells' firing at different theta phases, a finding that is paradoxical if one considers that the only role of the septum is to pace the hippocampal theta rhythm. Interestingly, cells in the supramammillary nucleus have also been found to fire a theta frequency. Like the cells in the septum, the individual neurons have different preferred phases with respect to the hippocampal theta rhythm (Kocsis & Vertes, 1997). This suggests that the supramammillary nucleus and structures to which it projects could be involved in reading the hippocampal phase code.

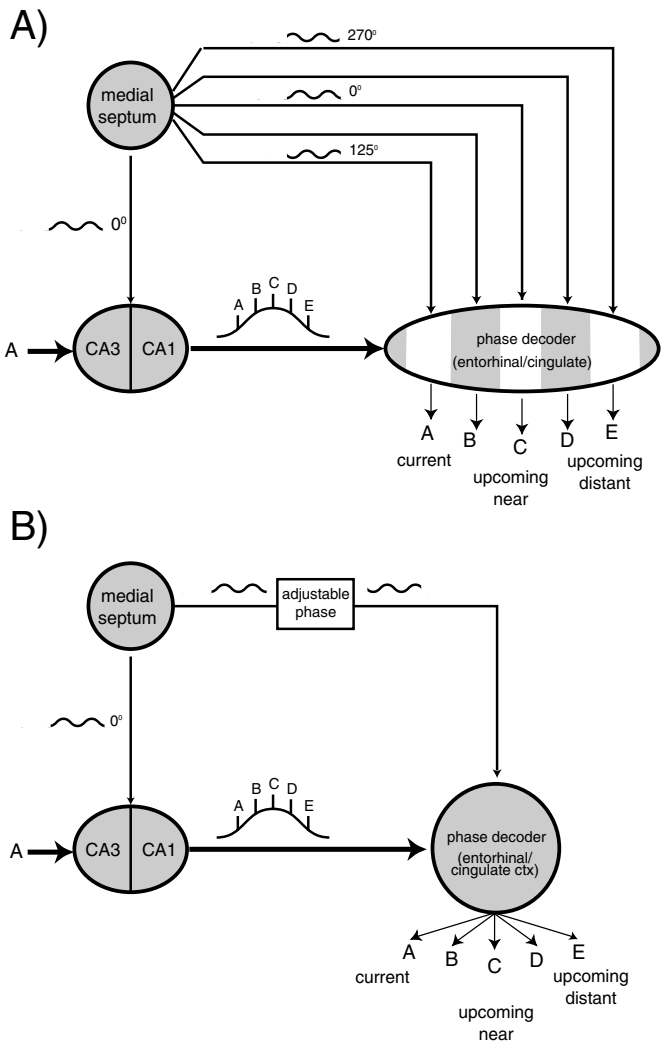


Figure 4: Two alternative principles of transfer of phase-decoded information between oscillatory networks. (A) Different regions in the phase decoder receive the theta drive at different phases. This allows the phase decoder to extract qualitatively different information simultaneously. The left-hand part of the phase decoder extracts representations corresponding to current location, and the right-hand part representations of upcoming distant locations. (B) The phase decoder receives the hippocampal phase-coded information and the theta drive from the septum. The phase of the theta input is adjustable and determines if the decoder is extracting representations of either current or predicted upcoming locations.

Another possibility is that the phase relationship between the hippocampus and the phase decoder changes dynamically (see Figure 4B). This mechanism requires about 5 to 10 times fewer cells than the previously proposed mechanism. When the rat is in a situation where predictions are important, for instance, navigating in a complicated but well-learned maze, the phase difference might be 270 degrees, corresponding to panel 3 of Figure 2B. If the rat is in a situation where no predictions are possible, for instance, foraging in an unknown environment, the phase difference might be 125 degrees, corresponding to panel 1 of Figure 2B. By this principle, qualitatively different information is transferred depending on the relative phase of theta input to the decoder. How can the phase relationship between the hippocampus and the decoder change dynamically? Again, the cells firing at different theta phases in the septum provide a possible solution: the drive from septal cells firing at a particular phase could be weighted according to the situation. The model proposed in Figure 4A requires more cells than the one in Figure 4B. Clearly, more experimental work is needed to investigate the phase relation between the hippocampus and the regions potentially performing the phase decoding in order to distinguish between the two mechanisms.

The proposed model for decoding is quite sensitive to the level of excitability; it is important that the sum of the synaptic input current and the current from the theta input are strong enough to bring the membrane potential of the cells just above threshold. However, the model is quite robust with respect to the ratio of theta current to synaptic current. Experimental work has revealed several physiological mechanisms promoting homeostatic stability of neuronal excitability (Bear, 1995; Desai, Rutherford, & Turrigiano, 1999; Turrigiano, 1999). Through these mechanisms, excitability is regulated by changes in intrinsic properties of the neurons and adjustments of excitatory and inhibitory synaptic inputs. I propose that similar physiological feedback mechanisms are responsible for adjusting the parameters to reasonable levels in the phase-decoding network. Further research is required to explore how such feedback mechanisms can help to adjust the network parameters to a robust regime.

Another class of models addressing transfer of information encoded by spike timing relative to an ongoing rhythm has been proposed by Ahissar (1998). This framework deals primarily with the decoding of the spike trains from single cells, not the decoding of a spatiotemporal code from an ensemble of cells. In the models, an oscillating network converts temporally encoded information to a rate code. The frequency of the oscillating decoder (the rate-controlled oscillator) is determined by the mean frequency of the incoming spike train. The decoding network compares the timing expectation defined according to the rate-controlled oscillator with the timing of an incoming spike. The difference in timing (phase information) is then converted to a rate code. This decoding scheme has been shown to be consistent with several experimental observations in the somatosensory cortex

(Ahissar et al., 1997, 2000). Although this framework has several components in common with the model proposed in this article, such as phase detection, it does not apply directly for reading the hippocampal phase code. The main reason is that due to the theta phase precession, the interspike intervals of place cells are shorter than a theta period (see Figure 2A). Thus, it is not possible to set the phase and frequency for the rate-controlled oscillator by the spike trains from individual place cells. However, it is possible that the decoding scheme proposed by Ahissar (1998) could apply to the hippocampal phase code if it was modified such that the frequency and phase of the rate-controlled oscillator were set according to the mean firing rate of the ensemble of place cells.

The theoretical framework developed in this article adds significance to the importance of oscillatory brain activity and the idea of phase coding. The principles of phase coding and information transfer between oscillatory networks can be generalized beyond the rat hippocampus. It has recently been proposed that the hippocampal sequence readout within theta cycles serves as a general mechanism for the encoding and recall of episodic memory in humans as well as in animals (Lisman, 1999). New methods are being developed for the purpose of localizing coherent oscillatory sources from human data recorded by magnetoencephalography and electroencephalography (Gross et al., 2001). Future research applying such approaches, as well as intracranial recordings in which single unit activity is related to the ongoing rhythmic activity, would be needed in order to test the ideas on information transfer between rhythmically coupled networks.

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