

Hippocampal Correlation Coding:  
Phase Precession and Temporal Patterns in CA3 and CA1

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## Abstract

Hippocampal correlation coding is a putative neural mechanism underlying episodic memory. In this thesis, we look at two related phenomena: phase precession and reverse replay of behavioral sequences. Phase precession refers to the decrease of the firing phase of a place cell with respect to the local theta rhythm during the crossing of the place field. Reverse replay refers to reactivation of previously experienced place field sequences in reverse order during awake resting periods.

First, we study properties of phase precession in single trials. Usually, phase precession is studied only on the basis of data in which many place field traversals are pooled together. We find that single-trial and pooled-trial phase precession are different with respect to phase-position correlation, phase-time correlation, and phase range. We demonstrate that phase precession exhibits a large trial-to-trial variability and that pooling trials changes basic measures of phase precession. These findings indicate that single trials may be better suited for encoding temporally structured events than is suggested by the pooled data.

Second, we examine the coordination of phase precession among different subregions of the hippocampus. We find that the local theta rhythms in CA3 and CA1 are almost antiphasic. Still, phase precession in the two regions occurs with only a small phase shift, and CA3 cells tend to fire a few milliseconds before CA1 cells. These results suggest that phase precession in CA1 might be inherited from CA3.

Finally, we present a model of reverse replay based on short-term facilitation. The model compresses temporal patterns from a behavioral time scale of seconds to shorter time scales relevant for synaptic plasticity. We demonstrate that the compressed patterns can be learned by the tempotron learning rule. The model provides testable predictions (synchronous activation of dentate gyrus during sharp wave-ripples) and functional interpretations of hippocampal activity (temporal pattern learning).

## Keywords:

Hippocampus, Temporal Coding, Phase Precession, Sequence Learning

## Zusammenfassung

Korrelationskodierung im Hippokampus bildet möglicherweise die neuronale Basis für episodisches Gedächtnis. In dieser Arbeit untersuchen wir zwei Phänomene der Korrelationskodierung: Phasenpräzession und Sequenzwiederholungen. Phasenpräzession bezeichnet die Abnahme der Phase des Aktionspotentials einer Ortszelle relativ zur Theta-Oszillation. Sequenzwiederholung beschreibt die Aktivität von Ortszellen in Ruhephasen; dabei werden vorangegangene Orts-Sequenzen in umgekehrter Reihenfolge wiederholt.

Wir untersuchen Phasenpräzession in einzelnen Versuchsdurchläufen. In bisherigen Studien wurden Daten zur Phasenpräzession in vielen Versuchsdurchläufen zusammengelegt. Wir zeigen, dass dies zu einer verzerrten Schätzung von grundlegenden Eigenschaften der Phasenpräzession führen kann. Weiterhin demonstrieren wir eine starke Variabilität der Phasenpräzession zwischen verschiedenen Versuchsdurchläufen. Daher ist Phasenpräzession besser geeignet zeitlich strukturierte Sequenzen zu lernen, als man aufgrund der zusammengelegten Daten vermutet hatte.

Desweiteren untersuchen wir die Beziehung von Phasenpräzession in unterschiedlichen Teilen des Hippokampus. Wir zeigen, dass die extrazellulären Theta-Oszillationen in CA3 und CA1 außer Phase sind. Dennoch geschieht Phasenpräzession in beiden Regionen fast gleichzeitig, und CA3 Zellen feuern oft kurz vor CA1 Zellen. Diese zeitliche Beziehung ist im Einklang mit einer Vererbung von Phasenpräzession von CA3 nach CA1.

Wir entwickeln ein mechanistisches Modell für Sequenzwiederholungen in umgekehrter Reihenfolge basierend auf Kurzzeitfazilitierung. Mit Hilfe des Tempotrons beweisen wir, dass die entstehenden zeitlichen Muster geeignet sind, um von nachgeschalteten Strukturen ausgelesen zu werden. Das Modell sagt voraus, dass im Gyrus Dentatus synchrone Zellaktivität kurz vor einer Sequenzwiederholung in CA3 zu sehen ist, und es zeigt, dass Sequenzwiederholungen zum Lernen von zeitlichen Mustern genutzt werden können.

## Schlagwörter:

Hippokampus, Zeitliche Kodierung, Phasenpräzession, Sequenzlernen

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# Chapter 1

## Introduction

The brain processes sensory input to generate behavioral output. Nerve cell activity plays a major role in this processing, and neuroscience tries to correlate different activity patterns with certain behavioral and cognitive states. How information is encoded by nerve cell activity is a fundamental question. Most prominent is the so-called rate code in which the rate of nerve cell activity (number of action potentials per time unit) contains information. For example, some cells in the visual system increase their firing rates if there is a vertical bar in their receptive fields. Alternatively, information can be transmitted in the nervous system by temporal coding in which the timing of action potentials is important. For example, light intensity is encoded in some cells in the visual system in the response latency. Furthermore, the activity of an ensemble of cells can be correlated. For example, cells can be active in a certain order, so that the activity of the cells forms a temporal pattern. This type of coding is referred to as correlation coding and has been demonstrated in a particular region of the brain, the hippocampus. Correlation coding in the hippocampus is a promising candidate for fundamental memory processes.

In this thesis, we look at a phenomenon called phase precession in behaving rats performing a simple spatial task that leads to correlation coding in the cell population. The topics of my research on phase precession are single-trial phase precession and its coordination among different regions of the hippocampus. Furthermore, I present a model for the replay of sequences of events. We examine how short-term facilitation can generate temporal patterns and whether these patterns can be discriminated by downstream structures for learning.

In the second chapter, I provide a brief summary on episodic memory and describe the challenge of identifying neural correlates of episodic memory. In addition, I explain the relevant hippocampal physiology and review potential

functional roles of the hippocampus in spatial navigation and memory.

The third chapter focuses on correlation coding in the hippocampus, i.e. on phase precession and sequence replay. I summarize experimental studies, functional roles and mechanistic models of these phenomena. Finally, I discuss several gaps of knowledge that serve as a motivation for the work presented in the following chapters.

The fourth chapter deals with single-trial phase precession in the hippocampus. So far phase precession has mostly been studied on the basis of data pooled over several trials. I show that, due to trial-to-trial variability, basic properties of phase precession are different in single trials and pooled data. I argue that single-trial phase precession is important to understand the mechanisms underlying phase precession.

The fifth chapter relates phase precession in the CA3 and the CA1 region of the hippocampus. Phase precession in these two regions occurs almost simultaneously, with CA3 being active briefly before CA1. In contrast, CA3 and CA1 theta oscillations are out of phase. I conclude that phase precession in CA1 could be inherited from CA3.

In the sixth chapter, I hypothesize how phase precession and reverse replay of sequences are related. I demonstrate that short-term synaptic plasticity can generate activity patterns of cell populations in which behavioral time scales are compressed to time scales of synaptic plasticity rules. As a proof of concept I apply the tempotron learning algorithm to show that these patterns are suitable for discrimination learning. In conclusion, sequence replay provides temporal patterns that can be used by downstream neurons for fundamental memory processes.

The seventh chapter provides a general discussion that integrates the findings from the previous chapters in a broader perspective. Furthermore, I sketch the relevance of my findings for future studies that help to understand the role of hippocampal correlation coding in memory.

The last chapter contains several appendices with supplemental results from the preceding chapters. For example, additional methods to create surrogate single trials are presented.

Overall, in this thesis, I reveal previously unknown neurophysiological properties of hippocampal phase precession and develop a new mechanistic model for sequence replay. Thereby, I contribute to the identification of neural mechanisms underlying episodic memory.

# Chapter 2

## Episodic Memory and the Hippocampus

*“Episodic memory receives and stores information about temporally dated episodes or events, and temporal-spatial relations among these events.”*

- Endel Tulving (1972)

In this introductory chapter I present the relevant background for the studies in the following chapters. First, I provide some background on so-called episodic memory. Then, I describe the neurophysiology of the hippocampus, followed by a summary on putative functions of the hippocampus.

### 2.1 Episodic Memory and Correlation Coding

Humans spend a lot of time with indulging past events. For example, we retrieve pleasant past experiences such as a Christmas Eve or a special holiday. The important characteristic of such episodic memories is that we can remember them very well although we experienced them only once. Why is this something extraordinary? Other types of learning, e.g. motor learning that is employed for learning how to ride a bike, or even simpler types of learning, as operant conditioning, require many trials or repetitions to complete learning. Thus, to store episodic memories after a single experience, a powerful neural mechanism is required. It is not known how the brain stores episodic memories. However, it has been proposed that correlation

coding in the hippocampus may play a major role (Buzsáki, 2005). Thus, in order to reveal the neural basis of episodic memories, it is of great interest to understand neurobiological details underlying correlation coding.

### **2.1.1 Properties of episodic memory**

What properties enable a neural mechanism to store episodic memories? Episodic events usually occur only once, so the learning must occur within a single trial (one-shot learning). The items or events that belong to an episodic memory can be quite abstract and be derived from different modalities. Further, they are embedded in a temporal context in which order is preserved. For example, an episodic memory can be the experience of a dinner. The memory can include the name of the restaurant, its location, other guests, the menu, the conversation, the taste of the food, the occurrence of a spilled glass of wine, etc. All these items are connected somehow to form the episodic memory although they can be separated by a considerable amount of time. In summary, a neural mechanism for storing episodic memories must be able to concatenate temporally-separated, multimodal stimuli and abstract concepts to an ordered sequence after a single experience. In the next chapter we will see that correlation coding in the hippocampus can account for these requirements.

Of course, we do not remember everything we ever experienced. Thus there is some selection of events that we instead forget. Important events are believed to undergo a process termed consolidation. For example, the hippocampus is often regarded as the brain region where recent memories are initially stored. During consolidation, the more important memories are somehow transferred to cortical areas where they are stored for longer time periods. Thereby, the hippocampus can continuously store new memories without disturbing the long-term storage of previously experienced important events. Intuitively, ‘importance’ and temporal proximity play a major role in the process of memory consolidation, which permits long-term storage of such memories over years. It seems plausible that a recent important event is ‘thought’ about a lot afterwards and thus consolidated through repeated retrieval.

### **2.1.2 Episodic-like memory in non-human animals**

The brain performs many different types of memory function. Much effort has been made to assign certain brain regions to specific types of memory. There is evidence for the human hippocampus to be critical for episodic memory (Vargha-Khadem et al., 1997; Tulving and Markowitsch, 1998).

It should be noted that an influential formulation by Endel Tulving restricts episodic memories to humans (e.g. Tulving, 2002). Still, recent work suggests that also some animals fulfill the criteria of episodic memories, such as the ability of ‘mental time traveling’ (Clayton et al., 2003). Further, it is possible that some animals possess simpler forms of episodic memory, or memory systems that followed a different evolutionary path and perform similar but not identical functions. Therefore, respective studies often use the term ‘episodic-like’ memory to indicate that some aspects of the studied system, as conscious experience, might differ from the classic definition of episodic memory.

Importantly, episodic memory does not just include the knowledge of how certain events are connected, but rather includes the memory of the *experience* itself (Tulving and Markowitsch, 1998). This is difficult to grasp from a neurobiological perspective, but naively one could say that if the same cell population is active during the actual experience and the retrieval of an episodic memory, this feature might be retained.

Keeping these remarks in mind, we can now turn to the neurobiological details. In the next section I provide the basic neurobiological details that are necessary to understand my work on hippocampal correlation coding in the following chapters.

## 2.2 Hippocampal Physiology

The hippocampus is often described as a trisynaptic loop (Anderson et al., 1971, see Figure 2.1). Input is first transmitted from the dentate gyrus to the recurrent network in the CA3 region. Next, it is projected to CA1 and finally to the output region, the subiculum. This view is a strong simplification, but many modeling studies employ a form of the trisynaptic loop with different extensions (e.g. Treves and Rolls, 1994; Wiskott et al., 2006; Koene and Hasselmo, 2008). However, it is clear that the trisynaptic loop alone does not implement the function of the hippocampus. Hippocampal anatomy and physiology have been described in great detail elsewhere (O’Keefe and Nadel, 1978; Andersen et al., 2007). Here I just briefly summarize the most important issues that are relevant to understand the following chapters.

A more detailed image of a hippocampal slice is shown in Figure 2.2, illustrating the different layers and location of dendritic trees and axons of projection neurons. Due to the anatomical arrangement of hippocampal cells and projections, major connectivity pathways can be retained in hippocampal slices (Amaral and Witter, 1989; Andersen et al., 2000). Strictly speaking, the hippocampus consists only of the three subdivisions of the cornu ammonis:

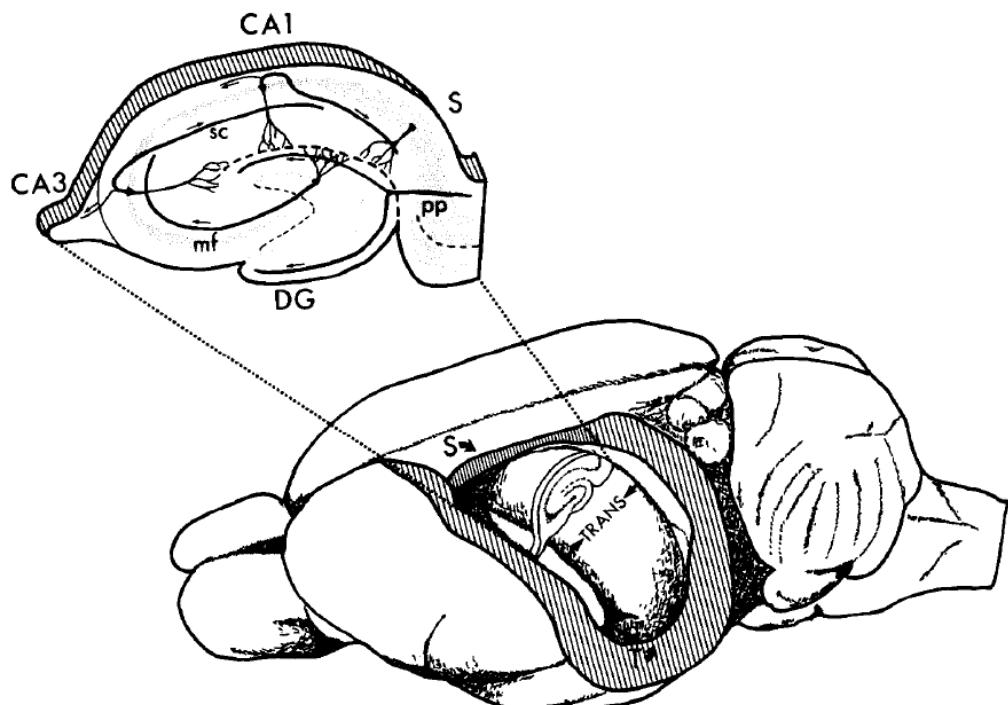


Figure 2.1: The hippocampus (from Amaral and Witter, 1989; with permission from Elsevier). (Bottom picture) Illustration of the anatomical position of the hippocampus in the rat brain. Cortical areas usually lying on top of the hippocampus are not shown. The C-shaped hippocampus is situated between the rostrally located septum (S) and temporal cortex (T). A slice along the transverse axis (TRANS) reveals the typical trisynaptic loop (top picture). Input arrives via the perforant path (pp) in the dentate gyrus (DG). From there mossy fibers (mf) project to the CA3 region. From CA3 the Schaffer collaterals (sc) contact CA1, which in turn projects to the subiculum (S), the output region of the hippocampus.

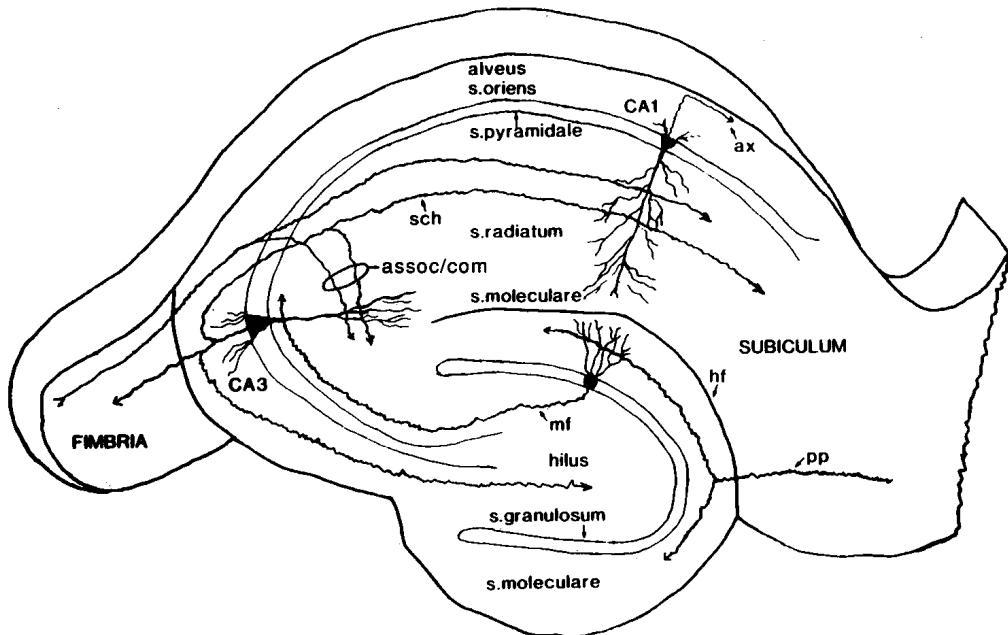


Figure 2.2: A hippocampal slice illustrating main subregions, layers and connectivity (after Amaral<sup>1</sup>; abbreviations: perforant path (pp), hippocampal fissure (hf), mossy fiber (mf), stratum (s.), associational commissural (assoc/com), Schaffer collaterals (sch), and axon (ax).)

nis (CA) (Andersen et al., 2007). Closely related structures are the dentate gyrus and the subiculum, which comprise major hippocampal input and output regions, respectively. Overall, the hippocampal *formation* contains the hippocampus, the dentate gyrus, the subiculum, the presubiculum, the parasubiculum, and the entorhinal cortex. The entorhinal cortex provides the cortical input to the hippocampus. Different layers of the entorhinal cortex project to different parts of the hippocampus: layer II to the dentate gyrus and CA3, layer III to CA1. Granule cells in the dentate gyrus project to CA3 via glutamatergic mossy fibers. In the rat CA3 region, there are about 225.000 pyramidal cells forming a dense excitatory recurrent network (Rapp and Gallagher, 1996). CA3 pyramidal neurons send their axons to the ipsilateral and contralateral CA1 via the Schaffer collaterals and associational commissural pathway, respectively. In the CA1 region there are about 400.000 pyramidal neurons (in rats) projecting to the subiculum (Rapp and Gallagher, 1996; Ahmed and Mehta, 2009). CA1 and subicular pyramidal neurons send hippocampal output back to the entorhinal cortex.

In addition to the pyramidal neurons, different parts of the hippocampus

contain many different types of interneurons (Freund and Buzsáki, 1996). In this thesis we are mostly interested in the response properties of pyramidal neurons, but interneurons modulate the responses of pyramidal neurons and are important for hippocampal oscillations (see below). Also neglected are the various neuromodulatory inputs. Dopamine, acetylcholine, serotonin, and noradrenaline play an important role in hippocampal function (Schmitz et al., 1998; Hasselmo et al., 2002; Lisman and Grace, 2005; Hasselmo, 2006; Harley, 2007; Perez-Garcia and Meneses, 2008; Rossato et al., 2009; Zhang et al., 2009).

In this thesis, two hippocampal features are of particular importance: pyramidal neurons with spatially-selective activity patterns and hippocampal oscillations in the local field potential (LFP) that reflect the activity of cell populations.

### 2.2.1 Place cells

The discovery of hippocampal place cells in rats supported a functional role of the hippocampus in spatial navigation (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). A place cell responds with an increase in spiking activity when the animal moves through a particular region of the environment (the place field; Figure 2.3). In the population of place cells, different cells can have different, potentially overlapping, place fields. Thereby, the place cell population encodes the spatial location of the rat in the environment. The stereotypical place cell exceeds its firing rate above baseline in a circular-shaped place field. Experimental studies have reported place-field sizes between 30 and 50 cm (e.g. Diba and Buzsáki, 2008; Lu and Bilkey, 2009). However, in larger environments, place-field size depends on the anatomical location of the place cell along the dorsal-ventral axis, with place-field sizes of up to 10 meters in the ventral hippocampus (Kjelstrup et al., 2008). Outside the place field, the firing rate is usually rather low (like 1 Hz or less; Wilson and McNaughton, 1993). Inside the place field, the firing rate can be 20 Hz or even more (Dragoi et al., 2003). The firing rate also varies within the place field. Usually the firing rate is symmetrically distributed, so that it is highest in the center of the field (O'Keefe and Burgess, 1996). However, some studies found an experience-dependent change such that the firing rate became highest at the end of the place field (Mehta et al., 2000). Other studies did not find a strong bias for experience-dependent skewed place fields (Huxter et al., 2003; Hafting et al., 2008). An experience-dependent increase in the size of the place field has also been reported (Mehta et al., 1997; Ek-

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<sup>1</sup>websource: <http://itb.biologie.hu-berlin.de/~kempter/HippoJC/hippocampus.jpg>

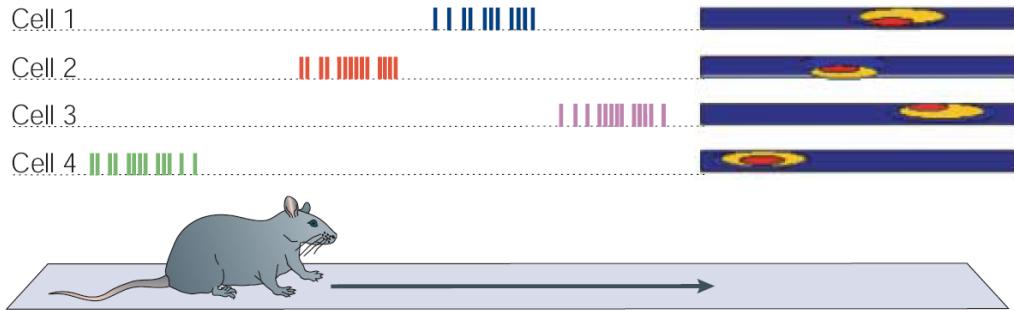


Figure 2.3: Hippocampal place cells (from Nakazawa et al., 2004; with permission from Macmillan Publishers Ltd). Illustration of activity of four place cells of a rat moving on a linear track. (Left) Spikes (vertical bars) during a single run from the left to the right end of the track. Note that different cells are active at different parts of the track. (Right) Place fields of the four place cells marked through color-coded firing rates. The population of hippocampal place fields cover the whole environment with overlapping place fields.

strom et al., 2001). This increase is asymmetric and opposite to the running direction of the animal.

In one-dimensional environments, place cells are often unidirectional, which means that they are active only for one direction of movement (O’Keefe and Recce, 1993). So, for example on a linear track some cells would fire only during runs from the left to the right, others from the right to left, but few cells would fire at the same location for both directions. In two-dimensional environments, place cells fire independent of the running direction (Muller et al., 1994).

Although place cells appear to cover the whole environment of the animal, there is a debate on the parameters that determine the distribution of place fields in the environment. For example, the presence of rewards at particular locations can induce place field shifts towards the reward location (Breese et al., 1989, but see Speakman and O’Keefe, 1990). It has also been proposed that goal locations are encoded through a gradient in the place field density (Bilkey and Clearwater, 2005; Bilkey, 2007).

### 2.2.2 Oscillations

Hippocampal oscillations have recently gained much attention in scientific research (Buzsáki, 2006). They are usually measured in the LFP, a signal that is believed to reflect mostly synaptic currents of a large number of neurons in the surrounding of the recording site (Andersen et al., 2007).

The LFP is recorded in the extracellular space and is obtained by low-pass filtering the recorded signal to exclude the high-frequency signals reflecting action potentials.

In the hippocampus, oscillations in the theta, gamma and high-frequency band are most interesting. Theta oscillations (4 to 12 Hz) are associated with exploratory behavior of the animal (O'Keefe and Nadel, 1978). Gamma oscillations (30 to 100 Hz) might be related to cognitive functions (Bragin et al., 1995; Montgomery and Buzsáki, 2007). High-frequency oscillations around 200 Hz are present during so-called sharp wave-ripple events in the LFP (O'Keefe and Nadel, 1978; Buzsáki et al., 1983). They occur during behavioral resting periods and slow-wave sleep and might play a role in the consolidation of learning (Buzsáki, 1989). In this thesis, the theta rhythm and sharp wave-ripple events are the most relevant oscillations.

## **Theta**

Theta oscillations appear in the LFP in all hippocampal regions and layers (Buzsáki, 2002). Due to the parallel organization of dendrites and afferents, transmembrane currents are present in the extracellular field. Randomly distributed dendrites and afferents would rather generate a closed field, so that the synaptic currents would cancel out. With increasing depth of the recording electrode, there is an increasing phase shift of the theta oscillation (Figure 2.4). Neural mechanisms that cause theta oscillations in the hippocampus are under debate but are likely to involve subcortical structures.

Some types of interneurons are phase-locked to the extracellular theta rhythm (Klausberger et al., 2003; Klausberger and Somogyi, 2008). Further, the intracellular membrane potential of CA1 pyramidal neurons is theta-modulated (Kamondi et al., 1998; Lee et al., 2006), so that extracellular peaks correspond to intracellular troughs. This observation is in line with the view that in the pyramidal cell layer the theta oscillations in the LFP reflect synaptic currents from inhibitory synapses of certain interneurons on pyramidal cells. Thereby, the easily measurable extracellular signal provides us with an idea about the intracellular subthreshold activity in behaving animals.

## **Sharp wave-ripples**

Sharp wave-ripple events (O'Keefe and Nadel, 1978; Buzsáki et al., 1983) occur during awake resting periods and slow-wave sleep. Such an event appears in the LFP as a sharp wave of about 100 ms duration together with a typical ripple oscillation of about 200 Hz (Figure 2.5). These events in the

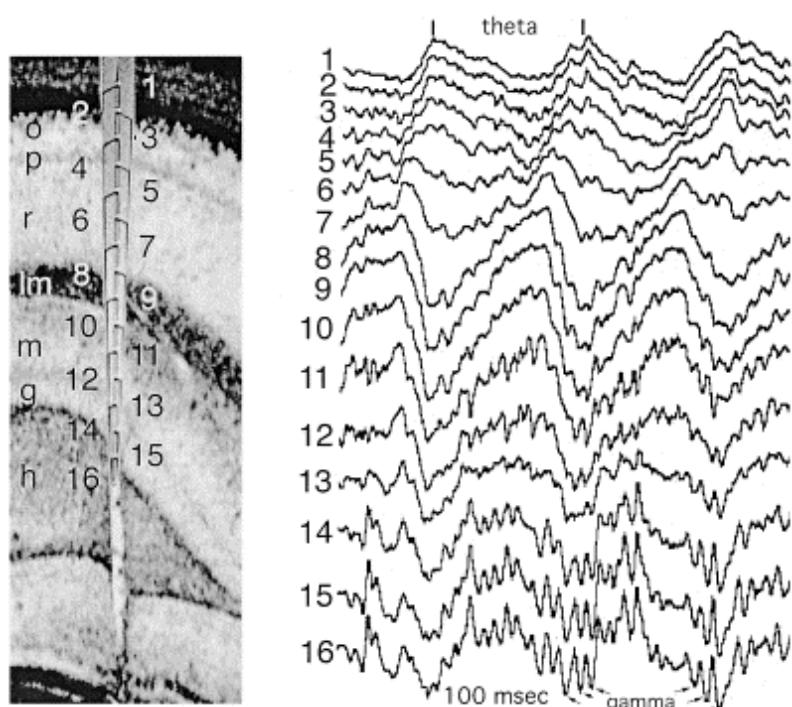


Figure 2.4: Hippocampal theta oscillations (from Buzsáki, 2002; Bragin et al., 1995; with permission from Elsevier). LFP signals (right; vertical bar denotes 1 mV) are shown for 16 recording sites located in different layers (left; spacing between sites is 100  $\mu$ m). Note the phase shift of the theta oscillation with increasing electrode depth. Abbreviations are (from top to bottom): stratum oriens (o), stratum pyramidale (p), stratum radiatum (r), stratum lacunosum-moleculare (lm), stratum moleculare (m), stratum granulare (g), and hilus (h).

LFP are accompanied by synchronous activation of many pyramidal cells and interneurons (Ylinen et al., 1995; Klausberger et al., 2003; Klausberger and Somogyi, 2008). They are thought to reflect retrieval (Koene and Hasselmo, 2008) or consolidation (Buzsáki, 1989; Peyrache et al., 2009; Ramadan et al., 2009) of recently stored sequences. Sharp wave-ripple events have also been demonstrated in in-vitro preparations (Maier et al., 2003; Kubota et al., 2003; Behrens et al., 2005).

## 2.3 Hippocampal Function

It is still unclear what the hippocampus, one of the most studied brain regions, is actually doing. Two discoveries have lead to two influential lines of research: the discovery of place cells (O'Keefe, 1976) and memory impairments following temporal lobe lesions, including the hippocampus and entorhinal cortex (e.g. in patient HM; Scoville and Milner, 1957; Corkin, 2002).

### 2.3.1 Spatial navigation

The existence of place cells lead to the hypothesis of the hippocampus as a cognitive map (O'Keefe and Nadel, 1978). This map is formed by the population of hippocampal cells and is a representation of the environment. This representation is thought to allow the animal to navigate. Studies showing impaired spatial navigation after hippocampal lesions (O'Keefe and Nadel, 1978) have supported this hypothesis. A widely used behavioral task is the Morris water maze (Morris, 1981) in which the rat is required to swim in a circular pool until it manages to find a hidden platform where it can rest. Performance is often tested by removing the platform and measuring where in the swimming pool the animal is looking for the platform. A key finding was that rats with hippocampal lesions were impaired in the Morris water maze task (Morris et al., 1982). Since then many variants of this task have been developed to study various behavioral deficits (e.g. reviewed in D'Hooge and De Deyn, 2001). For example, the platform location can be changed at a certain stage of training to enforce new learning. However, it is difficult to differentiate impairments of spatial navigation from other impairments, such as motor, memory or emotional impairments. For example, the Morris water maze is a very aversive setting for rodents, which gives rise to high stress levels due to the fear of drowning. Therefore, the interpretation of the animal performance on the water maze task is problematic.

The hippocampus does not just contain place cells. Cell activity is also

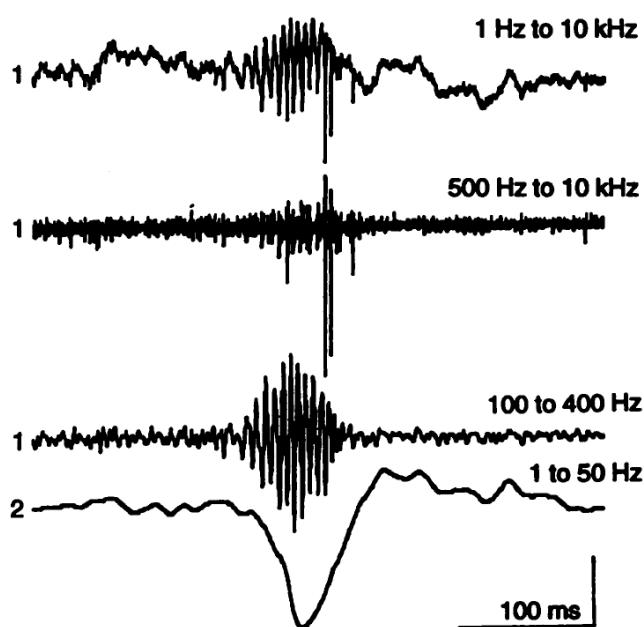


Figure 2.5: Hippocampal sharp-wave ripples (from Buzsáki et al., 1992; with permission from AAAS). Electrode 1 in the CA1 pyramidal cell layer shows high-frequency ripple activity. Simultaneous recordings at electrode 2 in stratum radiatum reveal a sharp wave at the same time as the ripple activity. The traces are filtered as indicated by the given frequency bands. Calibration bar denotes 0.5 mV for trace #1, 0.25 mV for traces #2 and #3, and 1.0 mV for trace #4.

modulated by non-spatial parameters (Hölscher, 2003). For example, place cells can acquire responses to conditioned stimuli in their place field (Moita et al., 2003). Further, in odor recognition memory tasks, activity of hippocampal cells codes for task-relevant factors such as odor identity (Wiebe and Stäubli, 2001). For (lab) rats performing spatial tasks, it should not be surprising that ‘places’ are a useful memory item. Thus, the label ‘place cell’ can also be misleading. In addition, there may well be differences among species: the rat hippocampus may be specialized to perform typical rat tasks, which are different from typical human tasks. In human patients, recordings made during surgery to detect the origin of epileptic seizures revealed very specific cell responses e.g. to visual presentation of certain celebrities (Quiroga et al., 2005).

### 2.3.2 Memory

Alternative, or in addition, to a functional role of the hippocampus in spatial navigation, much evidence supports a hippocampal role in memory. To specify its role, hippocampus-dependent learning tasks have been identified. These include the Morris water maze (see above), trace- (but not delay-) conditioning<sup>1</sup> (Solomon et al., 1986; Weiss et al., 1999), and the learning of sequences (Fortin et al., 2002). However, not only the nature of the task but also task difficulty determines whether the hippocampus is required to learn the task (Beylin et al., 2001; Agster et al., 2002). It seems that there is no easy answer to the question of the role of the hippocampus in memory, indicating that the hippocampal function simply does not strictly conform to existing neuropsychological categories. Therefore, understanding the hippocampal algorithm, i.e. the physiological processes, in detail will be essential to solve the puzzle of hippocampal function.

The various proposals on the hippocampal role in memory have been reviewed elsewhere in great detail (e.g. Hölscher, 2003; Andersen et al., 2007). Most proposals focus on a role in declarative memory, i.e. episodic and semantic memory, based on the influential finding in patient HM (Scoville and Milner, 1957). After medial temporal lobe lesion, he was unable to form new long-term episodic memories although he could still learn new procedural (e.g. motor) skills (Corkin, 2002). While episodic memory concerns the experience of past events (see above), semantic memory concerns general

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<sup>1</sup>The terminology is somewhat counter-intuitive: in trace conditioning there is a time interval between the offset of the conditioned stimulus (an arbitrary sensory cue) and the occurrence of the unconditioned stimulus (e.g. a reward). In delay conditioning the onset of the unconditioned stimulus coincides with the offset of the conditioned stimulus, so that there is *no* delay between them.

facts independent of personal experience (Tulving and Markowitsch, 1998). A major question is whether interaction of the hippocampus with the entorhinal cortex and other parts of the temporal lobe implements declarative memory. Alternatively, there could be a further functional subdivision, so that e.g. the hippocampus is primarily involved in episodic memory and the entorhinal cortex in semantic memory (Tulving and Markowitsch, 1998). In general, many proposals on hippocampal memory function share common requirements for the underlying neural mechanism. For example, an episodic memory contains a sequence of events that are temporally separated. In some cases this sequence could be a sequence of places, which, of course, is then also related to spatial memory.

Currently, more emphasis is posed on attempts to reconcile the hippocampal role in spatial navigation and episodic memory (Redish, 2001; Andersen et al., 2007). For example, the hippocampus could simply perform several functions. Also, there could be functional subdivisions within the hippocampus, e.g. between the ventral and dorsal part (Moser and Moser, 1998). Furthermore, the spatial activity might reflect the spatial nature of the task that the animals are performing. Thus, place cell activity might reflect a component of episodic-like memory in a spatial task. In summary, the controversy on the functional role of the hippocampus is not resolved. Any insight into neural coding in the hippocampus might thus contribute to clarify its function.

# Chapter 3

## Hippocampal Correlation Coding

In this chapter I will explain two forms of hippocampal correlation coding: phase precession and sequence replay (Figure 3.1). In both of them, the activity of a neuron is correlated with the activity of other neurons, so that there is a preferred time interval between action potentials of different cells. This correlated activity leads to a certain pattern in the order of activity of the cells in the population.

The hippocampus exhibits rate coding, temporal coding, and correlation coding. Place cells encode the animal's location in the environment with a rate code. The animal's location *within* the place field is also encoded in timing of a spike within a theta oscillation cycle. The sequence of overlapping place fields visited by the animal is, in addition, encoded in the correlation between different place cells.

### 3.1 Phase Precession

The temporal relation of action potentials of hippocampal pyramidal cells to the theta oscillation in the LFP is one of the few known examples of correlation-coding in the brain (Dayan and Abbott, 2001). To relate spike times to the LFP, each spike is assigned a theta phase between  $0^\circ$  and  $360^\circ$ , where  $0^\circ$  corresponds to the trough of the theta oscillation. The spike phases decrease from theta cycle to theta cycle during the crossing of the place field of a pyramidal cell (O'Keefe and Recce, 1993). Hence, the spike phase is negatively correlated with both the position of the animal within the place field (*phase-position correlation*) and the time that has passed since the animal entered the place field (*phase-time correlation*) (Huxter et al., 2003). This

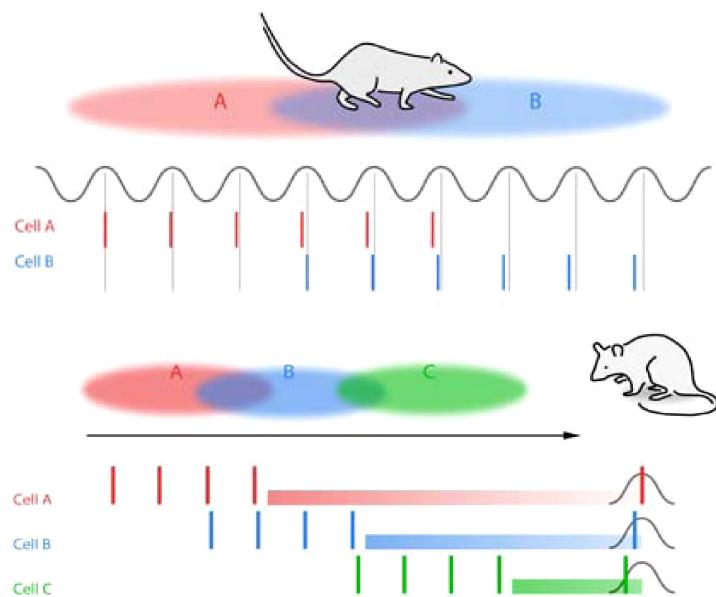


Figure 3.1: Illustration of phase precession and sequence replay in the hippocampus (from Bernstein Newsletter, July 2008). (Top) Phase precession. The rat crosses two overlapping place fields A and B. During the crossing, each cell fires a burst of six spikes (colored vertical lines). These spikes have a certain temporal relation to the ongoing theta oscillation (black line). Maxima of the oscillation are marked by gray vertical lines. The first spike within a place field occurs here at the maximum of the oscillation. With each successive oscillation cycle the spike occurs earlier in the theta cycle. Note that within a given theta cycle cell A always fires before cell B, preserving information about which field was entered first. (Bottom) Sequence replay. After the crossing of three place fields (first field A, then B, then C) the rat takes a rest. During immobility the recently crossed place cells become active again. The order of their activity is reverse to the original sequence during movement (first C, then B, then A).

phenomenon is called phase precession (Figure 3.1).

Phase precession leads to the temporal compression of behavioral sequences (Figure 3.2): within one theta cycle (approximately 125 ms), the order of activity among a group of place cells with overlapping place fields corresponds to the order in which the animal crosses the place fields (Skaggs et al., 1996); in particular, the spatial distances between place field centers are encoded in the time lag between the respective place cells' activity within one theta cycle (Dragoi and Buzsáki, 2006; Lenck-Santini and Holmes, 2008; Diba and Buzsáki, 2008). Thus, phase precession allows the compression of temporal sequences from a behavioral timescale of seconds to the timescale of a theta cycle (Mehta et al., 2002), a timescale relevant for spike-timing dependent plasticity (STDP; Levy and Steward, 1983; Gerstner et al., 1996; Markram et al., 1997; Bi and Poo, 1998; Kempter et al., 1999). This compression could provide a basic mechanism for a neural representation of temporal order relevant for episodic memory (Buzsáki, 2005).

The next paragraph contains a brief summary of hallmark publications on phase precession.

### 3.1.1 Experimental studies

Phase precession was discovered by O'Keefe and Recce (1993) in CA3 and CA1 pyramidal cells. Phase was measured with respect to theta oscillations at the same recording sites that were used for unit recording. The authors established the phase-position and phase-time correlations for data pooled over several trials. They also measured a phase change of up to 360 degrees and proposed that two oscillators with different frequencies might generate phase precession.

Next, Skaggs et al. (1996) reproduced these findings and extended them with respect to two-dimensional environments. They also recorded more cells in parallel and thus found out that phase precession begins and ends at similar phases in different CA1 cells. They also showed that within each theta cycle the order of firing of the overlapping place cells matches the order in which the place fields have been entered.

Ekstrom et al. (2001) tested whether experience-dependent expansion of place fields (Mehta et al., 1997) affects phase precession. When the size of the place field increases, the amount of the overall phase change could stay constant or increase as well. Ekstrom et al. (2001) found that in animals where the place field expansion was pharmacologically blocked, the slope of phase precession (degrees per cm) was steeper than in control animals. Accordingly, the overall phase change was rather similar in animals with and without place field expansion.

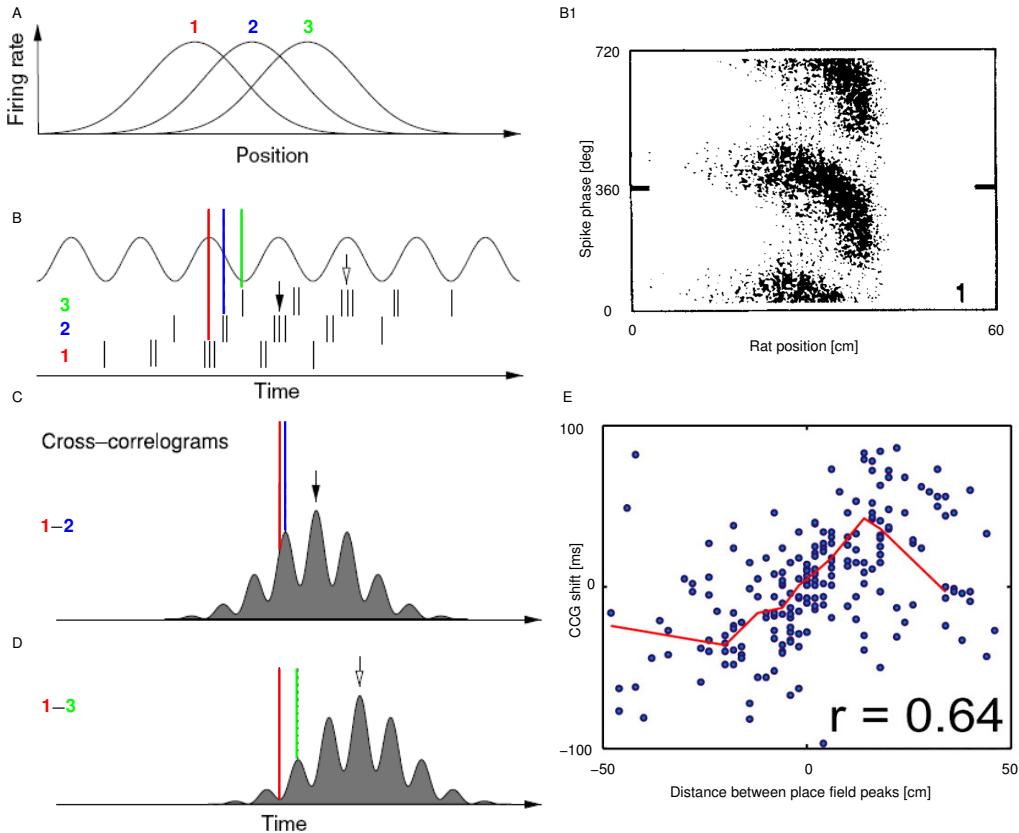


Figure 3.2: Phase precession leads to correlation coding (illustration only; A-D modified from Lengyel et al., 2005; with permission from Springer Science + Business Media). (A) Firing-rate profiles of three overlapping place fields. (B) Place-cell activity during the crossing of the three place fields. Oscillation at the top illustrates the theta oscillation. Place field 1 is entered first; the cell spikes first. When place field 2 is entered, place field 1 has already undergone some phase precession, so that place field 1 is active at an earlier phase than place field 2. The same happens when place field 3 is entered and all three place fields are active at different times in the theta cycle (illustrated by the colored lines). The black and white arrowhead mark the time of the peak activity of place field 2 and 3, respectively. (B1) Phase precession in a CA1 place cell (experimental data; modified from Skaggs et al., 1996; with permission from John Wiley and Sons). Animal runs from the left to the right. Each dot marks a spike. Two oscillation cycles are drawn on the y-axis. (C,D) Cross-correlograms of cell pairs. The distance between two place fields is reflected in location of the largest peak (black and white arrowheads) relative to zero-lag (red line). It is also reflected on a shortened time scale by the location of first peak next to the zero-lag (blue and green lines). (E) This peak in the cross-correlogram correlates with the distance of the place field peak in pairs of hippocampal pyramidal cells (modified from Dragoi and Buzsáki, 2006; with permission from Elsevier).

Harris et al. (2002) demonstrated that phase precession also occurs during non-spatial behavior. Phase precession was observed while the rat was running in a wheel and also during REM sleep. Furthermore, phase precession was also found in an open field environment (see also Huxter et al., 2008, below)

Yamaguchi et al. (2002) addressed the issue that phase precession is often not linear. They found that phase precession can be well fitted by two normal distribution functions. The first one (covering the beginning of the place field) has a phase precession of about 180 degrees, while the second distribution (at the end of the place field) exhibits almost no phase-position correlation.

Mehta et al. (2002) proposed a mechanistic model of phase precession in which place-field skewness is essential (Figure 3.3). In their data, especially in experienced rats, the firing rate increased during the crossing of a place field, suggesting a functional relation. In the model of Mehta et al. (2002), the place cell receives oscillating inhibitory input combined with a slower excitation. This combination leads to phase precession. In line with their model they found skewed place fields in their data in late trials; in contrast they found a weaker phase-position correlation in early trials in which place fields were less skewed. They also provided a functional interpretation of phase precession as a mechanism to compress events from a second to a millisecond time-scale in which STDP acts.

In contrast, Huxter et al. (2003) found evidence for firing rate and phase being independent. They could not reproduce the consistent increase in firing rate towards the end of the field. Moreover, they also did not find a correlation between place field skewness and phase precession, such that only skewed place fields would show phase precession. Huxter et al. (2003) confirmed the finding from O’Keefe and Recce (1993) of phase-position correlations being stronger than phase-time correlations in data pooled over several trials. Further, they found a correlation between running speed of the animal and firing rate, such that in faster runs there is a higher firing rate of the place cell.

Zugaro et al. (2005) used single-pulse stimulation during phase precession to deactivate hippocampal activity for one or two theta cycles and to reset the theta phase. After this perturbation, phase precession continued as if nothing had happened. This experiment excludes certain models of phase precession, which are e.g. sensitive to theta phase resetting, such as the two-oscillator model (see below).

Jones and Wilson (2005) examined the firing phase of cells in the medial prefrontal cortex with respect to CA1 pyramidal cell layer theta. They argued that prefrontal phase precession preferably occurred at times when there was a cognitive demand on spatial working memory. However, the phase

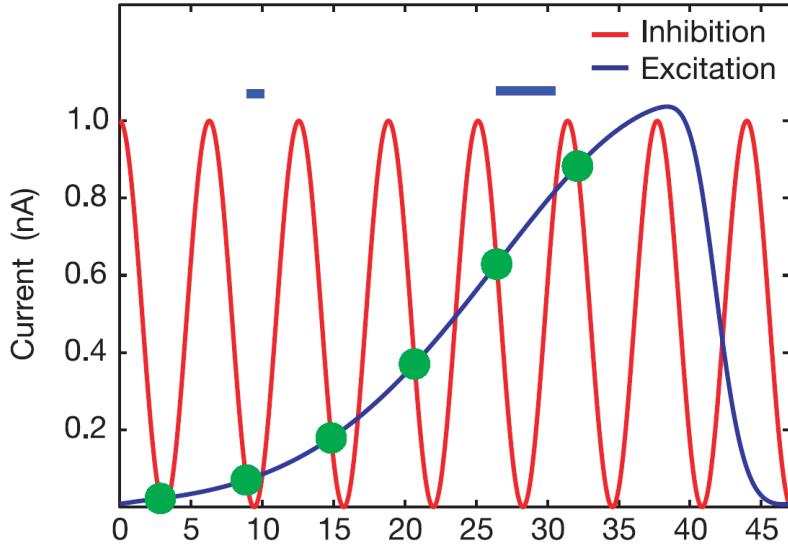


Figure 3.3: A model of hippocampal phase precession (from Mehta et al., 2002; with permission from Macmillan Publishers Ltd). During the crossing of a place field, the place cell receives asymmetric excitatory input (blue line) in addition to oscillatory inhibitory input (red line). When the amount of excitation exceeds inhibition, the cell starts firing (green dots). Due to increasing excitation, the cell starts to fire at earlier phases in each theta cycle. Furthermore, towards the end of the place field, the cell becomes active over larger fractions of the theta cycle (blue bars).

precession in the prefrontal cortex appeared only at some time points and showed large variability. Therefore, any functional relevance of this quite weak phase precession remains doubtful. Still, this finding could be evidence for different contributions of hippocampal activity in driving prefrontal cortex cells according to cognitive demands.

More recently, Maurer et al. (2006a) argued that place cells can exhibit several place fields in one environment and that in each of these phase precession occurs. Moreover, these fields can even overlap and still each can show up to 360 degrees of phase precession. However, it remains unclear how to assign spikes to different, but overlapping place fields. Also, the shown examples of spike phases are not cyclic, so that a data point appears at -100 degrees, but not at 260 degrees. For these reasons, their results are difficult to interpret without further confirmation.

Phase precession has also been found in hippocampal interneurons (Maurer et al., 2006b; Ego-Stengel and Wilson, 2007). Although interneurons are active over large parts of the environment, their activity can also be spa-

tially modulated. At certain parts of the track, some interneurons exhibited episodes of phase precession.

In contrast to previous studies, Dragoi and Buzsáki (2006) studied phase precession in pairs of place cells. They found that through phase precession the distance between place fields is represented in a compressed manner within a theta cycle (see Figure 3.2E).

Foster and Wilson (2007) compared the order of place cell activity within theta cycles to the order in which the animal crossed the place fields (Figure 3.4). According to previous findings, for overlapping place fields, the place field that has been entered first should also fire first in the theta cycle. So the order of firing in a theta cycle should correspond to the order of place field crossings (resulting in a ‘theta sequence’). Foster and Wilson (2007) confirmed the existence of such theta sequences in their data. Still, their data contained many examples where the theta sequence did not correspond to the behavioral sequence (Figure 3.4B). Methodologically they introduced a shuffling algorithm in which spike times are jittered based on the variability in the spike phase at a given animal position. Note that this variability was estimated on the basis of data pooled over trials. The authors claim that this procedure did not affect phase precession, but did affect the prevalence of theta sequences.

Geisler et al. (2007) specified the role of running speed in phase precession. They found that when the rat runs faster, phase precession occurs within fewer theta cycles, but at the same time the amount of the phase change between two theta cycles increases, as well as the number of spikes in a theta cycle. Therefore, the temporal slope (degrees per theta cycle) increases in with faster runs, although the spatial phase precession remains constant.

Huxter et al. (2008) studied phase precession not on a linear track, but instead on a two-dimensional open field environment. They found that phase precession occurs in two-dimensional environments independent of the running direction of the animal. This is evidence against a mechanism underlying phase precession that is based on place field asymmetries (Mehta et al., 2002).

Lenck-Santini and Holmes (2008) tried to link phase precession to memory function. They demonstrated that phase precession is weaker in animals with epilepsy. The authors suggest that performance deficits of these animals in the water maze task might be related to the disturbed phase precession.

Hafting et al. (2008) discovered phase precession also in the entorhinal cortex. In particular, grid cells in layer II showed robust phase precession, which was not found in layer III cells. Activity of layer III cells was instead rather phase-locked to the theta rhythm. In addition, phase precession in layer II was not abolished by inactivation of the hippocampus. Based on

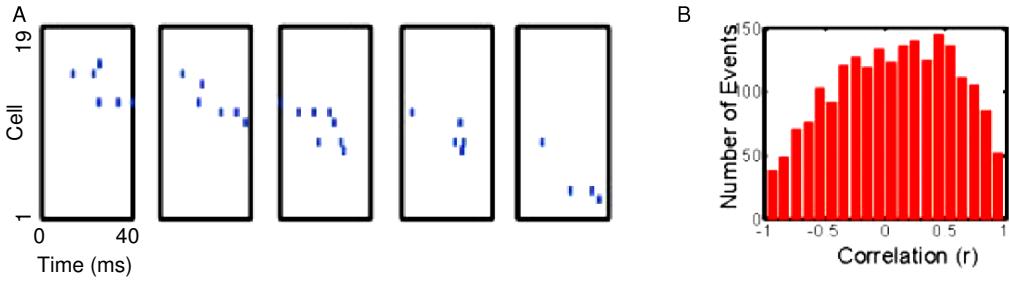


Figure 3.4: Theta sequences (modified from Foster and Wilson, 2007; with permission from John Wiley and Sons). **(A)** Five examples for theta sequences. Different place cells (y-axis) are ordered according to the location of the place field from top to bottom, so that place cells at the top are crossed first (cell 19 has a place field at the beginning of the track; cell 1 has a place field at the end of the track). Action potentials are indicated by vertical bars. Note the (positive) correlation between place field location and the time of activity; the order of activity on a millisecond-timescale corresponds to the order of the place field locations. **(B)** Distribution of correlation coefficients of theta sequences pooled over three rats.

these findings it can be concluded that phase precession in the entorhinal cortex is not inherited from the hippocampus.

Despite many studies on phase precession, its neural mechanism remains unknown. Recent studies follow three trends: (1) Phase precession is studied in other regions than CA3 and CA1. (2) Phase precession is studied in other tasks than linear tracks, including non-spatial tasks. (3) Neural codes arising from phase precession are related to cognitive function, e.g. to memory.

### 3.1.2 Relation to memory

Phase precession imposes a temporal structure on the activity of the cell population that matches the millisecond timescale of STDP (see above; Skaggs et al., 1996; Mehta et al., 2002; Melamed et al., 2004). According to STDP, in reciprocally connected cells A and B, if cell A fires a few milliseconds before cell B, the connection from the cell A to cell B is strengthened, and the connection from cell B to cell A is weakened. Therefore, the STDP window is asymmetric; the change in synaptic weight depends on which cell fires first. Interestingly, hippocampal phase precession compresses events from a behavioral time scale of seconds to the millisecond-timescale of synaptic plasticity. Thereby, connections between cells can be strengthened although they represent events which are separated by several seconds. This temporal com-

pression solves the fundamental problem of bridging time gaps in associative learning as required, for example, by episodic memory.

Another feature of the correlation code generated through phase precession is that the order of the events is preserved. The order is preserved because of the asymmetry of STDP: during phase precession only connections between place cells are strengthened that correspond to the sequence of crossed place fields. For example, if the rat crosses place field A and then place field B, only connections from A to B are strengthened but not from B to A. Hence, the running direction and the path taken by the animal determine which connections are strengthened, preserving a neural representation of the behavioral sequence.

### 3.1.3 Mechanistic models

In various models, different neurobiological mechanisms have been proposed to explain phase precession. With the discovery of phase precession, O’Keefe and Recce (1993) already provided the first model of how phase precession could be generated. Their ‘two-oscillator model’ (Figure 3.5) suggests that each place cell sums up two oscillating inputs with similar amplitudes. Outside the place field, the inputs also match in frequency but are out of phase, so that they cancel out. Therefore the cell does not fire outside its place field. Within the place field, one of the oscillators increases its frequency slightly. As a consequence, the two oscillations do not cancel out anymore, and the peaks of the resulting compound wave exceed the firing threshold of the cell. Spikes occurring at the peaks of the compound wave would exhibit phase precession relative to input oscillation with the slower frequency. Current technological advances allow intracellular recordings in behaving animals (Lee et al., 2006, 2009). These techniques can measure the membrane potential of place cells during phase precession. For example, it could be tested whether, in the place field, the membrane potential of a place cell matches a compound wave of two added oscillations with different frequencies.

In network models of phase precession, Jensen and Lisman (1996) and Tsodyks et al. (1996) proposed that phase precession occurs due to recurrent inputs from neighboring place fields. At early phases (i.e. at phases where phase precession ends), place fields are assumed to be driven by (different) strong external inputs. Activity in these cells then spreads to other cells. Thereby, those cells are active at a later phase (i.e. at phases that occur during phase precession). The activity spreads to exactly those cells that are on the path the rat has taken several times in the past. In the same way, activity of these cells then spreads further to cells that are, again, active at later phases. So the firing phase of the cell depends on its distance to the

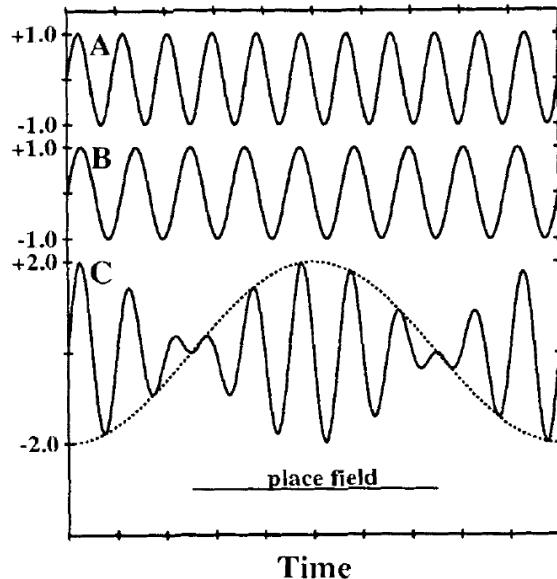


Figure 3.5: Sketch of the two-oscillator model of phase precession (from O’Keefe and Recce, 1993; with permission from John Wiley and Sons). The place cell receives two oscillatory inputs shown in (A) and (B) with frequencies of 11 and 9 Hz, respectively. The sum of these inputs (C) exhibits peaks that yield the times when the cell is active. These peaks phase precess with respect to the oscillation in (B), which corresponds to the theta oscillation in the LFP. The dotted line indicates the extent of the place field.

directly activated place cell. As the rat moves through the environment, this distance changes from theta cycle to theta cycle, resulting in phase precession in individual cells. This model requires a specific network connectivity that allows the activity to spread in an ordered manner through the network. In particular, it is necessary that the environment is familiar to the animal so that the corresponding connections between the place cells have been strengthened and weakened accordingly. So this model predicts that phase precession does not occur in unfamiliar environments. A major problem of this model are two-dimensional environments, where place fields are not unidirectional. In that case, the activity would spread to place fields in all directions.

Phase precession was also modeled as the result of interfering excitatory dendritic and inhibitory somatic oscillatory inputs (Kamondi et al., 1998; Magee, 2001; Harris et al., 2002). During the crossing of a place field, the amplitude of the excitatory input increases and thereby the inhibitory input is overcome earlier in each oscillation cycle. This interference results in phase

precession. In a variant of this model (Harris et al., 2002) the excitatory input does not increase throughout the place field but instead decreases towards the end of field again to match the actual firing-rate profile of typical place cells. To avoid phase *recession*, an additional adaptation mechanism had to be assumed.

Mehta et al. (2002) found that place fields become more skewed with experience so that the firing rate increases during the place field crossing. In their model, the firing threshold of a place cell is theta-modulated. Together with a gradually increasing ramp-like excitation, phase precession occurs because the threshold is crossed earlier with increasing excitation (see above in Figure 3.3). Besides the problem that not all place fields have a skewed firing-rate profile, this model cannot work in two dimensions where the animal does not always enter the place field from the side with the lowest firing rate.

Thurley et al. (2008) proposed that short-term synaptic facilitation plays a critical role in the generation of phase precession. Short-term facilitation refers to an increase of the amplitude of excitatory postsynaptic potentials (EPSPs) due to repetitive stimulation of the synapse (Zucker and Regehr, 2002). In the model of Thurley et al. (2008), the place cell receives phase-locked input (Figure 3.6). The resulting EPSPs increase in amplitude with each successive theta cycle due to short-term facilitation. With increasing EPSP amplitude the theta-modulated firing threshold is reached at an earlier phase, resulting in phase precession.

Currently, there is no consensus on a particular model of phase precession. All models can more or less account for most of the experimental data. It is well possible that phase precession is generated by different mechanisms in different brain regions and also at different stages of exposure to a new environment. For example, initially phase precession could be primarily the result of short-term facilitation (Thurley et al., 2008; Leibold et al., 2008). Later, when the environment becomes familiar, e.g. CA3 network mechanisms (Tsodyks et al., 1996) might become more important for the generation of phase precession. In general, more constraints from experimental data are necessary to falsify current mechanistic models of phase precession.

## 3.2 Sequence Replay

The movement of an animal causes the corresponding place fields to be active in a particular order. During sleep and resting periods, this order is reflected in reverberating neuronal activity accompanied by sharp wave-ripple events in the LFP. Thereby, even when the animal does not move, previous spatial sequences are present in the activity patterns.

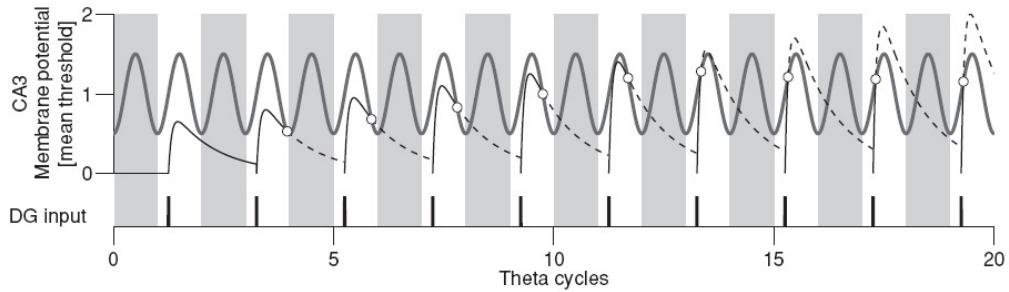


Figure 3.6: Phase precession through synaptic facilitation (from Thurley et al., 2008). The CA3 pyramidal cell fires a spike (white circles) when incoming EPSPs (thin lines) reach the oscillating firing threshold (thick line). Phase-locked input from dentate gyrus is marked by vertical bars at the bottom. The amplitude of the EPSPs increases with theta cycles due to short-term facilitation.

### 3.2.1 Experimental studies

Sequence replay occurs during slow-wave sleep following a session of running on the linear track (Lee and Wilson, 2002). CA1 cells were found to fire in the same order as during behavior but in a temporally compressed manner of about 20 times faster than during behavior.

In addition, sequence replay was found in awake animals during resting periods between trials of running on a linear track. Previous sequences of place-field activity are replayed predominantly in a reverse order in CA1 (Foster and Wilson, 2006).

Diba and Buzsáki (2007) extended this finding to forward preplay: during resting periods, the order of place cell activity in both CA3 and CA1 also matches future behavior in some cases. Hence, in the awake animal, sharp wave-ripples are accompanied by sequences of place cell activity that reflect recent past and immediate future spatial behavior. Past behavior is replayed in a reverse order compared to the behavioral sequence; future behavior is preplayed in the same order as the behavioral sequence (Figure 3.7).

### 3.2.2 Relation to memory

The presence of sequence replay during slow-wave sleep (Lee and Wilson, 2002) is intriguing because in humans there is strong evidence for a relation between slow-wave sleep and memory (Marshall et al., 2006; Rasch et al., 2007). Thus, it is tempting to relate sequence replay during sleep to the process of memory consolidation, i.e. behavioral relevant sequences are re-

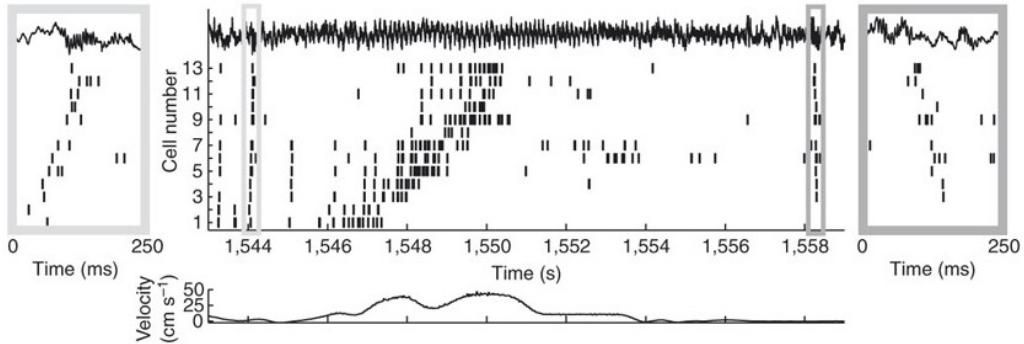


Figure 3.7: Hippocampal sequence replay and preplay (from Diba and Buzsáki, 2007; with permission from Macmillan Publishers Ltd). Single-trial example of a rat running on a linear track. Spiking activity of 13 place fields is illustrated through vertical bars; top trace gives the LFP. Place fields have been sorted to match their order of firing on the linear track. (Left) Resting period before running on an enlarged time scale shows forward preplay. (Middle) Running on the linear track (see bottom panel for speed profile). (Right) Resting period after running on the linear track on an enlarged time scale showing reverse replay. Note that in one-dimensional environments as a linear track, place fields are usually unidirectional, i.e. they are active only in one running direction. This allows to distinguish preplay from replay.

peated during sleep for long-term storage of the sequence. In contrast, it has also been argued that sequence replay during sleep may actually reflect active erasure of the neural imprint of the sequence memory in the hippocampus (Mehta, 2007). Erasure of hippocampal memories might restore baseline values of synaptic strengths to reduce energy costs (see Tononi and Cirelli, 2006).

Even if sequence replay during sleep is important for long-term memories, it is unclear whether sequence replay in the awake animal has the same function. Reverse replay of sequences in the awake animal has also been related to reinforcement learning (Foster and Wilson, 2006). If sharp wave-ripples occur temporally coordinated with the release of dopamine in the hippocampus, place-reward associations could be learned in a distance-graded manner. The discovery of sequence preplay (Diba and Buzsáki, 2007) allows further functional interpretations related to goal-directed behavior and planning. In general, it is difficult to reveal a causal relation between sequence replay and cognitive functions. However, recently Girardeau et al. (2009) managed to eliminate sharp wave-ripple events in rats after training on a spatial task. In line with a function in memory consolidation, they found that elimination of

sharp wave-ripple events led to an impairment of spatial memory.

### 3.2.3 Mechanistic models

The replay of sequences during resting periods and sleep has received less attention from theoretical studies than phase precession. Diba and Buzsáki (2007) proposed a scheme in which each place cell receives a graded excitatory input depending on the animal's location (see also Buzsáki, 1989). Within the place field the input causes the cell to fire, but outside the place field of the cell this input is usually not strong enough for that. However, also outside the place field the amplitude of the excitatory input depends on the distance to the place field. If then, during a resting period, the firing threshold of all place fields is suddenly decreased, the cells with the place fields closest to the actual position of the animal would fire before cells with place fields further away. The resulting sequences match the order of cell activity in reverse replay and forward preplay. However, in this model, all hippocampal cells with a place field in the current environment would be reactivated during sequence replay. For example, in two-dimensional environments, place cells that do not belong to the behavioral sequence would be reactivated as well. Thus, the model requires an additional mechanism that restricts the reactivation to recently crossed place fields.

Molter et al. (2007) proposed a model in which, during spatial behavior on a linear track, the synaptic weights between overlapping place cells in the CA3 recurrent network are increased. They discriminate two behavioral states: awake resting at the end of the track and sleeping. During sleep, random inputs activate the stronger forward connections of place cells that produce the same place field sequence as during behavior. In the awake animal, their model produces reverse replay because of the animal's position at the end of the track from where no forward connections exist. To obtain strong forward and backward connections, the model requires e.g. a rather symmetric STDP window that strengthens synapses between cells irrespective of which cell fired first.

Koene and Hasselmo (2008) propose that in CA3, during running on a linear track, both forward and backward sequences are encoded. Their model requires that for CA3 cells connections to fields in the running direction are strengthened (as described for phase precession above). In addition, their model requires that for some CA3 cells connections to fields opposite to the running direction are strengthened. Therefore the model assumes the existence of both forward and reverse 'theta sequences' (see above; Foster and Wilson, 2007) during running on the linear track. However, phase precession should only generate forward theta sequences, i.e. the sequence of place cell

activity in a theta cycle corresponds to the sequence of place field crossings. Still, the data published by Foster and Wilson (2007) also contains reverse theta sequences, i.e. the sequence of place cell activity in a theta cycle corresponds to the reverse sequence of place cell activity. In their study it was not assessed whether the incidence of reverse theta sequences was significant. Anyway, the model Koene and Hasselmo (2008) suggests that e.g. a subset of CA3 cells participate preferably in reverse theta sequences.

In general, mechanistic models are facing the problem to account for both reverse replay and forward preplay. A basic idea was that while rats are running on a linear track, phase precession imposes a certain temporal structure on the spike patterns. This structure induces plasticity among a sequence of place cells that corresponds to the running direction of the animal. Therefore, connections strengthened during phase precession can only account for forward preplay (unless the STDP window shape also strengthens connections opposite to the running direction). This suggests that preplay and replay phenomena might be due to distinct neural mechanisms.

### 3.3 Functional Role of Correlation Coding

Correlation coding during phase precession and sequence replay probably induces synaptic plasticity, e.g. in the recurrent CA3 network. Recently, it was shown that physiological spike patterns of overlapping place fields induce LTP in-vitro in CA1 (Isaac et al., 2009). However, the overall effect on the network dynamics remains unknown. STDP during reverse replay would counteract the STDP during phase precession, while STDP during forward preplay would further strengthen it. It is likely that the plasticity rules are different during phase precession and replay/preplay phenomena because of different network states affected by oscillations and neuromodulators (Buzsaki, 1989; Zhang et al., 2009). Furthermore, synaptic plasticity induced during phase precession and replay phenomena could have separate functions such as initial storage and consolidation, respectively. Phase precession and sequence replay during sharp wave-ripple events have many characteristics that would allow a functional role in the storage, the retrieval and the consolidation of episodic memories. Still, the functional role of correlation coding in the hippocampus is far from clear. Competing functional theories of these neural phenomena exist.

Alternative to a functional role of phase precession in memory, a competing hypothesis proposes a functional role in spatial navigation (e.g. Molter and Yamaguchi, 2008). This hypothesis stresses the fact that the spike phase contains information about the animal's position within the place field.

Therefore, the spike phase simply encodes the animal position at a higher resolution than place-field firing-rates, which can be used for navigation. However, in two-dimensional environments with bidirectional place fields, the phase code provides ambiguous information about the absolute position of the animal. Still, through phase precession the sequence of cells in a theta cycle encodes the running direction of the animal (Huxter et al., 2008).

Phase precession has been studied almost exclusively in rats during spatial navigation tasks (O’Keefe and Recce, 1993; Skaggs et al., 1996; Huxter et al., 2003; Mehta et al., 2002; Dragoi and Buzsáki, 2006; Geisler et al., 2007; Huxter et al., 2008; Hafting et al., 2008) or during sleep after spatial navigation tasks (Harris et al., 2002). Only in few cases, wheel running has been used to study phase precession in a non-spatial task (Harris et al., 2002; Pastalkova et al., 2008). However, up to now phase precession has never been demonstrated in other learning tasks such as trace conditioning. The question is whether we confine the function of phase precession to spatial navigation just because the tested behavioral paradigms are limited.

## 3.4 Current Knowledge Gaps and Problems

### 3.4.1 Methodological issues

In experimental work on phase precession, methodological differences between studies are a problem. In particular, there are differences with respect to (1) the site of the reference theta oscillation in the LFP, (2) the animal task, (3) the data analysis. This lack of a common standard introduces differences between studies, and these differences can in principle account for contradictory results, such as whether place field skewness correlates with phase precession (Mehta et al., 2002; Huxter et al., 2003).

The site of the reference theta is important. It has been taken from CA3, CA1 and the entorhinal cortex. Often, theta is obtained from one of the electrodes from which also single units are extracted, which means that often the theta in the pyramidal cell layer is used. However, also in other parts of the hippocampus theta is present and can even be less noisy than in the pyramidal cell layer. Importantly, there is a phase shift of theta across different layers; the absolute spike phase always depends on the layer from which the reference theta is recorded (Buzsáki, 2002).

Different studies of phase precession have employed different tasks for the animal. Most often a linear track was used on which the animal runs back and forth to obtain food rewards at the ends (O’Keefe and Recce, 1993; Mehta et al., 2002; Huxter et al., 2003). Also, triangular mazes (Skaggs et al.,

1996) and more recently ‘true’ two-dimensional open field environments have been used to study phase precession (Huxter et al., 2008). In few cases, also non-spatial behaviors have been associated with phase precession, e.g. activity during REM sleep or activity during wheel running (Harris et al., 2002; Pastalkova et al., 2008). Furthermore, in studies of phase precession, animals are usually motivated through rewards given at some location. It would be interesting to see whether phase precession changes when no rewards are present. Also, the various tasks require different amounts of pretraining. Place fields change with experience or exposure to some environment. It is still unclear how phase precession really looks like in the first trial of a new place field (but see Mehta et al., 2002; Cheng and Frank, 2008). As several models of phase precession claim that phase precession is a retrieval process and therefore requires previous exposure to the environment, it would be important to study phase precession in new environments. Further, memory demands of the task could in principle also affect phase precession. In general, it is unknown which factors have an effect on phase precession. Therefore, task differences between studies introduce further uncertainties for the interpretation of the results.

Finally, data analysis is an important issue, as the analysis of phase precession requires a lot of preprocessing. Apart from general issues as spike sorting techniques, which are usually lab-specific, there are further issues for which there are no accepted standards. Most importantly, various methods exist to estimate the phase of an ongoing theta rhythm (see Siapas et al., 2005). The method determines the interpretation of the phase. In some cases, the phase is proportional to the time interval between two local maxima or minima of the theta rhythm. However, in other cases, the shape of the theta oscillation is taken into account, such as a saw-tooth shape (Buzsáki, 2002; Montgomery et al., 2009), effectively stretching or squeezing time intervals. Further, more basic issues concern criteria for selecting (place) cells, place field borders, or the quantification of phase precession.

### **3.4.2 Open questions**

#### **Mechanism of phase precession**

Revealing mechanisms underlying phase precession will be a big step in understanding its role in learning and memory. All mechanistic models of phase precession match to some degree the available experimental data. Therefore, it is required to test model predictions and to reveal new properties of phase precession that provide new model constraints. For example, phase precession is usually studied on the basis of data pooled of many trials. Properties

of single-trial phase precession as well as the trial-to-trial variability of phase precession are largely unknown.

As described above, a crucial feature of a neural mechanism of episodic memory is that a single experience of an event is sufficient for long-term storage. Therefore, it is of fundamental importance to study any candidate mechanism on a single-trial basis. In the next chapter, I investigate single-trial phase precession.

### **Relation between phase precession in different brain regions**

Initially, phase precession was related to the activity of place cells and restricted to hippocampal regions CA3 and CA1. It is not clear to what extent phase precession is present in the remaining hippocampal regions: few examples from unknown cell types exist for the dentate gyrus (Skaggs et al., 1996). Recently some phase precession has been proposed to exist in the subiculum (Kim and Frank, 2008). Phase precession has also been found outside the hippocampus, i.e. in certain layers in the entorhinal cortex (Hafting et al., 2008). Also, some (though rather weak) phase precession has been found in the prefrontal cortex (Jones and Wilson, 2005).

An intriguing question is whether phase precession is generated locally in various brain regions or whether it can be inherited. To answer this, the temporal relation between phase precession in different regions is important. In Chapter 5, I study the relation between CA3 and CA1 phase precession.

### **Function**

The functions of phase precession and sequence replay remain unknown. It seems likely that both are related. Therefore, models are needed that connect the two phenomena. In Chapter 6, I propose a model for reverse replay and examine its performance in providing temporal patterns suitable for learning.

# Chapter 4

## Single-Trial Phase Precession in the Hippocampus

As described in the previous chapter, phase precession creates a correlation code in the population of hippocampal pyramidal neurons and may be important for learning and memory. However, phase precession is usually analyzed on the basis of data pooled over trials, although the proposed functions of phase precession operate on a single-trial basis. To close this gap, we provide a thorough investigation of phase precession in single trials in this chapter (Schmidt et al., 2009).<sup>1</sup>

### 4.1 Summary

During the crossing of the place field of a pyramidal cell in the rat hippocampus, the firing phase of the cell decreases with respect to the local theta rhythm. This phase precession is usually studied on the basis of data in which many place field traversals are pooled together. Here we (Schmidt et al., 2009) study properties of phase precession in single trials. We found that single-trial and pooled-trial phase precession were different with respect to phase-position correlation, phase-time correlation, and phase range. While pooled-trial phase precession may span  $360^\circ$ , the most frequent single-trial phase range was only around  $180^\circ$ . In pooled trials, the correlation between phase and position ( $r = -0.58$ ) was stronger than the correlation be-

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<sup>1</sup>The research presented in this chapter has also been published as an article and is the result of a collaboration with several researchers. I conceived the project, developed the analysis tools, performed the analyses of the experimental data, and wrote the manuscript. The experimental data was recorded by Kamran Diba in the lab of György Buzsáki at the Rutgers University in Newark (USA).

tween phase and time ( $r = -0.27$ ), whereas in single trials these correlations ( $r = -0.61$  for both) were not significantly different. Next, we demonstrated that phase precession exhibited a large trial-to-trial variability. Overall, only a small fraction of the trial-to-trial variability in measures of phase precession (e.g. slope or offset) could be explained by other single-trial properties (such as running speed or firing rate), while the larger part of the variability remains to be explained. Finally, we found that surrogate single trials, created by randomly drawing spikes from the pooled data, are not equivalent to experimental single trials: pooling over trials therefore changes basic measures of phase precession. These findings indicate that single trials may be better suited for encoding temporally structured events than is suggested by the pooled data.

## 4.2 Introduction

During the crossing of the place field of a CA1 pyramidal cell, the spike phases decrease from theta cycle to theta cycle (see Section 3.1; O’Keefe and Recce, 1993). This phenomenon is called phase precession. Phase precession is a candidate mechanism for a neural representation of temporal order relevant for episodic memory (Buzsáki, 2005).

Phase precession is usually studied on the basis of data in which many place field traversals are pooled together (e.g. O’Keefe and Recce, 1993; Skaggs et al., 1996; Huxter et al., 2003). However, functional hypotheses on phase precession, including temporal coding (Harris et al., 2002; Mehta et al., 2002; Huxter et al., 2003; Thurley et al., 2008; Leibold et al., 2008), sequence learning or recall (Lisman et al., 2005; Hasselmo and Eichenbaum, 2005), and spatial navigation (Burgess et al., 1994; Koene et al., 2003; Lengyel et al., 2005) rely on experiences occurring in single trials. Pooling data over trials may lead to a biased estimate of properties of phase precession and neglects potential trial-to-trial variability.

In this chapter we study properties of phase precession in single trials and compare them to properties of pooled-trial phase precession. We find that phase-position correlations, phase-time correlations, and phase ranges are different in single trials and pooled trials. Further, we quantify trial-to-trial variability in phase precession and examine whether external factors, such as a variable running speed, can account for it. Finally, we demonstrate, on the basis of surrogate data, that pooling phase precession over trials changes basic measures of phase precession. Our findings indicate that single trials may be better suited for encoding temporally structured events, such as episodic memories, than is suggested by the pooled data.

## 4.3 Methods

### 4.3.1 General

Experimental data has been used in a different study (Diba and Buzsáki, 2008) in which experimental procedures have been described in detail. Briefly, three male Sprague-Dawley rats were trained to run back and forth  $\sim$ 20 times on a linear track (170 cm long) to retrieve water rewards at both ends. Then the track was shortened (to 100 cm) and the rat ran another  $\sim$ 20 times back and forth. Changes in place field activity due to shortening of the track have been described in detail in Diba and Buzsáki (2008). All protocols were approved by the Institutional Animal Care and Use Committee of Rutgers University. After learning the task, the rats were implanted with 32 and/or 64- site silicon probes in the left dorsal hippocampus under isoflurane anesthesia. The silicon probes, consisting of 4 or 8 individual shanks (spaced 200  $\mu$ m apart) of 8 staggered recording sites (20  $\mu$ m spacing) (Csicsvari et al., 2003), were lowered to CA1 and CA3 pyramidal cell layers. Following recovery from surgery ( $\sim$ 1 week) the animals were tested again on the track. The position of the animals was tracked with an LED and later linearized along the long axis of the track. For this study, all units and LFP were taken from CA1 recording sites. Spikes that occurred near reward sites were excluded from the analysis by checking whether the position of the rat corresponds to one of the two reward platforms. This exclusion was done to ensure that spikes during non-theta states, e.g. sharp wave-ripple events during sequence replay (Foster and Wilson, 2006; Diba and Buzsáki, 2007), did not enter the analysis. All major results were reproduced in an analysis including spikes at reward sites. We also used the running speed of the rat as a criterion for spike selection (see next section).

### 4.3.2 Place fields

Place fields were determined by a firing-rate criterion. The peak firing rate had to be at least 2 Hz. The borders of the place fields were set at the location where the firing rate dropped below 10% of the place field peak firing rate. All results were also reproduced with a 20% criterion. Spikes outside the place fields were discarded. For each cell, place fields were determined separately for the long and short tracks and for leftward and rightward runs along the linear tracks. Place fields were also determined separately for each recording session. For rat #1 there were 12 recording sessions yielding 118 place fields, for rat #2 there were 11 sessions and 158 place fields, and for rat #3 there were 33 sessions and 890 place fields. In total, 1166 place fields

with overall 20602 single trials were analyzed. Animal position within a place field was normalized to values between 0 and 1. Only CA1 place fields with a significant negative linear correlation of at least 0.4 between spike phase and relative position in the place field were used in the analysis.

A trial consisted of a single crossing of a place field. In some trials, if animals stopped within a place field, theta oscillations in the LFP typically disappeared and the theta phase of a spike could not be reliably determined. Therefore, spikes that occurred when the instantaneous running speed was smaller than 10 cm/sec were discarded. In addition, trials in which the average running speed was smaller than 10 cm/sec were excluded from both the single-trial and pooled-trial analyses. Further, single trials were required to span at least two theta cycles, with at least three spikes in total, in order to be included in the analysis. However, exclusion of such trials did not affect the overall results.

### 4.3.3 Quantifying phase precession

For spike phase estimation, the CA1 LFP was band-pass filtered between 6 and 10 Hz and the Hilbert transform  $\mathcal{H}$  was applied. Thereby, the phase at time  $t$  was defined as the four-quadrant inverse tangent of the analytic signal  $a(t)$ :  $a(t) = x(t) + i\mathcal{H}(x(t))$ , where  $x(t)$  is the band-pass filtered LFP and  $i$  the imaginary unit. For comparability and consistency, the resulting phase was shifted by  $180^\circ$ . We always refer to the LFP in the CA1 pyramidal cell layer theta, and  $0^\circ$  corresponds to troughs in the filtered LFP.

*Correlation coefficient.* Phase precession was quantified with a linear correlation coefficient to allow comparison with previous studies. To reduce problems arising from the circularity of phase, for each place field the phase was shifted to minimize the linear correlation coefficient (O'Keefe and Recce, 1993; Mehta et al., 2002).

*Phase range.* Phase ranges of spikes were estimated by fitting a line in phase-position plots employing a circular-linear fit described below (see below for alternative methods). The slope of the line times the spatial range of the trial (defined below) determined the single-trial phase range. For the estimation of the range of phase precession, the slope was limited to the interval  $[-4\pi, 0]$ . This restriction avoided fitting lines with arbitrary high slopes that could cross all data points. Positive slopes were also excluded as we were interested in the range of phase precession with negative values. For example, a slope of  $-2\pi$  and a spatial range of 0.5 yields a phase range of  $-\pi$ . For other analyses than the phase range (e.g. estimating slope or phase offset), the slope was limited to the interval  $[-4\pi, 4\pi]$ .

As an alternative to the circular-linear fit (see below), we also tested a

cylinder fit to estimate the phase range. The cylinder fit was performed by minimizing the mean square distance between a helix on a cylinder and the data points (spikes). The helix was parameterized by  $(\phi_0 + c y, y)$ , in which  $y$  is the curve parameter measuring the spatial distance, and  $c$  and  $\phi_0$  are the fit parameters that translate space into phase:  $\phi_0$  denotes the phase offset and  $c$  the slope of the helix. Each spike was described by the cylinder coordinates  $\phi$  (phase) and  $x$  (spatial distance). The distance between the helix and a spike was calculated via the length

$$d = \frac{|\phi_0 + c x - \phi|}{\sqrt{1 + c^2}}$$

on a curve that is orthogonal to the helix and connects the spike and the helix in the shortest possible way. For the estimation of the phase range, the cylinder fit was constrained to slopes in the interval  $[-2.5\pi, 0]$

Phase ranges for single trials were also estimated by using differences of spike phases. The phase range was taken as the circular difference between the spike phase of the first spike in the first theta cycle in a trial and the spike phase of the first spike in the last theta cycle of that trial.

In addition to this method based on single spikes, we also used the circular mean phase of spikes within a theta cycle. Then we do not rely on single spike phases, and phase estimates are more robust. So the circular mean spike phase of the first and the last theta cycle in a trial were obtained. The circular difference between the two yielded the phase range.

*Phase offset and slope.* To avoid inappropriate linear fits (e.g. Figure 4.1 and also Figure 8.2 in the Appendix; column 5, row 4), a circular-linear fit (see below) was used to estimate the slope and the phase offset of phase precession (Figures 4.3, 4.6 and 4.7). The phase offset was assessed by the phase value of the fitted line at relative position zero.

*Circular-linear fit.* Given a random sample of data  $(\phi_1, x_1), \dots, (\phi_n, x_n)$  on the surface of a cylinder where  $\phi_j$  is an angular and  $x_j$  is a linear measurement ( $j = 1, \dots, n$ ), a linear model was fitted:

$$\Phi = 2\pi a X + \phi_0 .$$

The two parameters of this model are the slope  $a$  and the phase offset  $\phi_0$ . The model allows prediction of the mean angle  $\Phi$  given the position  $X$ . To obtain an estimate of the slope  $a$ , the mean resultant length

$$R(a) = \sqrt{\left[ \frac{1}{n} \sum_{j=1}^n \cos(\phi_j - 2\pi a x_j) \right]^2 + \left[ \frac{1}{n} \sum_{j=1}^n \sin(\phi_j - 2\pi a x_j) \right]^2} ,$$

was maximized. As it is independent of  $\hat{\phi}_0$ , the estimate  $\hat{a}$  of the slope  $a$  is  $\hat{a} = \arg \max_a R(a)$ , which demands numerical methods. The estimate  $\hat{\phi}_0$  for the phase offset then follows from (Gould, 1969; Fisher, 1995)

$$\hat{\phi}_0(a) = \arctan^* \frac{\sum_j \sin(\phi_j - 2\pi a x_j)}{\sum_j \cos(\phi_j - 2\pi a x_j)}$$

where the function  $\arctan^*$  is the quadrant-specific inverse of the tangent.

#### 4.3.4 Other single-trial properties

In addition to the above measures that quantify phase precession, we calculated nine other single-trial properties (Figures 4.5 and 4.6).

We took into account (1) the number of spikes and (2) the firing rates within single trials. The firing rates were determined by the number of spikes within the place field minus 1, divided by the time passed between the first and last spike in that run. (3) Theta cycles per trial were counted by the number of theta cycles between the first and the last spike of the trial, including the border cycles. Theta cycles started and ended at the peaks of the band-pass filtered LFP. (4) Running speed was estimated by the distance between the animal position at the first and the last spike divided by the time passed between the first and last spike in the place field. Furthermore, each spike was assigned a theta frequency and amplitude with respect to the LFP at the time the spike occurred. Trial-specific (5) theta frequency estimates were obtained by calculating the mean over all spikes in a trial. (6) Single-trial skewness was determined with respect to the relative location of the spikes within the place field. Formally, sample skewness is defined as

$$(1/m) \sum_{i=1}^m (x_i - \langle x \rangle)^3 / [(1/m) \sum_{i=1}^m (x_i - \langle x \rangle)^2]^{\frac{3}{2}}$$

where  $x_i$  denotes the relative location of spike  $i$  in the place field,  $m$  is the number of spikes in a single trial, and  $\langle x \rangle$  is the sample mean. Negative skewness corresponds to a greater number of spikes towards the end of the place field. (7) The spatial range is the fraction of the place field covered by a single trial. It was calculated as the difference between the relative position in the place field of the first and the last spike in a trial. (8) The theta amplitude was estimated for each spike as the difference between the maximum and the minimum of the filtered LFP signal in the corresponding theta cycle divided by two. The mean over all amplitude values of all spikes in a trial yielded the trial-specific theta amplitudes. Finally, we considered (9) the trial index (lap number) in a recording session.

### 4.3.5 Variance decomposition

Variance decomposition was used to determine the contributions of within-cell variance and between-cell variance to the total variance present in a population of  $N$  cells. For example, if the firing rate of a place cell is similar across trials but very different across cells, the within-cell variance will be small and the between-cell variance large. Formally, the population variance  $\sigma_{Pop}^2$  can be decomposed into the sum of within-cell and between-cell variances:  $\sigma_{Pop}^2 = \sigma_{within}^2 + \sigma_{between}^2$ . The within-cell variance  $\sigma_{within}^2$  is given by the weighted mean of cell-specific variances  $\sigma_n^2$  for  $n = 1, \dots, N$  cells. The weighting occurs according to the number of trials  $T_n$  in cell  $n$  and the population mean number of trials  $\bar{T} = (1/N) \sum_{n=1}^N T_n$ :

$$\sigma_{within}^2 = \frac{1}{N} \sum_{n=1}^N \frac{T_n}{\bar{T}} \sigma_n^2$$

The cell-specific variance is  $\sigma_n^2 = (1/T_n) \sum_{t=1}^{T_n} (x_{n,t} - \bar{x}_n)^2$  with the single-trial property  $x_{n,t}$  of cell  $n$  in trial  $t$  and a cell-specific mean  $\bar{x}_n = (1/T_n) \sum_{t=1}^{T_n} x_{n,t}$ . The between-cell variance is given by the weighted variance across cell means:

$$\sigma_{between}^2 = \frac{1}{N} \sum_{n=1}^N \frac{T_n}{\bar{T}} (\bar{x}_n - \bar{x})^2$$

with the population mean  $\bar{x} = 1/(N\bar{T}) \sum_{n=1}^N \sum_{t=1}^{T_n} x_{n,t}$ .

For the circular variable ‘phase offset’ we used a variance decomposition method based on the mean resultant length (Harrison et al., 1986):

$$r = \frac{1}{N\bar{T}} \sum_{n=1}^N \sum_{t=1}^{T_n} \cos(\phi_{n,t} - \bar{\phi})$$

with the phase offset  $\phi_{n,t}$  in cell  $n$  and trial  $t$ , and the circular population mean  $\bar{\phi}$  of the phase offset. The weighted average of cell-specific variation measures is given by  $\bar{r}^2 = (1/N) \sum_{n=1}^N (T_n/\bar{T}) r_n^2$  with the cell-specific mean resultant length  $r_n = (1/T_n) \sum_{t=1}^{T_n} \cos(\phi_{n,t} - \bar{\phi}_n)$  and the cell-specific circular mean  $\bar{\phi}_n$ . The measure of the population variance was decomposed into between and within variance through

$$1 - r^2 = [\bar{r}^2 - r^2] + [1 - \bar{r}^2]$$

where  $[\bar{r}^2 - r^2]$  is the measure for the circular between-cell variance and  $[1 - \bar{r}^2]$  the measure for the circular within-cell variance.

### 4.3.6 Correlation analyses

In our analyses, all calculated correlation coefficients are usually Pearson product-moment correlation coefficients. For the correlation analyses (Figure 4.6) that included the phase offset and another linear variable, a circular-linear correlation coefficient was calculated instead.

The correlation analyses can be done in two different ways. Either for each place field the correlations between pairs of single-trial properties are calculated, and afterwards an average correlation across the population is determined; or, alternatively pairs of single-trial properties are pooled across cells and animals, and then the correlation coefficient is calculated for the pooled data. For the analyses in Figure 4.6, the latter method was used. The matrix for the other method is shown in Figure 8.4 in the Appendix. In most cases the two methods yielded comparable results.

### 4.3.7 Surrogate data

Surrogate single trials were generated by randomly drawing spikes from the pooled place field data. The phase and position of these spikes were kept. The surrogate single trials had the same number of spikes as the corresponding experimental trials. In the basic version (used in Figure 4.7) spikes were drawn without replacement: each spike from the place field could only be used in one surrogate trial. We also created surrogate methods with additional constraints to closer match the properties of experimental trials (see Appendix).

## 4.4 Results

Experimental data on phase precession were obtained from three rats running back and forth on a linear track to retrieve water rewards at both ends. Electrophysiological recordings were done in the hippocampal CA1 region using silicon probes. To quantify phase precession in single trials, we used spikes from CA1 pyramidal cells with place fields on the linear track together with the LFP in the CA1 pyramidal cell layer.

### 4.4.1 Differences between single-trial and pooled-trial phase precession

*Single trials exhibit phase precession.* Phase precession is commonly quantified through the correlation coefficient between spike phase and animal

position; in previous approaches data from different trials (place field traversals) were pooled. Figure 4.1A shows five example place fields exhibiting phase precession, evident from a significant negative correlation between spike phase and animal position. In addition, examples of single trials from the same cells are shown (Figure 4.1B). For quantitative analyses, we determined phase-position and phase-time correlation coefficients for single trials and pooled trials of 1166 place fields.

*Phase-position correlations.* The distribution of phase-position correlation coefficients of our 20602 single trials contained a large fraction with negative values (Mean  $\pm$  SEM:  $-0.61 \pm 0.0023$ ; Figure 4.2A). Furthermore, *significant* correlation coefficients were almost exclusively negative ( $-0.75 \pm 0.0015$ ). Trials were labeled significant when the *p*-value of the linear correlation was below 0.05 and the corresponding trial had at least 5 spikes. The distribution of pooled-trial correlation coefficients ( $-0.58 \pm 0.0032$ ) was different from that of the single-trial correlation coefficients.

*Phase-time correlations.* Similar to the phase-position correlations, the distribution of single-trial phase-time correlations had a large fraction with negative values ( $-0.61 \pm 0.0023$ ), especially the significant ones ( $-0.74 \pm 0.0015$ ; Figure 4.2B). The distribution of pooled trials ( $-0.27 \pm 0.0058$ ) was different from that of single trials and reflected a weaker mean correlation. Since in time-based measures, pooling faster and slower trials combines ‘steep’ and ‘flat’ phase precession slopes, this likely produced a weaker phase-time correlation compared to the phase-position correlation. In line with this argument, the standard deviation of single-trial running speed across trials in a place field correlated with the phase-time correlation in pooled trials ( $r = 0.31$ ;  $p = 5 \cdot 10^{-27}$ ). Also, the difference between the phase-time and the phase-position correlations correlated with the standard deviation of the running speed ( $r = 0.23$ ;  $p = 7 \cdot 10^{-15}$ ). Thus, place fields with a strong negative pooled phase-time correlation were those which the rat usually crossed with similar running speeds. Moreover, we found that the position of the animal and the time that has passed since the animal entered the place field were more strongly correlated in single trials ( $0.98 \pm 0.0005$ ) than in pooled trials ( $0.47 \pm 0.0081$ ; Figure 4.2C). Comparing the distributions of correlation coefficients for single trials in Figures 4.2A and 4.2B, we did not find a significant difference between phase-position and phase-time correlations (Kolmogorov-Smirnov test:  $p = 0.60$ ).

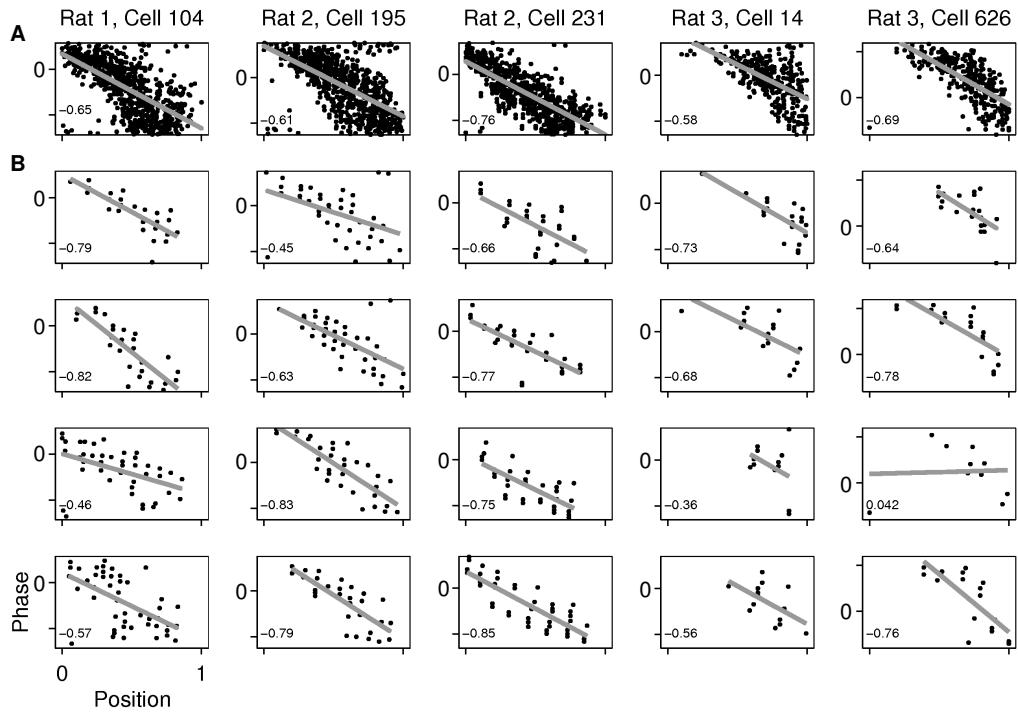


Figure 4.1: Pooled-trial (**A**) and single-trial (**B**) phase precession. Each dot represents a spike at a certain relative position in the place field (x-axis, normalized position with range from 0 to 1) at a certain theta phase in degrees (y-axis, full range  $360^\circ$ ; unlabeled tick at  $180^\circ$ ). The top row shows five example cells with phase precession pooled over up to 20 trials. The gray lines are linear fits, and the inset numbers give corresponding correlation coefficients. The four bottom rows depict robust phase-precession in sample single trials from the respective cells.

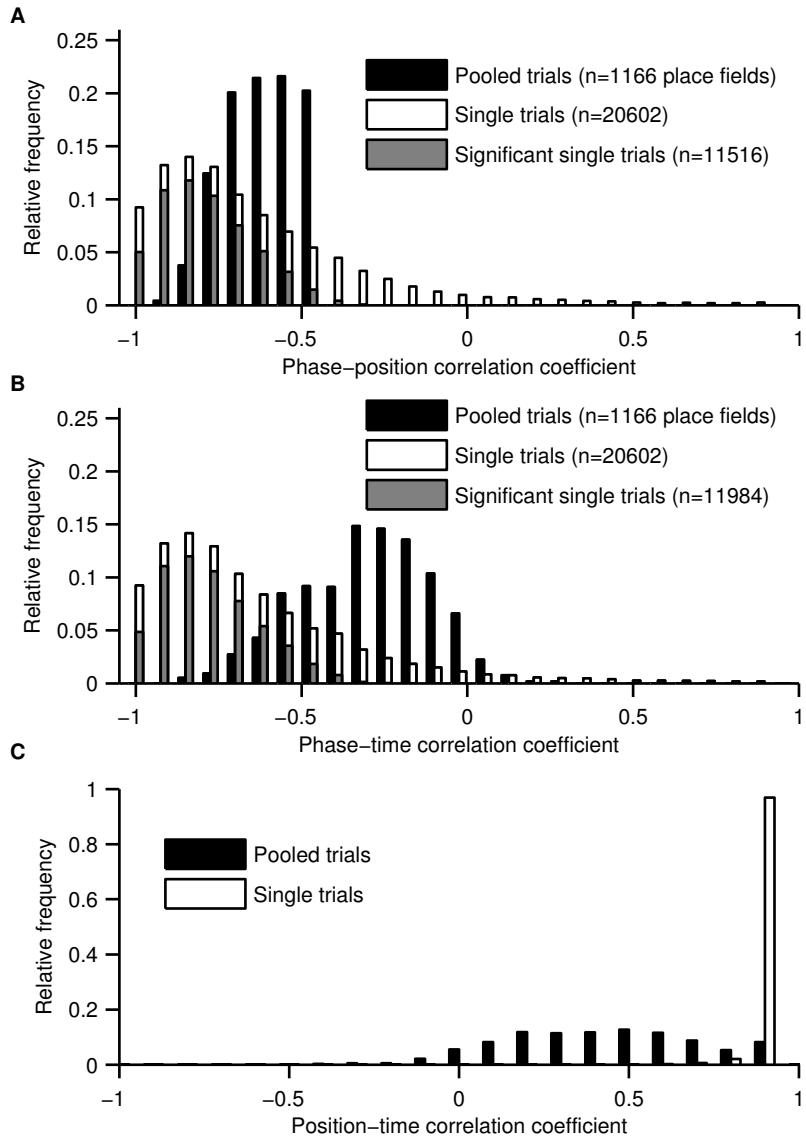


Figure 4.2: Correlation coefficients for pooled-trial and single-trial phase precession. **(A)** Histograms of correlation coefficients of spike phase with relative position in the place field. Single trials show stronger negative correlations than pooled trials. Only place fields with a pooled-trial phase-position correlation of at least -0.4 were included in the analysis (see Methods in Section 4.3.2). **(B)** Histograms of correlation coefficients of spike phase with time passed since the animal entered the place field. Correlations are considerably strong in single trials, but weak in pooled trials. The histograms of single trials ( $n = 20602$ ) in A and B include the shown significant trials ( $n = 11516$  for phase-position and  $n = 11984$  for phase-time). **(C)** Correlation coefficients between position and time passed since the animal entered the place field illustrate strong single-trial but weak pooled-trial correlations. Note that the last bin contains values in the interval [0.9, 1.0].

#### 4.4.2 Trial-to-trial variability

How does single-trial phase precession vary from trial to trial? To answer this question, we specified several measures for phase precession. Besides the phase-position correlation, we also used the phase offset, the slope, and the phase range to quantify phase precession (see Methods and insets in Figure 4.3A1-D1).

*Variability of measures for phase precession.* The overall distributions of phase-position correlation, phase offset, slope, and phase range suggest that there is substantial variability in the overall population of single trials (Figure 4.3A1-D1). These distributions were different from the corresponding distributions from pooled trials (Figure 4.3A2-D2). In particular, we found that single-trial phase ranges were considerably shorter than the pooled-trial phase ranges (Figure 4.3D; see below for details).

What is the origin of the observed variability of phase precession? In general, all trials from the same cell could have the same phase-position correlation, phase offset, slope and phase range. In this case, all variability originates from variability between cells, and not from variability within cells. Alternatively, the mean values for the measures of phase precession could be the same for all cells, but in each cell there may be a lot of variability across trials. In that case, all variability originates from variability within cells, and not from variability between cells.

We found that the distributions reflect trial-to-trial variability rather than variability between cells. To quantify the trial-to-trial variability, we determined the contributions of within- and between-cell variance in our dataset through variance decomposition (see Methods in Section 4.3.5). We identified that indeed a large fraction of the variance originated from within-cell variance: 85% for the phase-position correlation, 72% for the offset, 87% for the slope, and 74% for the phase range. We illustrate this result for 60 sample place fields in Figures 4.3A3-D3. In conclusion, considerable trial-to-trial variability of phase precession exists in the phase-position correlation, phase offset, slope, and phase range.

*Phase range is smaller in single trials than in pooled trials.* The phase range describes by how much the theta phase of spikes changes between the beginning and the end of the place field. It is often stated that phase precession spans up to 360° (O’Keefe and Recce, 1993; Skaggs et al., 1996; Tsodyks et al., 1996; Bose and Recce, 2001; Booth and Bose, 2001; Yamaguchi et al., 2002; Maurer et al., 2006a; Geisler et al., 2007) and models of phase precession are judged with respect to their ability to produce up to 360° phase precession (Tsodyks et al., 1996; Kamondi et al., 1998). Following O’Keefe and Recce

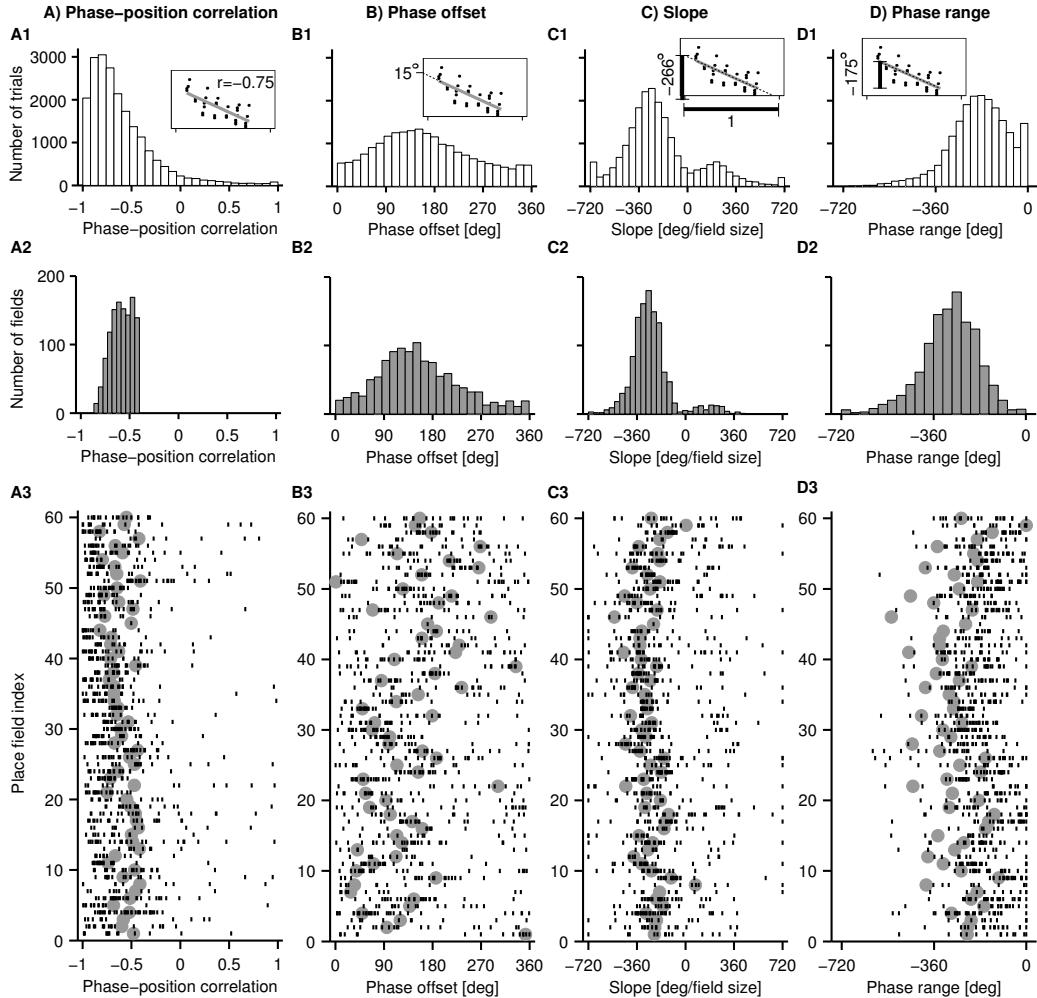


Figure 4.3: Variability of phase precession. We considered variability of the measures phase-position correlation (**A**), phase offset (**B**), slope (**C**), and phase range (**D**) for single trials (**A1-D1**) and pooled trials (**A2-D2**). Insets in **A1-D1** show an example single trial (same as in Figure 4.1, column 3, row 4) with the corresponding values of the measures. Note that considerable variability exists in all four measures. Positive slopes fitted to single trials (**C1**) can be due to bimodal phase distributions (Kjelstrup et al., 2008; see also Figure 8.2). (**A3-D3**) Trial-to-trial variability within randomly selected example place fields. Single-trial values of the four measures (black bars) are shown for 60 place fields (rat 1: place field index 1-20, rat 2: 21-40, rat 3: 41-60). Large variability exists within a given place field, while the variability of pooled-trial values (gray circles) is comparatively small across place fields.

(1993) we used fitted lines to estimate phase ranges for both pooled and single trials (Figure 4.3D1 and D2).

Applying a circular-linear fit (see Methods in Section 4.3.3), we found phase ranges of  $-296.8^\circ \pm 3.2^\circ$  (Mean  $\pm$  SEM; Figure 4.3D2) for pooled trials. These phase ranges were comparable to the ones found by O’Keefe and Recce (1993) ( $-257.5^\circ \pm 18.8^\circ$ ) with no significant difference (Kolmogorov-Smirnov test:  $p = 0.19$ ). In single trials, however, the same method yielded much smaller phase ranges ( $-191.2^\circ \pm 0.8^\circ$ , Figure 4.3D1). The single-trial distribution contained more short phase ranges than the pooled-trial distribution.

To exclude the possibility that the circular-linear fit created biases in the phase ranges, we confirmed the results with linear-linear fits (pooled-trial phase range:  $-236.5^\circ \pm 2.0^\circ$ ; single-trial phase range:  $-150.5^\circ \pm 0.6^\circ$ ) and cylinder fits (pooled-trial phase range:  $-286.7^\circ \pm 3.0^\circ$ ; single-trial phase range:  $-162.7^\circ \pm 0.7^\circ$ ; see Methods). The phase ranges derived from the linear fit were smaller and the slope was underestimated because a linear-linear fit is often inappropriate for circular-linear relations (e.g. single trial in Figure 4.1, column 5, row 4).

Single-trial phase ranges estimated through spike-phase differences (see Methods) yielded  $-190.3^\circ$  and  $-178.2^\circ$  for single spikes and mean phases, respectively. Thus, for all tested methods, we found that the most frequent single-trial phase range is around  $180^\circ$ . We conclude that pooling over several trials enlarges the apparent phase range.

To understand why the phase ranges are smaller in single trials than in pooled trials, we introduced the *spatial range* of a trial (see Methods in Section 4.3.4), which was defined as the fraction of the place field covered between the first and last spike of that trial ( $0.61 \pm 0.21$ ; Median  $\pm$  standard deviation; Figure 4.4A). The spatial range is a single-trial quantity; in contrast, for place fields, boundaries are defined through firing-rate thresholds of pooled trials (see Methods in Section 4.3.2). At the boundaries of a place field, the firing rate was usually relatively low. Thus, in only few trials, spikes occurred at the beginning and/or end of the place field. These trials therefore strongly biased the pooled-trial phase range. Most single trials had a *spatial range* smaller than 1 (Figure 4.4A), and the majority of single-trial *phase* ranges remained well below the pooled-trial ones (Figure 4.4B).

What happens to phase precession when a place cell starts to fire relatively late in the place field? Does phase precession then begin at an earlier phase (as if some phase precession has already happened), or does it begin at the phase it would usually begin? We found that the relative position of the first spike in the field in a trial correlated weakly with the theta phase of this spike ( $r = -0.06$ ), but stronger with the phase offset of that trial ( $r = 0.20$ ).

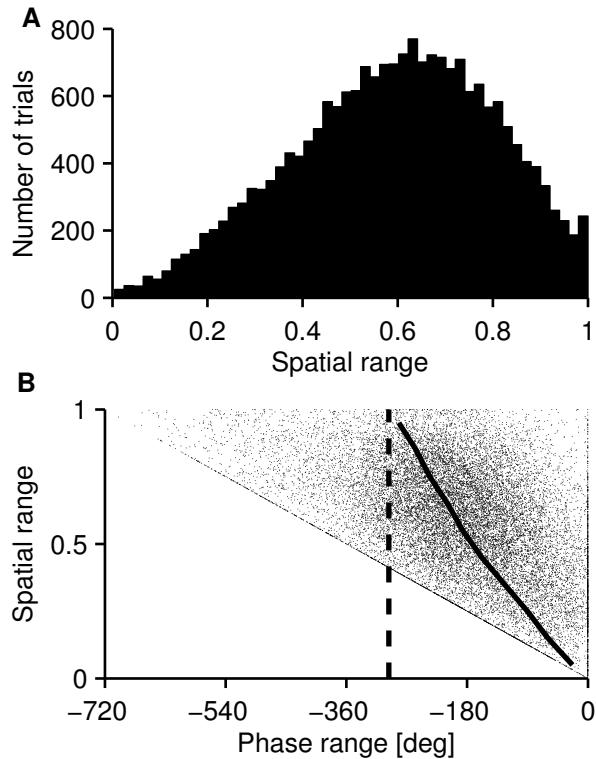


Figure 4.4: Spatial range and phase range in single trials. **(A)** Single-trial spatial range (Median  $\pm$  Standard Deviation:  $0.61 \pm 0.21$ ). The spatial range is the fraction of the place field covered between the first and the last spike of a trial. **(B)** Spatial range and phase range were correlated ( $r = -0.51$ ,  $p < 10^{-323}$ ). Each data point indicates a single trial ( $n = 20602$ ). The vertical dashed black line at  $-297^\circ$  marks the mean pooled-trial phase range. The black line gives the mean single-trial phase range in 0.1-sized bins of spatial range. The triangular shape of the region covered with data points was a result of constraining the circular fit to slopes between  $-720^\circ$  and  $0^\circ$ . Even if the circular fit was constrained to slopes between  $-720^\circ$  and  $720^\circ$  (not shown), we still observed a negative correlation ( $r = -0.20$ ,  $p < 10^{-323}$ ).

Thus, place cells started firing at a similar phase even if the first spike in a trial occurred at a later position in the place field, which contributes to the variability of phase precession.

*Evidence for inherent trial-to-trial variability.* Given the trial-to-trial variability with respect to phase-position correlation, phase offset, slope, and phase range, it is important to ask whether the variability in any of these measures is inherent or is controlled by an external factor. For example, does ‘running speed’ determine the slope of phase precession? Does the phase-position correlation become stronger over trials? To answer such questions, we determined the extent to which measures of phase precession can be predicted from a linear model based on other single-trial properties.

We examined the following single-trial properties: (Figure 4.5; Median  $\pm$  Standard Deviation): (1) number of spikes ( $10 \pm 8.7$  spikes), (2) firing rate ( $18.2 \pm 12.2$  Hz), (3) number of theta cycles ( $5.0 \pm 5.4$ ), (4) running speed of the rat ( $68.2 \pm 22.6$  cm/sec), (5) theta frequency ( $8.3 \pm 0.4$  Hz), and (6) skewness ( $-0.08 \pm 0.6$ ). Furthermore, we considered (7) the spatial range ( $0.61 \pm 0.21$ ; Figure 4.4A), (8) the theta amplitude, and (9) the trial index, or lap number, in that recording session (not shown). Together with the four measures of phase precession in Figure 4.3, we have 13 properties. For each pair of properties we calculated the correlation coefficient (Figure 4.6; see also Methods in Section 4.3.6). We found, for example, a highly significant ( $p = 1.6 \cdot 10^{-73}$ ) but weak ( $r = -0.13$ ) correlation between the running speed and the phase-position correlation coefficient (Figure 8.4A, Appendix). Therefore, assuming a linear relationship, running speed alone could explain only  $r^2 = 1.69\%$  of the variance in the phase-position correlation in single trials. None of the nine examined single-trial properties exhibited a strong correlation with the phase-position correlation, the slope, or the phase offset, although these three measures were correlated to each other to some extent. The phase range correlated with the spatial range (see above), the number of theta cycles, and the number of spikes. Thus, more theta cycles in a trial allow a larger phase range as well as a larger number of spikes. We conclude that, according to this analysis, most of the trial-to-trial variability in phase precession is inherent unless it is controlled by another factor which we have not identified.

#### 4.4.3 Single trials are not equivalent to randomly drawn spikes from the pooled data

So far we have revealed the existence of substantial trial-to-trial variability in phase precession, which could not be explained by the other single-trial

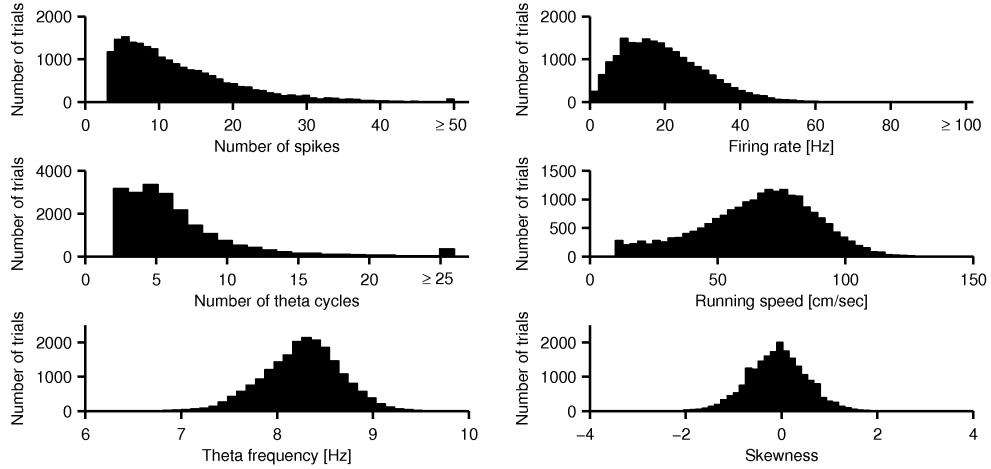


Figure 4.5: Properties of single trials. Values were derived from single place-field crossings, i.e. from the time between the first and the last spike within the place field. Note that for some properties few values were outside the range shown here (0.36% of the values for number of spikes, 0.13% for firing rate, and 1.6% for number of theta cycles), and were thus collapsed into the last histogram bin. Trials with average running speeds below 10 cm/sec, less than 3 spikes, or less than 2 theta cycles were excluded from the analysis.

properties. A large fraction of this variability appears to be independent of these properties. Pooling trials with different running speeds etc. would be valid if all spikes/trials are drawn from the same joint probability distribution of spike phase and position. However, it is unknown whether the pooled data actually serves as a proper predictor for single trials.

If all spikes from a given place field are drawn from the same joint probability distribution, this distribution can be estimated by the pooled data. Further, randomly drawn spikes from the pooled data should have similar properties as experimental trials. We tested this hypothesis using surrogate trials consisting of spikes randomly picked from the pooled data (Figure 4.7A; see Methods in Section 4.3.7).

We found that surrogate single trials exhibited lower correlations between spike phase and animal position than did the original experimental single trials (Kolmogorov-Smirnov test:  $p = 2 \cdot 10^{-50}$ ; Figure 4.7B). The pooled-trial phase precession was, naturally, the same in experimental and surrogate data. The higher correlation coefficients observed in single trials relative to surrogate trials indicates that single-trial phase precession showed less phase variance than expected from the pooled data alone.

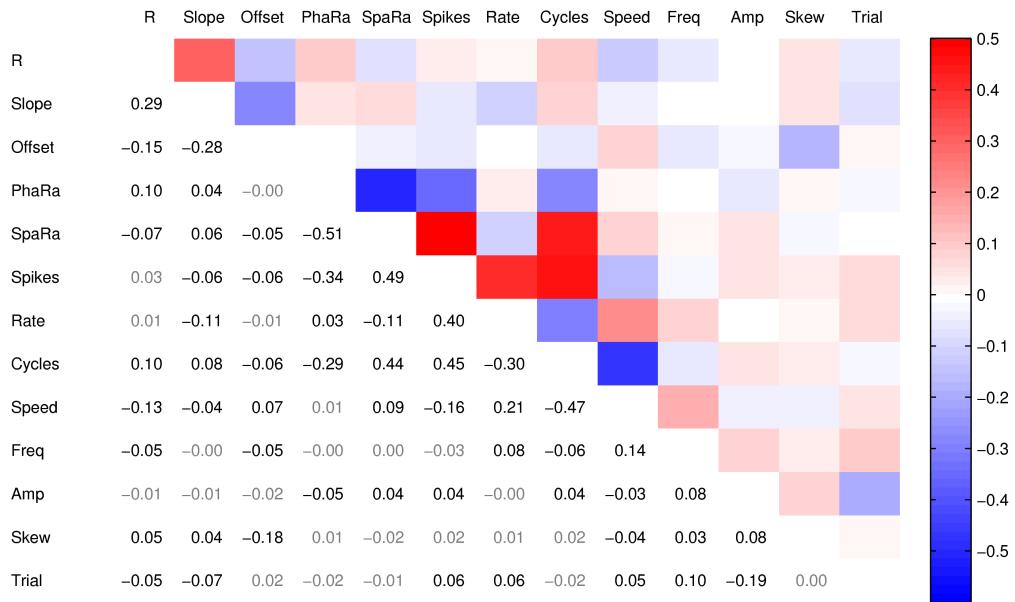


Figure 4.6: Correlations between properties of single trials. Matrix of correlation coefficients of pairs of single-trial properties. Shown are correlations between phase-position correlation ('R'), 'Slope', phase offset ('Offset'), phase range ('PhaRa'), spatial range ('SpaRa'), number of spikes ('Spikes'), mean firing rate ('Rate'), number of theta cycles ('Cycles'), running speed ('Speed'), theta frequency ('Freq'), theta amplitude ('Amp'), skewness ('Skew'), and within-session trial index ('Trial'). In the upper right triangle, correlation coefficients are color-coded; in the lower left triangle, numerical values are given. Highly significant correlation coefficients ( $p < 0.0001$ ) are written in black, others in gray. Note that for the circular variable phase offset, a circular-linear correlation coefficient is shown.

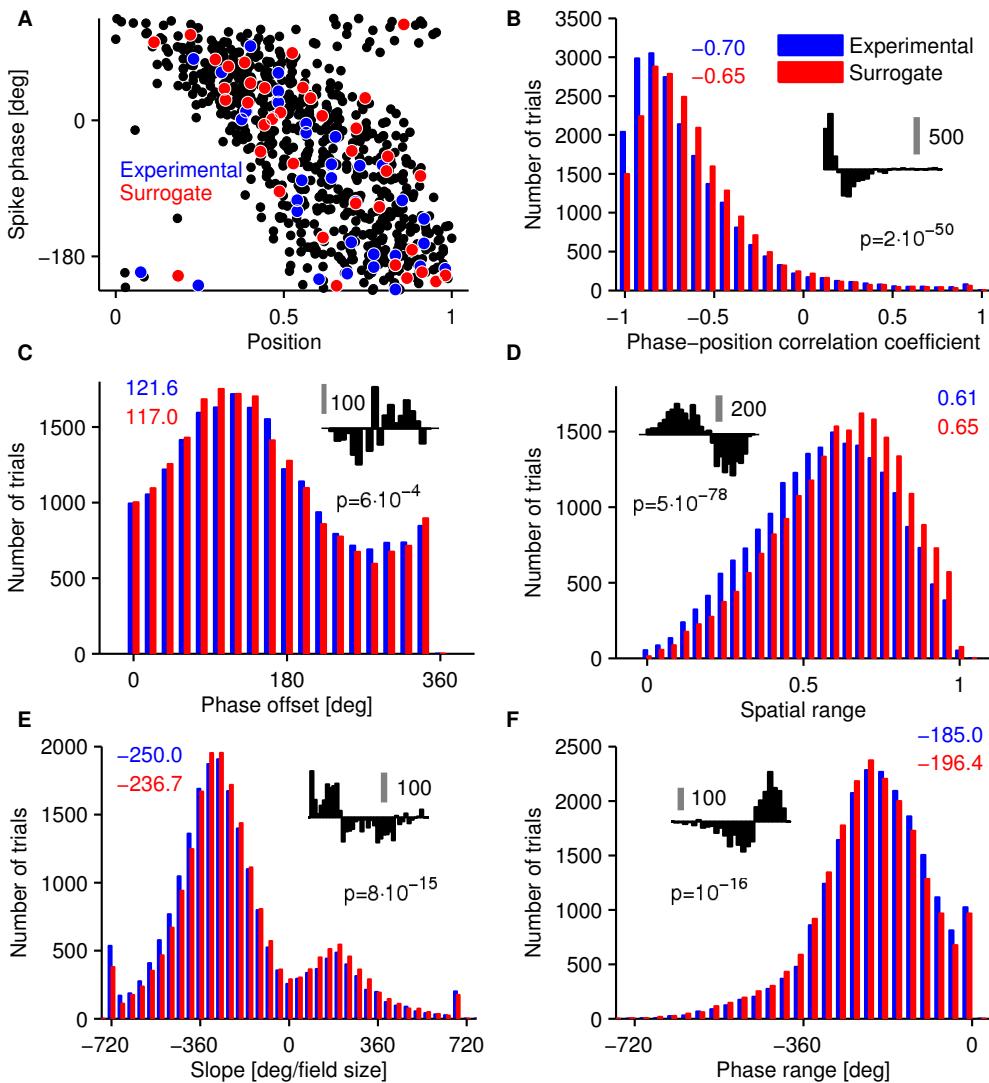


Figure 4.7: Surrogate single trials. **(A)** Illustration of the method to create surrogate single trials. Black dots represent spikes from an example place field (rat 2, cell 195). Blue dots indicate spikes from a single trial (phase-position correlation  $r = -0.49$ ). Red dots are spikes randomly picked from the population of the black dots with the spike number being equal to the blue dots. Thus, the red dots form a surrogate single trial (phase-position correlation  $r = -0.59$ ). **(B-F)** Distributions of single-trial measures from surrogate and experimental trials. Colored numbers give median value for experimental and surrogate distribution, respectively. For ‘phase offset’ the circular mean is given instead of the median. Black numbers give  $p$ -values for Kolmogorov-Smirnov tests. Insets show the difference between the distributions, and the gray scale bars give the respective number of trials. Note that experimental trials have stronger phase-position correlations than surrogate trials (B).

We further established the validity of these results by using several different surrogate methods and other quantifications of phase precession (see Appendix). For example, there is often more than one spike in a theta cycle, and spikes from the same burst within a cycle are separated into different surrogate trials by the above surrogate method. It could well be that this burst structure is important for the single-trial phase-position correlations, and that a separation of bursts causes the found difference between experimental and surrogate data. We therefore looked at circular *mean phases* of spikes in the same theta cycle instead of single spike phases (see Figure 8.2 in the Appendix for examples). Using circular mean phases instead of spike phases to create surrogate trials also lead to a significant difference ( $p = 4 \cdot 10^{-88}$ ; see Figure 8.1, Appendix). Several further surrogate methods were tested to include other characteristics of single trials such as running speed or spatial range (see Section 8.1.1, Appendix), which are not accounted for by the very simple surrogate method we used here. However, all of our surrogate methods based on pooled data failed to explain the phase-position correlations observed in experimental trials.

In addition to the phase-position correlation, we found that other measures of phase precession (slope, phase offset, phase range, and spatial range) were different in the surrogate data. The histograms in Figure 4.7C-F reveal that surrogate trials underestimated slope and phase-position correlations, but overestimated the phase range and the spatial range. While the differences between experimental and surrogate trials appeared to be rather small but significant for phase offset, slope, and phase range, the differences in phase-position correlation and spatial range were clearly visible. We conclude that single trials are not equivalent to randomly drawn spikes from the pooled data. Thus, analyzing phase precession based only on pooled data might lead to a blurred picture of its basic properties.

We finally note that differences in phase-position correlations between experimental and surrogate trials are well explained by the substantial trial-to-trial variability. Surrogate trials are composed of spikes originating from trials with different slopes, phase offsets, and phase-position correlations, which weakens their phase-position correlation. We provide supporting evidence for this idea by showing that even pooling only trials with very strong phase-position correlations reduces the corresponding pooled-trial phase-position correlations (Figure 4.8).

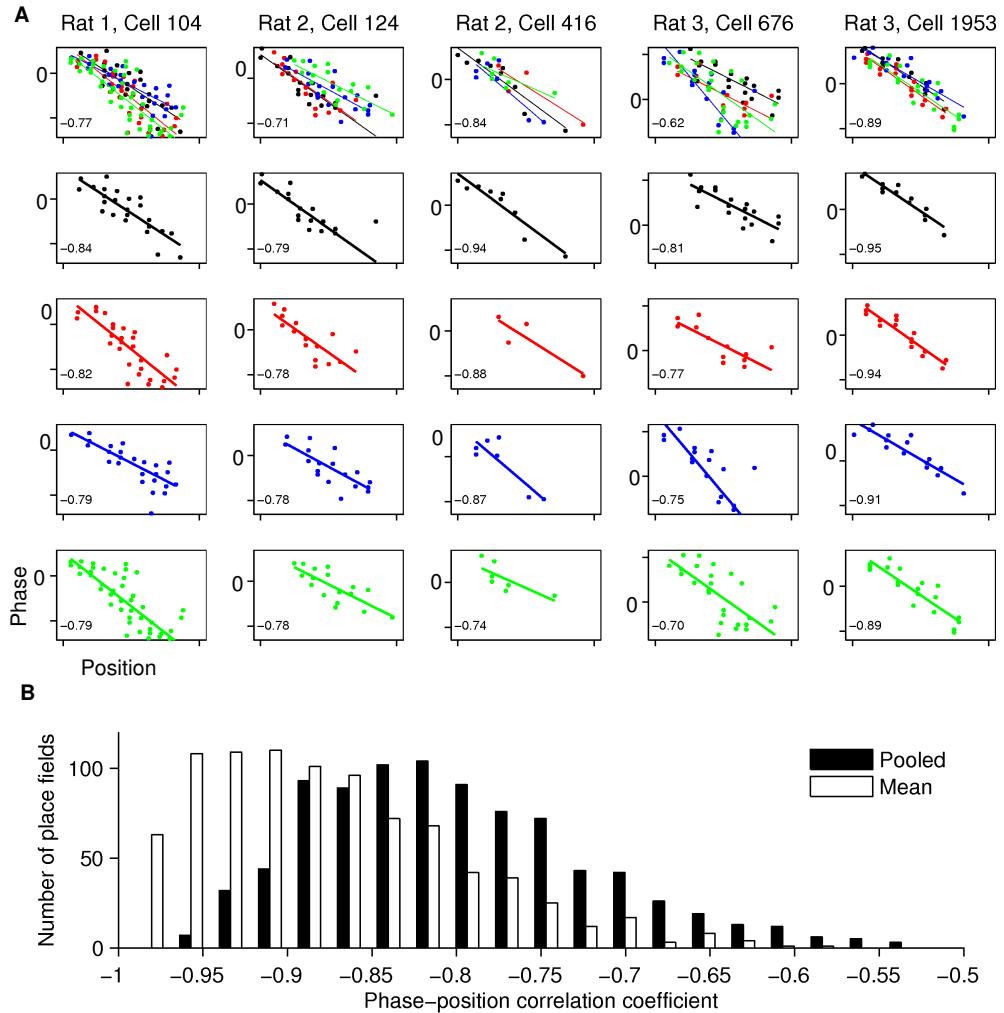


Figure 4.8: Effect of pooling trials on the phase-position correlation coefficient. **(A)** Single-cell examples. In the top row, the four trials from each place field with the strongest phase-position correlation coefficient have been pooled. The remaining four rows give respective single trials separately. Colored lines are circular-linear fits. Numbers denote linear phase-position correlation coefficients of pooled data (top row) and single trials (bottom rows) **(B)** Population data. From each place field with at least 15 trials, the four trials with the strongest phase-position correlation coefficient have been selected. For each cell, the arithmetic mean phase-position correlation coefficient of those four trials was calculated (white bars). In addition, for each place field, the same four trials were pooled and a corresponding pooled-trial phase position correlation coefficient was determined (black bars). The two distributions differ significantly from each other ( $p < 1.5 \cdot 10^{-55}$ ; Kolmogorov-Smirnov test).

## 4.5 Discussion

Our data shows that CA1 place cells of rats exhibit clear phase precession in single trials. Phase-position and phase-time correlations were very similar in single trials, but different in pooled trials in which phase-time correlations were considerably weaker (O’Keefe and Recce, 1993; Huxter et al., 2003). This difference may arise from the adjustment of phase precession to the running speed of the animal (O’Keefe and Recce, 1993; Tsodyks et al., 1996; Bose and Recce, 2001; Geisler et al., 2007).

A direct comparison of measures of phase precession obtained from single trials and pooled data might be tricky since the distributions of these measures are generated in different ways. Still, it is crucial to understand how measures of phase precession change when data is pooled over trials, especially as this is common practice. For example, pooling over trials increases the phase range of phase precession because few single trials span the entire place field. As an alternative method for comparing single trials with pooled data, we created surrogate single trials with the same number of spikes as in the experimental trials by randomly drawing spikes from the pooled data. We found that phase-position correlations in the resulting surrogate trials were considerably weaker than in the corresponding experimental trials. As the strength of the phase-position correlation determines how well behavioral sequences are represented on a theta timescale (Dragoi and Buzsáki, 2006; Foster and Wilson, 2007), our findings demonstrate that phase precession is better suited for encoding temporally structured events than is suggested by the pooled data.

These results have implications for mechanisms underlying phase precession and corresponding computational models (e.g. Tsodyks et al., 1996; Kamondi et al., 1998; Magee, 2001; Booth and Bose, 2001; Mehta et al., 2002; Harris et al., 2002; Hasselmo and Eichenbaum, 2005; Lisman et al., 2005; Thurley et al., 2008). A variety of models are typically justified on the basis of comparisons of simulations with phase-precession from pooled data rather than single trials. Our results provide stricter constraints for models of phase precession: single-trial, rather than pooled-trial, features should be reproduced. Especially, the single-trial phase range of only 180° provides a strong new constraint for mechanistic models of phase precession (Thurley et al., 2008).

Phase precession exhibited a considerable trial-to-trial variability. We quantified this trial-to-trial variability in terms of the slope, the phase offset, the phase range, and the phase-position correlation of a linear model. Within a single trial, spike phases were not independent but depended on previous spike phases in this trial. However, despite our best efforts to identify the

source of the trial-to-trial variability, we found that it could not be accounted for by any obvious extrinsic parameters such as firing rate or running speed. Instead, we found that a large part of the variability in pooled-trial phase precession was apparently due to intrinsic trial-to-trial variability. The source of this intrinsic variability remains unknown. Studies of noise in single neurons indicate that it is likely synaptic in origin (Diba et al., 2004; Jacobson et al., 2005).

Our analysis of phase precession in single neurons cannot reveal the variability and interdependence of phase precession across neurons. An assembly of neurons (Harris et al., 2003; Pastalkova et al., 2008) with very similar but nonidentical properties might, for example, cover a phase range much larger than  $180^\circ$  in every single trial. Moreover, the variability of phase precession across neurons within a single trial might be much smaller than the trial-to-trial variability in one neuron. In this case, the trial-to-trial variability of an assembly of neurons may be considerably smaller than that of single members. Part of the unaccounted variability can derive from the lack of monitoring an assembly.

#### **4.5.1 Previous studies on the phase precession in single trials**

Many previous studies on phase precession showed single trials only in illustrative examples (O’Keefe and Recce, 1993; Harris et al., 2002; Mehta et al., 2002; Huxter et al., 2003; Zugaro et al., 2005; Maurer et al., 2006a; Lenck-Santini and Holmes, 2008; Hafting et al., 2008; Kjelstrup et al., 2008). Quantitative analysis was in most cases restricted to pooled trials, especially for the estimation of basic properties such as phase-position and phase-time correlations, or phase ranges. In these pooled-trial analyses, stronger phase-position than phase-time correlations supported a spatial functional role of phase precession such as spatial navigation. The equivalence of the two measures in single trials is in agreement with a broader functional role of phase precession in which encoding time may be as relevant as encoding space. Additionally, this supports the implication of phase precession in sequence learning and episodic memory (Jensen and Lisman, 1996; Redish and Touretzky, 1998; Hasselmo, 2005; Buzsáki, 2005; Yamaguchi et al., 2007; Pastalkova et al., 2008).

To study the functional role of phase precession, other recent studies used two different approaches. First, spikes were shuffled across trials (Foster and Wilson, 2007), which is similar to the method we used to create surrogate single trials. They studied how well the firing order of cells within a theta

cycle (a ‘theta sequence’) corresponded to the order of place fields through which the rat passed. Foster and Wilson (2007) found that, after shuffling, single-trial theta sequences were reduced, but phase precession was preserved. We note that only the pooled-trial phase precession was preserved in their study; it is likely that the reduced prevalence of theta sequences was a result of reduced phase precession in single trials. In the second approach, Dragoi and Buzsáki (2006) jittered spike phases to reveal coordination among cell assemblies, and they analyzed the rising and falling portions of the place field separately. However, their phase-jittering method was based on the phase variance determined from pooled trials, and they did not assess the effect of phase-jittering on single-trial phase precession. Indeed, the phase-position correlation on a single-trial basis may have been considerably weakened. Thus, single-trial phase precession may in fact play a fundamental role for theta sequences.

Finally, Mehta et al. (2002) looked at single-trial phase-position correlations as a function of trial number. They found that the phase-position correlation and skewness became stronger with increasing trials. In our data (Figure 4.6), this effect was significant only for the phase-position correlation, but comparably small in scale to the correlation with other factors such as running speed or theta frequency. Furthermore, in line with Hafting et al. (2008), single-trial skewness did not increase over trials in our data, failing to support a causal role for the asymmetric expansion of place fields in phase precession (see also Huxter et al., 2003).

#### 4.5.2 Phase range, spatial range, and temporal range of single trials

Our findings show that the phase range in single trials is smaller than previously assumed on the basis of pooled trials (O’Keefe and Recce, 1993; Skaggs et al., 1996; Tsodyks et al., 1996; Bose and Recce, 2001; Booth and Bose, 2001; Yamaguchi et al., 2002; Maurer et al., 2006a; Geisler et al., 2007; but see Mehta et al., 2002; Harris et al., 2002; Huxter et al., 2003, 2008). Most single trials also had a smaller spatial extent than did the place field, and the phase range correlated with this spatial extent. These findings are independent of the definition of the boundaries of place fields. By defining a place field, we excluded spikes outside the place field on the basis of a firing-rate criterion. However, this exclusion concerned only a few spikes and thus occurred in very few trials. Given the substantial differences we observed between pooled-trial and single-trial phase range, it seems unlikely that this difference was due to place field boundaries. Similarly, by excluding spikes in the reward areas we

might have cut-off the beginning or end of phase-precessing place fields and thereby artificially reduced the phase range. However, this would have also affected the pooled-trial phase range, which in our data set is the same as reported in previous studies.

The phase range could be influenced by the methods for estimating the theta phase of spikes. Due to band-pass filtering of the LFP, we ignored certain aspects of the waveshape (Buzsáki, 2002). If theta phases are estimated through, for example, linear interpolation between local minima and maxima, asymmetric theta waveforms (i.e. sawtooth shapes) affect the phase estimation. With our phase-estimation method, the phase ranges told us something about the temporal fraction of the theta cycle that was used by phase precession. Thus, a phase range of about  $180^\circ$  in a single trial can be interpreted as a temporal range of phase precession of about 62.5 ms for 8 Hz theta. This temporal range is independent of the method used for phase estimation.

The phase range of phase precession has implications for functional interpretations. From a sequence-learning perspective (Skaggs et al., 1996; Melamed et al., 2004), the sequential activity of place cells in the hippocampus can imprint asymmetric changes in the synaptic matrix through spike-timing-dependent plasticity (Markram et al., 1997). Synapses from neurons activated earlier in the sequence to neurons activated later in the sequence are strengthened whereas synapses in the other direction are weakened. A phase range of  $360^\circ$  can lead to strengthening of synapses in the ‘other’ direction because a cell fires spikes at the entry of its place field only a few milliseconds before the spikes of another cell at the end of its place fields. The resulting problem of a distorted sequence representation can be avoided with only  $180^\circ$  of phase precession, as observed in single trials.

## Concluding remarks

The brain computes information online and typically does not have the opportunity to pool over trials. In comparison to pooled data, our account of the ongoing neural activity in single trials provides a richer perspective of the spiking behavior in CA1. In the case of phase precession, pooling over trials blurs properties of single trials, and suggests more variability than is actually observed in the data. In particular, the precise coding of time in single trials further supports a functional role of phase precession in sequence learning and episodic memory.

# Chapter 5

## Coordination of CA3 and CA1 Phase Precession

In the previous chapter I studied single-trial phase precession in CA1. However, phase precession occurs also in other hippocampal regions, e.g. in CA3. Here we compare simultaneously recorded phase precession in CA3 and CA1.<sup>1</sup>

### 5.1 Summary

It is unknown how phase precession is coordinated among different subregions of the hippocampus and whether the relation between spike phases and the local theta rhythm is similar. Here we focus on CA3 and CA1. We find that the local theta rhythms in CA3 and CA1 are almost antiphasic (155.8 degrees difference). Still, phase precession in the two regions occurs with only a small phase shift (about 10 degrees), and CA3 cells tend to fire a few milliseconds before CA1 cells. These results reveal how phase precession is coordinated among CA3 and CA1 and suggest that phase precession in CA1 might be inherited from CA3.

### 5.2 Introduction

Hippocampal phase precession has been found in pyramidal cells in both CA3 and CA1 (O’Keefe and Recce, 1993; Skaggs et al., 1996), and also

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<sup>1</sup>This work is the result of a collaboration with several researchers. I conceived the project, developed the analysis tools, and performed the analyses of the experimental data. The experimental data was recorded by Kamran Diba in the lab of György Buzsáki at the Rutgers University in Newark (USA). A manuscript for the research presented in this chapter is in preparation.

in the entorhinal cortex (Hafting et al., 2008). However, only few studies (e.g. Dragoi and Buzsáki, 2006) made use of simultaneously recorded phase precession in CA3 and CA1, or compared phase precession in hippocampal subregions (Harris et al., 2002). Furthermore, either the same reference theta was used for both CA3 and CA1 data (Harris et al., 2002), or only the local theta was taken as a reference (Hafting et al., 2008). No study examined systematically the relation of the CA3 and CA1 reference theta during phase precession. The temporal relation of CA3 and CA1 is fundamental to judge the validity of certain models of phase precession and to test whether phase precession could be inherited among hippocampal subregions.

Here we compare phase precession in CA3 and CA1 and study the temporal relationship of CA3 and CA1 theta oscillations.

## 5.3 Methods

### 5.3.1 CA3 and CA1 local field potentials

Experimental data and data analysis methods are, with a few exceptions, the same as in the previous chapter on CA1. Here we also used data from CA3. Data from one rat was not included because it was not possible to deduce the number of units recorded from a certain recording channel (see below). We further did not exclude spikes based on the animal location (described in Section 4.3.1), as the speed criterion we used before was sufficient to prevent place fields contamination by spikes during resting periods.

LFP and unit recording sites were located in the CA3 and CA1 pyramidal cell layer. As a reference to determine the theta phase of spikes, only recording sites with sufficient unit activity ( $\geq 2$  units) were used. Those channels with sufficient unit activity were separated into two groups (CA3 and CA1). Within each group a median LFP was calculated, yielding one CA3 and one CA1 median LFP for each recording session. These LFPs were then band-pass filtered between 6 and 10 Hz and used in the subsequent analyses.

### 5.3.2 Distance between place fields

The location of a place field was estimated by taking the median position of all individual rat locations at the times of the spikes. The distance between two place fields was the difference between the medians.

## 5.4 Results

Figure 5.1 shows the activity of a CA3 and a CA1 pyramidal cell with spatially overlapping place fields, as evident from the firing-rate profiles in (A). Spike phases were estimated with respect to both the LFP in the CA3 pyramidal cell layer and the CA1 pyramidal cell layer theta (Figures 5.1B and C). Phase precession was prominent irrespective of whether the local theta rhythm in CA3 or CA1 is taken as a reference. However, phase precession appeared to depend strongly on the origin of the theta because the two LFPs are out of phase. We demonstrate this phase shift in Figure 5.1D, which shows the activity of both cells during a single place field crossing.

### 5.4.1 CA3 and CA1 theta are out of phase

To quantify the temporal relation of CA3 and CA1 theta during place field activity, we plotted in Figure 5.2A spike phases from 1121 hippocampal place fields with respect to the CA3 and the CA1 theta. There was a strong coherence between the two theta rhythms, and they were phase-shifted by 155.8 degrees (Figure 5.2B). As a unique reference for spike phases we chose the CA1 theta because it had a larger relative power in the theta band than the CA3 theta (Figures 5.2C and D). We conclude that CA3 and CA1 theta are out of phase during place field crossings.

### 5.4.2 Phase precession in CA1 and CA3 are shifted by a few degrees

To see whether the shift in CA3 and CA1 theta rhythms is reflected in the temporal relation of CA3 and CA1 spikes, we examined the population of 406 CA3 and 715 CA1 cells obtained from two rats (Figure 5.3). Intriguingly, in both regions phase precession occurred at very similar spike phases despite the strongly phase-shifted local theta oscillations. However, CA1 spikes phases were slightly shifted towards later phases, apparent in the difference of the normalized spike prevalence (Figure 5.3A, right panel). We quantified the phase difference between CA3 and CA1 phase precession by calculating the circular difference between the mean phase of CA3 and CA1 spike phases in the same relative position within the respective place field (Figure 5.3B). We found that the phase difference ranges from 8.0 to 34.8 degrees (mean 17.9 degrees), depending on the relative position in the place field. We also quantified single-trial phase precession by fitting a line to the phase-position data. For each single-trial we calculated the phase offset, i.e. the phase of the fitted line at the beginning of the place field (Figure

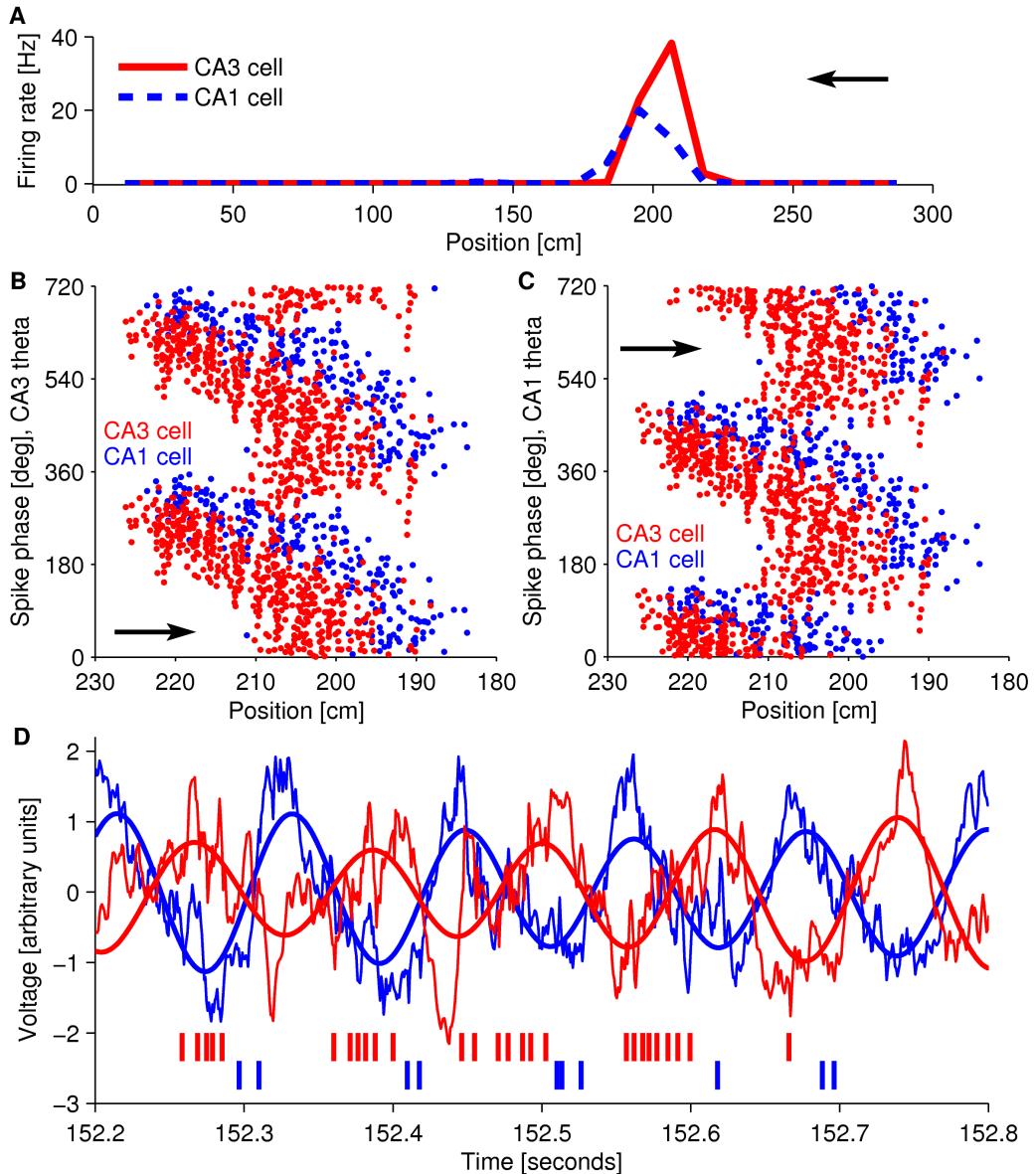


Figure 5.1: Phase precession in CA3 and CA1. **(A)** Firing-rate profile of a CA3 and a CA1 pyramidal cell on the linear track. **(B,C)** Phase precession in CA3 (red) and CA1 (blue). We measured spike phases with respect to the LFP in **(B)** CA3 or **(C)** CA1. Black arrows denote running direction of the rat. **(D)** Single-trial example of the same cells. Colored traces show zero-mean LFP (thin lines) and bandpass-filtered signals (thick lines). Vertical bars denote action potentials of the respective CA3 and CA1 cell with overlapping place fields. Scale on the y-axis refers only to LFP traces.

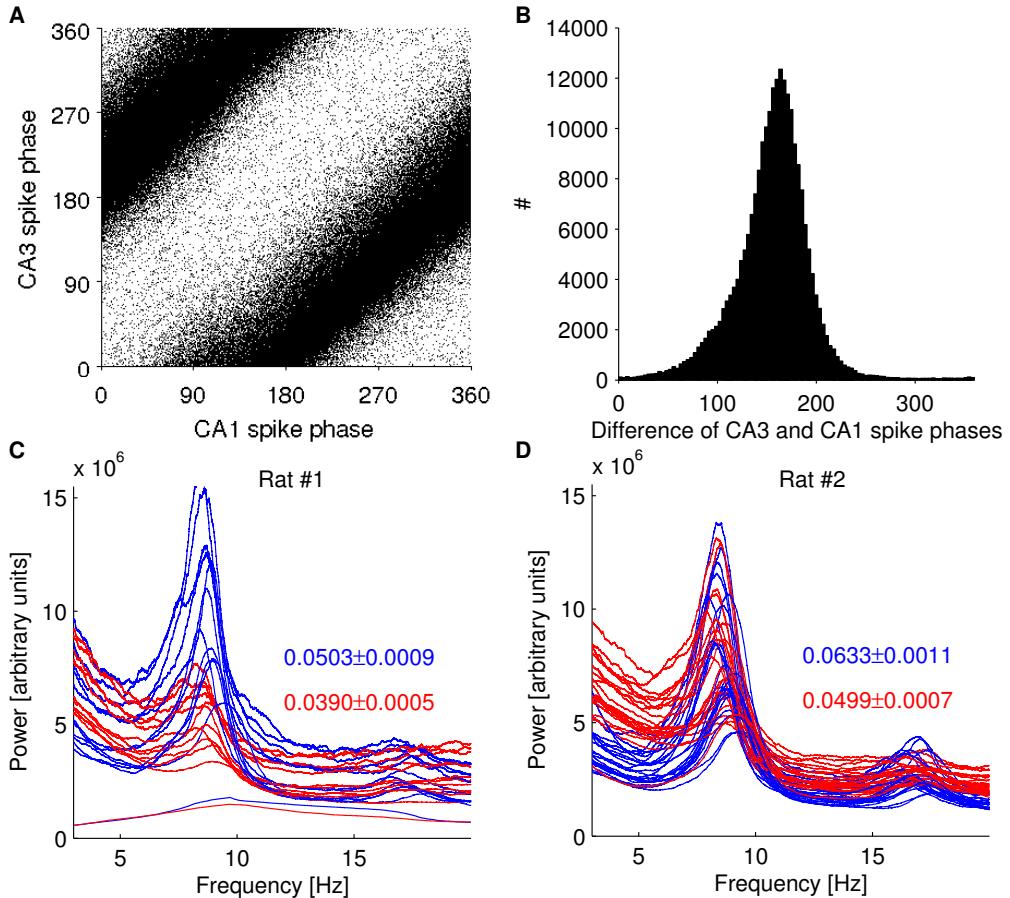


Figure 5.2: CA3 and CA1 theta and their relation during place field activity. **(A)** CA1 spike phases plotted against CA3 spike phases (237.727 spikes). **(B)** Histogram of circular differences between CA1 and CA3 spike phases with a peak at 155.8 degrees. **(C,D)** Power spectra of median LFPs from each session for both rats. Red traces correspond to CA3, blue traces to CA1. Inset number give relative contribution of the theta band (6 to 10 Hz) to the total power ( $\pm$  standard error of the mean).

5.3C). Again, we determined a circular mean phase offset for CA3 and CA1 cells, yielding a phase shift of 10.6 degrees.

### 5.4.3 CA1 spikes occur most frequently 5 ms after CA3 spikes

Apart from these measures that estimated the phase relation between CA3 and CA1 spikes we also studied their temporal relation. The corresponding cross-correlograms (Figure 5.4A) confirmed that spikes from CA1 place fields most likely occurred 5 ms after a spike from a CA3 cell. As the time lag of the peak in the cross-correlogram depends on the spatial distance between the corresponding place fields (Dragoi and Buzsáki, 2006), we additionally determined cross-correlograms as a function of place field distance (Figure 5.4B). CA3 cells often fired before CA1 cells even if the CA1 field was entered before the CA3 cell (many data points in the lower-right quadrant). In contrast, CA1 cells rarely fired before CA3 cells if the CA3 field was crossed first (few data points in the upper left-quadrant).

In summary, we found that the local theta rhythm in CA3 is almost antiphasic in relation to the CA1 theta rhythm. Still, phase precession in the two regions occurred with only a small phase shift in the range 10 degrees, so that CA1 cells tended to fire a few milliseconds after CA3 cells.

## 5.5 Discussion

We found that phase precession in CA3 and CA1 occurs at similar phases, despite strongly shifted CA3 and CA1 theta in the LFP. Furthermore, CA3 cells were active briefly before CA1 cells with a time offset of about 5 ms. These results have implications for the origin of phase precession in CA3 and CA1.

### 5.5.1 Inheritance of phase precession

A straightforward interpretation of the 5ms delay between CA3 and CA1 phase precession is that phase precession in CA1 is inherited from phase precession in CA3. Although the exact contribution of CA3 to CA1 activity remains unknown (Ahmed and Mehta, 2009), a time lag of 5 ms matches the time it takes for CA3 activity to propagate to CA1, e.g. during sharp wave-ripple events (Csicsvari et al., 2000; Both et al., 2008; Maier et al., 2009). Thus, a simple model, in which CA1 place cells are driven by CA3 place cells with similar place fields, could explain the experimental data.

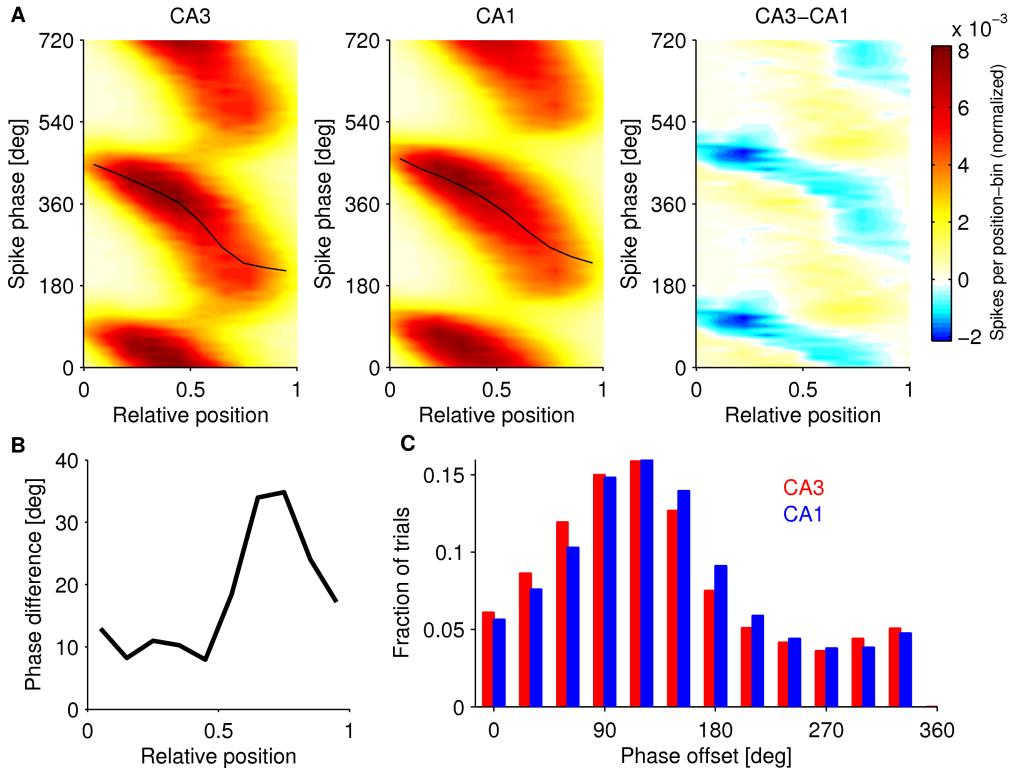


Figure 5.3: Spikes phases in CA3 and CA1 and their relation during place field activity. **(A)** Phase precession in the population of CA3 cells (left panel) and CA1 cells (middle panel). Color-code denotes the normalized number of spikes per position bin (see color-scale bar on the right). Black lines give circular mean phase of all spikes within 0.1-sized position bins. The right panel shows the difference between CA3 and CA1 population phase precession (i.e. the difference between the left and the middle panel) on the same color-scale. Cold colors reflect negative values, i.e. stronger prevalence of CA1 spikes at particular phases. **(B)** Phase difference between CA3 and CA1 phase precession. The graph shows the difference between the circular mean phases for each position bin (from A). The positive values correspond to smaller mean phases in CA3 than in CA1. **(C)** Phase-offset histograms.

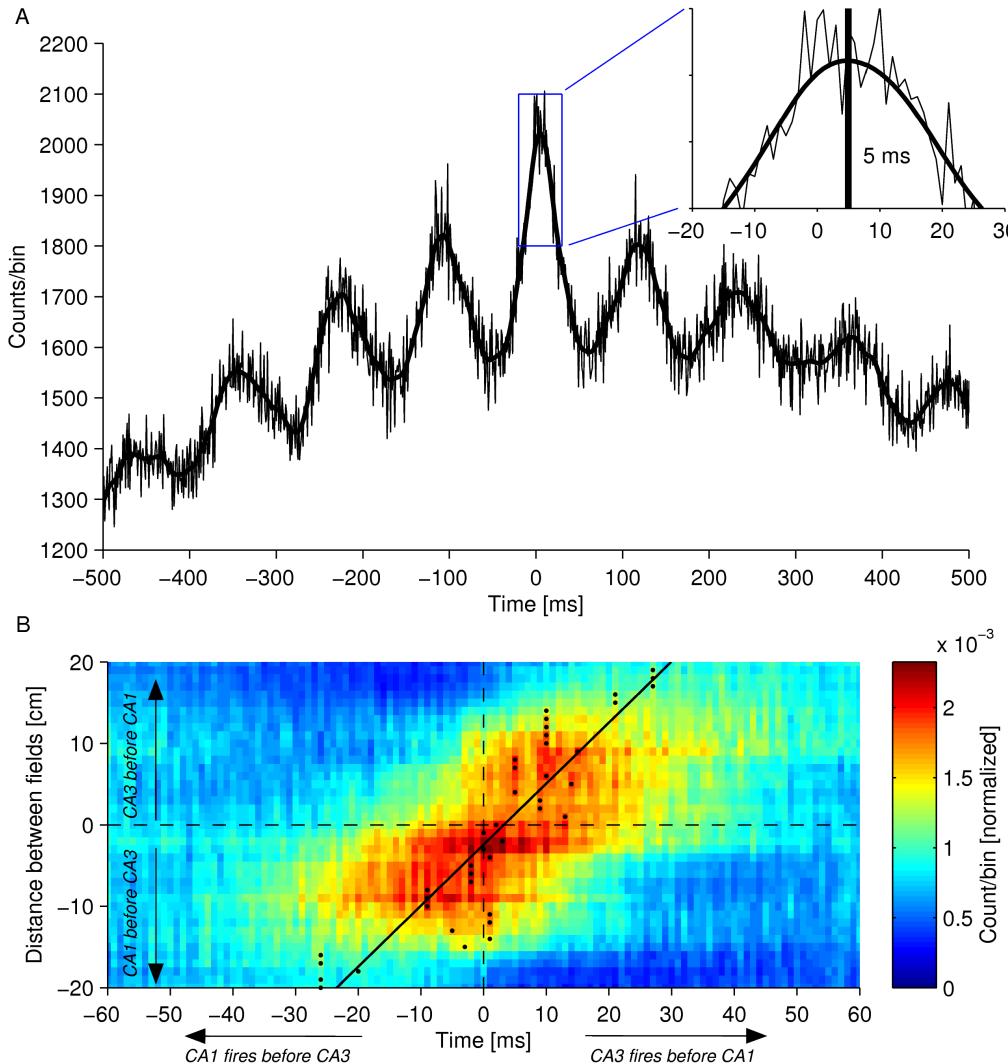


Figure 5.4: Cross-correlograms (CCGs) of simultaneously recorded CA3 and CA1 cells. (A) CCGs from all trials in which a CA1 and a CA3 cell were active are pooled (thin line). Thick lines give averaged values over a running window of 20 ms width. The peak value at 5 ms is marked in the inset with a vertical line. Positive time lags on the time-axis correspond to CA3 cells firing before CA1 cells. (B) Color-coded CCGs as a function of the distance between two place fields. CCGs from cell pairs with similar place field distances (5 cm bin size) are pooled and then normalized to an area of 1. Black dots denote CCG peaks for a given place field distance. Black line is a linear fit to the CCG peaks. Note that the line does not cross the center (indicated by the two dashed lines). Instead, for zero distance between place fields, the fitted line indicates that CA3 cells fire 3.5 ms before CA1 cells.

Alternatively, both CA3 and CA1 phase precession could be inherited from the entorhinal cortex. However, direct inheritance of CA1 phase precession from the entorhinal cortex seems unlikely because layer III of the entorhinal cortex, projecting to CA1, does not exhibit phase precession (Hafting et al., 2008; Mizuseki et al., 2009).

Each CA1 pyramidal cell receives about 30.000 inputs from CA3 (Ahmed and Mehta, 2009). Still, activation of only 100–300 excitatory synapses seem to be required to evoke an action potential in a CA1 pyramidal cell (Andersen, 1990; Bernard and Wheal, 1994). Given the hippocampal anatomy and physiology, CA3 activity should strongly modulate CA1 activity. However, the relative contribution of input from CA3 and input from entorhinal cortex layer III remains unclear (Ahmed and Mehta, 2009). Intriguingly, place-field activity in CA1 persists despite removal of CA1 inputs from either CA3 or entorhinal cortex layer III (Brun et al., 2002, 2008; Nakashiba et al., 2008). Unfortunately, it has not been examined whether also phase precession was still present in the different conditions. The proposed model of inheritance of phase precession implies that phase precession in CA3 and CA1 persists when inputs from entorhinal cortex layer III are removed, but disappears in CA1 without CA3 inputs.

Previous studies reported CA3 and CA1 pyramidal cells to be preferentially active at different theta phases (Dragoi and Buzsáki, 2006; Mizuseki et al., 2009). In contrast, we found that during place field activity, the two cell populations were active at similar phases. One possible explanation is regional variability within CA3. In our data set, recordings originate from the CA3b region in the left dorsal hippocampus (Diba and Buzsáki, 2007, 2008). It is well possible that in other subregions of CA3 different phase preferences for CA3 pyramidal cell activity exist. Furthermore, also the theta phase in the CA3 pyramidal cell layer might be shifted consistently across CA3 sub-regions. Recently, it has been demonstrated that theta oscillations in CA1 are traveling waves, so that at a given point in time the theta phase depends on the anatomical location along the septotemporal axis of the hippocampus (Lubenov and Siapas, 2009). Therefore, our results on the coordination of CA3 and CA1 phase precession are only one piece of the puzzle of the overall temporal organization in the hippocampus. However, our finding that, at least in subregions of CA3 and CA1, phase precession in CA1 occurs briefly after phase precession in CA3, remains valid. Systematic measurements from various CA3 and CA1 subregions will be necessary to reveal the whole picture on the nature of the CA3-CA1 interaction.

### 5.5.2 Mechanism underlying phase precession

We found that phase precession occurred at very different phases in CA3 and CA1 with respect to the local theta. In CA1, theta oscillations in the LFP are locked to the intracellular membrane potential in CA1 pyramidal cells (Kamondi et al., 1998) because theta oscillations in the LFP reflect synaptic currents of interneurons that also control the subthreshold membrane potential oscillations in pyramidal neurons. In CA3, however, the relation between extracellular theta oscillation in the pyramidal cell layer and intracellular membrane potential oscillations is unclear. Our finding that the extracellular theta oscillations in CA3 were weaker than in CA1 is in line with contributions of e.g. dentate gyrus theta to the CA3 theta through volume conduction (Montgomery et al., 2009). Therefore, it is crucial to determine the relation between extracellular and intracellular theta in CA3 to interpret our findings on the coordination of CA3 and CA1 phase precession.

Regarding the implications of these findings on mechanisms underlying phase precession, there are two extreme scenarios. First, if extracellular CA3 theta oscillations are coherent with intracellular subthreshold oscillation in CA3, phase precession in CA3 and CA1 could not be generated by the same mechanism. The reason for this is that in models the phase of the first spike occurs briefly before the trough of the theta oscillation (e.g. Mehta et al., 2002; Thurley et al., 2008), at which the pyramidal cells are assumed to be least inhibited. Accordingly, there is a fixed relation between the peaks and troughs of the oscillation and the start- and ending-phases of phase precession. Thus, either phase precession is generated by entirely different mechanisms in CA3 and CA1, or at least one of them is not generated locally, but instead inherited from another region. In a second scenario, if CA3 cells show subthreshold membrane potential oscillations that are coherent and in phase with those in CA1 cells, phase precession could be generated in both regions independently and by the same mechanism.

### 5.5.3 Outlook

The phase relation of theta in subregions of CA3 and CA1 is not yet fully established. Therefore, it is possible that the CA3-CA1 phase relation depends on further anatomical factors that are not covered in the present data set. Future studies that simultaneously record in other hippocampal and entorhinal regions will further deepen our understanding on the coordination of phase precession across regions. Further, defining the conditions of inheritance of phase precession can contribute to understand the functional relevance. Computational modeling can provide basic requirements of neural

networks for inheritance of phase precession in terms of necessary numbers of synapses, synaptic strengths, and temporal precision. Experimental studies can identify potential factors affecting the inheritance of phase precession like familiarity of the environment, cognitive requirements, reward exposure etc. Unconditional inheritance of phase precession across regions without any changes appears redundant from a functional point of view. We instead expect that there are context-dependent changes in phase precession among regions or conditions that gate phase precession in order to fulfill a potential function, e.g. in memory. Alternatively, if phase precession would be generated in several regions independently, we need to know whether the generating mechanism is the same. Anyway, the presence of phase precession in different brain regions requires new computational models of their interaction and function.

# Chapter 6

## Temporal Pattern Learning in the Hippocampus: Behavioral Sequences and Reverse Replay

So far, we looked at phase precession, which occurs while the rat is running e.g. on a linear track. In this chapter, we model activity that occurs when the rat is resting at the end of the track. At that time, place cells are reactivated in a sequence that corresponds to the reverse order in which the respective place fields were crossed during movement. Further, we propose that this reverse replay serves as a temporal pattern that can be learned by downstream structures (Leibold et al., 2008).<sup>1</sup>

### 6.1 Summary

Mechanism and function of hippocampal sequence replay are unknown. Here we (Leibold et al., 2008) present a model of reverse replay of sequences after recent spatial behavior. The model is based on short-term facilitation that decays at a behaviorally relevant time scale of seconds. Thereby, synapses of more recently crossed place fields are more facilitated than those of less recently crossed place fields. A synchronous read-out stimulus combined with an appropriate subthreshold oscillation leads to reverse replay. More generally, this mechanism can be used to compress patterns from a behavioral time scale of seconds to shorter time scales relevant for synaptic plasticity. We demonstrate that temporal patterns compressed by this mechanism

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<sup>1</sup>The research presented in this chapter is the result of a collaboration with several researchers and is also part of a published article. I conducted all modeling and computer simulations presented here and contributed to the writing of the paper.

to a time scale of milliseconds can be learned by the tempotron learning rule. This model provides testable predictions (e.g. synchronous activation of dentate gyrus during sharp wave-ripples) and functional interpretations of hippocampal activity (e.g. temporal pattern learning).

## 6.2 Introduction

Time scales of behavioral and cognitive phenomena, such as navigation in a maze or short-term memory, are in the order of seconds or longer. In contrast, the time scales of cortical neuronal dynamics are mostly in the range of a few milliseconds to hundreds of milliseconds. These time scales are well-adjusted to the time window for the induction of synaptic changes via spike-timing dependent synaptic plasticity (Markram et al., 1997; Bi and Poo, 1998; Kempter et al., 1999), which leads to the hypothesis that synaptic plasticity provides a means of learning to discriminate and recognize distinct cellular activity patterns. How to transfer slow behaviorally evoked temporal patterns to appropriate synaptic long-term changes and to enable the formation of long-term memories of behavioral sequences is largely unclear.

In the previous chapters, we studied the activity of place cells within their place field. However, place cells can also be active outside their place field. For example, during sharp wave-ripple events that occur while the animal is resting, place cells are reactivated in a reverse order compared to the order imposed by place field crossings during behavior (Foster and Wilson, 2006). Thus, the population of place cells exhibits correlation coding during spatial behavior (through phase precession) and also during resting periods following spatial behavior (through reverse replay). Therefore, the order of activity among cells seems to be essential for the functional role of phase precession and sequence replay.

In this chapter, we show that short-term synaptic facilitation, which is a candidate mechanism for phase precession (Thurley et al., 2008, see Figure 3.6 in Chapter 3), can also be used to generate the reverse replay of recent behavioral sequences. More generally, the same mechanism can be used to encode temporal stimulus properties via variable amplitudes of synaptic currents, which are then transformed to different spike times (Leibold et al., 2008). One important parameter is the input spike phase  $\psi$ , which determines the distribution of output spikes  $\phi$  within the theta cycle (Figure 6.1A and B).

Further, we exploit the fact that sequence replay provides a temporal pattern that compresses a behavioral sequence to a shorter time scale. We demonstrate that the compressed temporal patterns of sequence replay can

be learned by the recently developed tempotron learning rule. The tempotron (Gütig and Sompolinsky, 2006), analogous to the perceptron, is capable of learning to discriminate various temporal patterns. Thereby neurons can acquire response properties that correspond to a whole behavioral sequence. This is a very fundamental feature underlying reinforcement learning, goal-directed behavior, and episodic memory.

## 6.3 Methods

### 6.3.1 Generation of temporal patterns

We have defined 200 firing patterns of a population of 200 input lines such that each pattern contains one event (spike or burst) per input line occurring independently at random times  $t_n^{in}$  ( $n = 1, \dots, 200$ ) in the interval between 0 and 10 seconds. Each input event triggers the maximal facilitation  $A_{max} = 14 \frac{\mu A}{cm^2}$  of the synapse connected to the specific input line. The facilitation  $f_n$  then decays exponentially with a time constant  $\tau_f = 5$  seconds (Figure 6.3A).

To read out the states of facilitation, all synapses are simultaneously activated at a phase angle  $\psi$  with respect to an additional subthreshold oscillation with period 111 ms. The larger the delay between an input event and the readout stimulus, the smaller is the value of the facilitation  $f_n$  of the synapse at the time of readout. The readout stimulus therefore triggers a reverse replay of the pattern, and the replayed pattern is temporally compressed. Given an input spike phase and EPSC amplitude, the output spike phases are obtained from the simulation data shown in Figure 6.1B. The reversed and compressed pattern is then conveyed to a threshold unit and there elicits standardized EPSPs  $w_n (e^{-t/\tau} - e^{-t/\tau_s})$  (for  $t \geq 0$ ) with a membrane time constant  $\tau$ , a synaptic time constant  $\tau_s = \tau/4$  and a synaptic weight  $w_n$ .

### 6.3.2 Learning temporal patterns

Half of the above patterns were randomly classified as ‘+’ patterns, the others were termed ‘-’ patterns. The synaptic weights are trained via the tempotron learning rule (Figure 6.2; Gütig and Sompolinsky, 2006) such that the threshold unit emits a spike for ‘+’ patterns and does not fire for ‘-’ patterns. Unless stated otherwise, all parameters were taken as proposed by Gütig and Sompolinsky (2006). In particular, in each learning cycle, all patterns were presented in the same order. Learning was stopped when 100% of the patterns were classified correctly or when the maximal number of learning

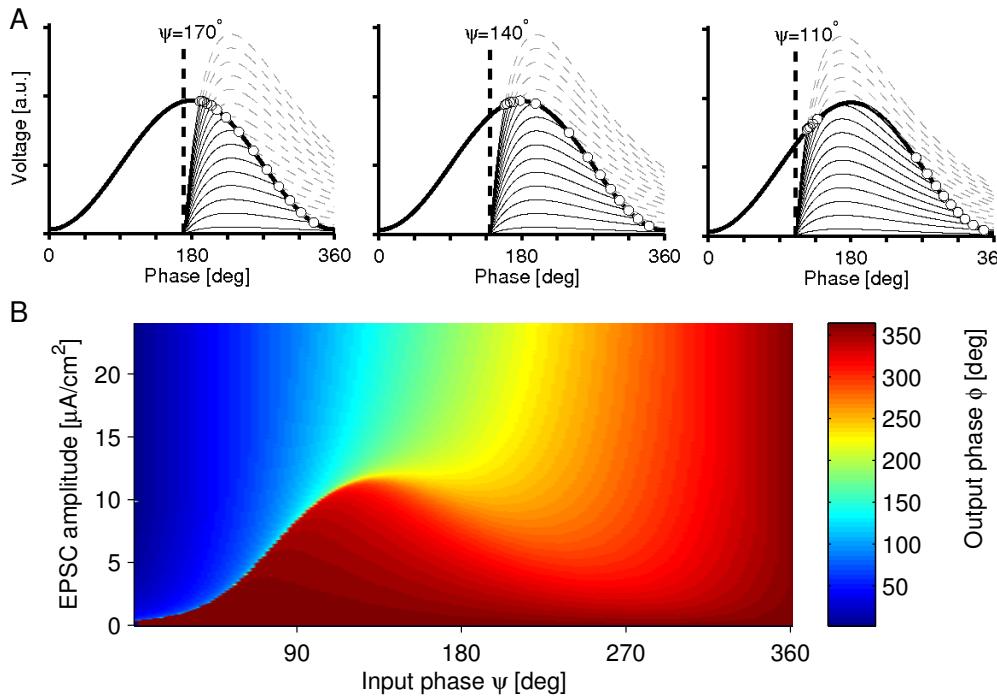


Figure 6.1: Spike phase as a function of input phase and input amplitude (modified from Leibold et al., 2008). **(A)** Examples for the relation between input phase  $\psi$  (thick dashed line) and phases of output spikes (white circles). Thick black line denotes the firing threshold of the cell. Thin dashed lines show EPSPs with increasing amplitude due to short-term facilitation. The timing of the spike depends on the EPSP amplitude. For an input phase of  $170^\circ$  (left panel), the output phase decreases rather continuously as a function of EPSP amplitude. In contrast, for an input phase of  $110^\circ$ , the output phase exhibits a ‘jump’ around the peak of the firing threshold. **(B)** Model simulations yield output spike phases  $\phi$  depending on the amplitude of the excitatory postsynaptic current (EPSC) and the input spike phase  $\psi$ .

cycles (here 100) was exceeded.

Simulations were run for different EPSP time constants  $\tau$  and different input phases  $\psi$  of the readout stimulus. We repeated simulations 50 times for each set of parameters.

## 6.4 Results

### 6.4.1 Temporally-compressed sequence replay through short-term facilitation

We hypothesized that short-term facilitation combined with subthreshold oscillations provide a general mechanism to generate temporal spike patterns (Leibold et al., 2008). Therefore, we examined simulations of behavioral sequences that are represented by place cell activity in the hippocampus (Figure 6.3). An example population of seven place fields is crossed at different times during spatial exploration. During resting behavior, the time that has passed since any of these place fields has been crossed is cell-specific. We propose that this delay is reflected in the degree of facilitation in each cell. Synapses from cells that have very recently been crossed are more facilitated than synapses from cells that have been crossed a longer time ago. Thus, the degree of facilitation of each synapse codes the time that has passed since the animal crossed the corresponding place field (Figure 6.3A). Thereby, the slow temporal correlations between the different neurons in the population are stored in the memory traces provided by synaptic facilitation with a decay time constant of 5 s, as is known from the hippocampal mossy fiber synapse (Gundlfinger et al., 2007; Salin et al., 1996).

During resting behavior, the degree of facilitation can be translated into a spike phase through a read-out stimulus (synchronous stimulation of all cells) in combination with a subthreshold membrane potential oscillation. Depending on the degree of facilitation, cells will fire earlier or later during an oscillation cycle (Figure 6.1). In our example of a place-field sequence, the order of activity evoked by the read-out stimulus is a reverse replay of the original place-field sequence (Figure 6.3A).

Through this mechanism the slow temporal pattern is transferred to the time span of at most one oscillation cycle, which is 111 ms in our example (Figure 6.3A). The peri-stimulus time histograms (PSTHs) of the temporal population patterns elicited by the readout stimulus at phase  $\psi$  are shown in Figure 6.3B. Depending on  $\psi$ , the PSTH can be unimodal for late and early input phases, or bimodal for intermediate input phases ( $50^\circ < \psi < 200^\circ$ ; Figure 6.3D). If hippocampal reverse replay was a result of mossy

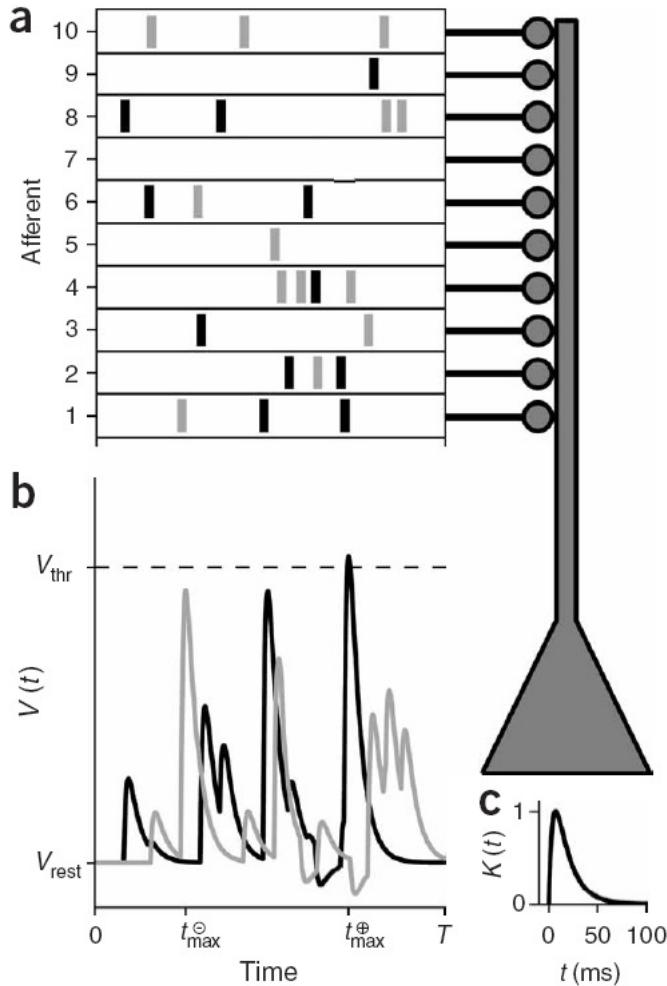


Figure 6.2: Tempotron learning (from Gütig and Sompolinsky, 2006; with permission from Macmillan Publishers Ltd.). (a) Schematic illustration of a tempotron receiving input from ten afferents with activity corresponding to two different temporal patterns. The goal of learning is that the tempotron is active for some patterns but not for others (discrimination learning). Learning occurs through modifying the afferent-specific input weights. (b) Examples of two activity traces evoked in the tempotron by two different patterns (gray and black). Each afferent spike evokes an EPSP (shown in c), and the sum of EPSPs is the activity trace. The tempotron is activated if the activity trace crosses the firing threshold (dashed line). If a pattern is correctly classified, the afferent weights are not changed. If a pattern does not elicit a spike in the tempotron although it should, the weights belonging to afferents that precede the maximum in the activity trace are increased. If a pattern evokes a spike although it should not, the weights of afferents preceding the threshold crossing in the activity trace are decreased.

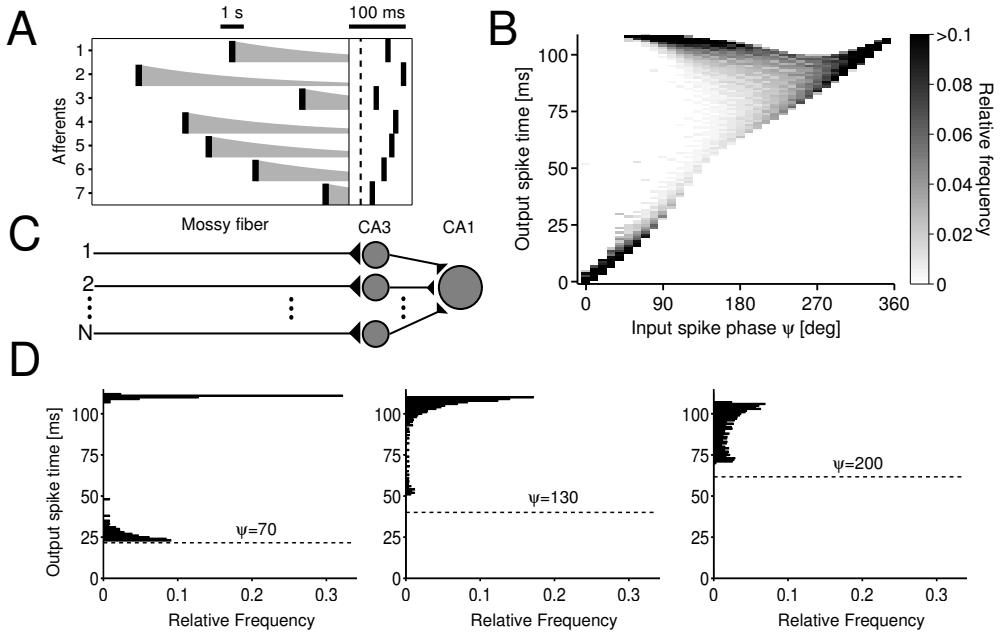


Figure 6.3: Learning to discriminate between temporal patterns on a time scale of seconds. **(A)** Schematic illustration of temporal compression through synaptic facilitation. Left: A temporal spike pattern (vertical bars) from a population of seven afferents on a time scale of seconds. The temporal pattern is preserved in the memory traces provided by the decay of synaptic facilitation (gray areas). Right: Readout stimulus (dashed line) in combination with subthreshold oscillation evokes a reverse replay of the pattern in the seven neurons (vertical bars). Note different temporal scale bars for temporal pattern (left) and reverse replay (right). **(B)** Depending on the input phase  $\psi$  of the readout stimulus, the compressed population patterns show distinct phase distributions (gray-scale PSTHs). **(C)** A downstream threshold unit (e.g. in CA1) with adjustable synaptic weights learns to discriminate between temporally compressed phase patterns of a population of neurons (e.g. in CA3). **(D)** Exemplary PSTHs from B for input phases  $\psi = 70^\circ, 130^\circ$  and  $200^\circ$  (dashed lines).

fiber synaptic facilitation, our model predicts that instances of reverse replay should be temporally correlated with synchronous readout of the state of facilitation – the synaptic memory buffer – of a large number of mossy fiber synapses, as indicated by the dashed lines in Figure 6.3A.

### 6.4.2 Learning to discriminate temporal patterns

Are the temporal patterns generated through short-term facilitation suitable for further processing downstream? As a proof of concept, we investigated the example of a downstream neuron (e.g. in CA1) that learns to discriminate between patterns of spike phases of a population of neurons (e.g. in CA3).

We assume sparse patterns, i.e., each input line fires only once, to obtain as few sub-second correlations as possible. To show how the compressed temporal pattern in a population of neurons can be discriminated by a downstream neuron (Figure 6.3C), we trained a threshold unit using the tempotron learning rule by Gütig and Sompolinsky (2006) in the original parameter regime. The tempotron rule is a supervised learning rule extending the perceptron rule (cf. Hertz et al., 1991) to the temporal domain. Whereas the perceptron rule allows to learn a linear classification task on a set of temporally static patterns, the tempotron rule is able to learn a classification task in a spatio-temporal pattern space as shown in Figure 6.3A.

Since the decay time constant  $\tau$  of the downstream EPSP has been identified as a crucial parameter for tempotron learning (Gütig and Sompolinsky, 2006), we have conducted computer simulations for three different values of  $\tau$ . The success of learning is illustrated in Figure 6.4A, which depicts the percentage of correctly classified patterns as a function of the input phase  $\psi$ . The results strongly depend on  $\tau$ . For downstream EPSPs with  $\tau = 10$  ms the tempotron rule performs best at an input phase of  $\psi \approx 200^\circ$ . For  $\tau = 20$  ms, an input phase of  $\psi = 130^\circ$  yields best, though moderate, performance. For an even larger decay time constant  $\tau = 30$  ms there is, again, a distinct peak of the percentage of correctly classified patterns at  $\psi = 70^\circ$ . A closer look at the PSTHs at these input phases (Figure 6.3D) reveals three different paradigms: (1) High performance is found for flat PSTHs with a width of several times  $\tau$  ( $\psi = 200^\circ$ ,  $\tau = 10$  ms). This case can be considered as the original tempotron paradigm (Gütig and Sompolinsky, 2006), in which most of the temporal information is conveyed via the decaying slopes of the EPSPs. (2) Learning can be moderately successful if the PSTH reveals a single peak that is narrower than the EPSP ( $\psi = 130^\circ$ ,  $\tau = 20$  ms). In this regime, the learning rule thus also extracts temporal information from the rising slope of the EPSP. (3) Finally, successful learning occurs for bimodally peaked PSTHs ( $\psi = 70^\circ$ ,  $\tau = 30$  ms). In this case, the temporal domain of the input

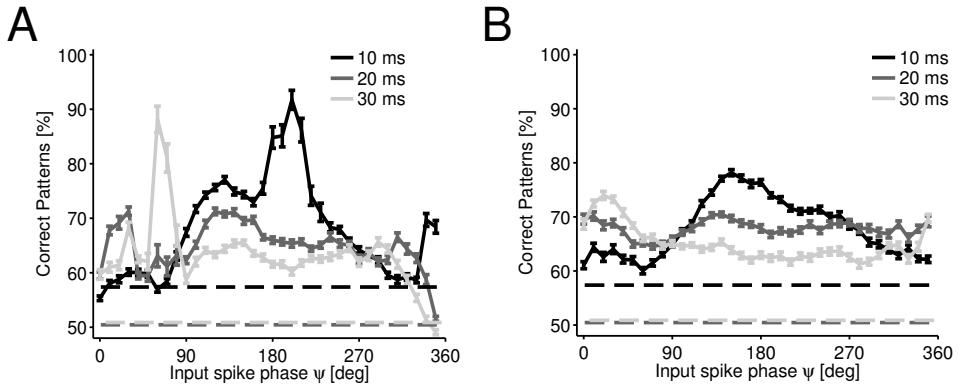


Figure 6.4: Tempotron performance depends on pattern distribution and decay time constant. **(A)** Fraction of correctly classified patterns after 100 learning cycles (mean  $\pm$  SEM,  $n = 50$  simulations) reveals an optimal input phase  $\psi$  that depends on the decay time constant  $\tau$  of the downstream EPSP (gray levels depict different values of  $\tau$ ). Dashed lines indicate fractions of correctly classified patterns for simulations without subthreshold oscillations. Standard errors for dashed lines are all smaller than 0.7%. **(B)** Adding a jitter (standard deviation 30°) to the phase of the readout stimulus reduces performance of learning. Dashed lines are the same as in A, since there is no phase jitter without an oscillation.

pattern can be considered to be divided into two intervals (corresponding to high and low synaptic amplitudes) with peaked unimodal PSTHs each. As in the previous case, the temporal information with the two subgroups is again also conveyed via the rising slopes of the EPSPs.

In a final series of simulations, we jittered the phase of the readout stimulus (Figure 6.4B). The phase  $\psi$  of the readout stimulus was drawn from a normal distribution with mean  $\bar{\psi}$  and standard deviation of 30°. In these simulations, the general dependence on input phase is preserved compared to the noise-less case, although the peak performances are strongly reduced. Interestingly, the moderate performance peaks for a unimodal PSTH ( $\psi = 130^\circ$ ) are almost unchanged.

To summarize, the success of the tempotron rule strongly depends on properties of the downstream neuron such as the decay time constant  $\tau$  of the EPSP. Moreover, using a model without subthreshold oscillations the success of learning is much smaller (dashed lines in Figure 6.4A and B). Thus, subthreshold oscillations that increase the temporal coding range can improve or, as in the present example, may even be necessary for learning.

## 6.5 Discussion

Here we showed how short-term synaptic plasticity can contribute to the temporal compression of slow behaviorally induced temporal patterns. The core idea is to map the temporal input pattern to a pattern of EPSC amplitudes. The memory time constant of synaptic short-term plasticity thereby determines the time window over which the slow temporal patterns can extend. Subthreshold oscillations have been used to efficiently translate the synaptic amplitudes into a temporal sequence of action potentials in a population of neurons. This temporal sequence of action potentials provides temporal correlations on a shorter time scale, which are suitable to trigger long-term synaptic plasticity and learning.

### 6.5.1 Temporal patterns

On the basis of computer simulations, we showed that a downstream neuron in CA1 can learn to discriminate between the temporally compressed spike patterns of a population of model CA3 pyramidal cells (Figures 6.3 and 6.4). As an example for temporal compression we have considered oscillations with a period of 111 ms and facilitation time constants of several seconds. These time scales match the typical period of hippocampal theta oscillations (4 to 12 Hz) (Buzsáki, 2002) and the decay of facilitation at the mossy fiber synapse (Gundlfinger et al., 2007; Salin et al., 1996), respectively. The input-phase dependence of learning is strongly modulated by the EPSP decay time constant of the downstream neuron (Figure 6.4). In general, successful learning requires the downstream EPSP to be adjusted to the PSTH of the population pattern. The results on optimal input phases for learning are thus not generic because they are derived for a specific learning paradigm with a given kinetics of the EPSPs, a given period length and shape of the subthreshold oscillation (Hopfield, 1995), and a given realization of the learning algorithm (Gütig and Sompolinsky, 2006).

### 6.5.2 Reverse replay

The temporally compressed firing pattern in the population of CA3 cells occurs in reversed order as compared to the slow original one. This reversal is independent of whether the replay occurs with or without subthreshold oscillations. Interestingly, such reverse replay of place field activity in the hippocampus was predicted by Buzsáki (1989) and recently also experimentally confirmed (Foster and Wilson, 2006; Diba and Buzsáki, 2007). If this hippocampal reverse replay was a result of mossy fiber synaptic facilitation,

our model predicts that instances of reverse replay should be temporally correlated with synchronous activation of a large fraction of the presynaptic dentate gyrus granule cells.

To improve the biological relevance of the performed simulations, it would be interesting to create temporal patterns that are more similar to those during reverse replay. For example, the distribution of spike times during reverse replay could be adjusted to experimentally observed activity patterns of pyramidal cells during replay. Available experimental data (e.g. Klausberger and Somogyi, 2008) suggests a unimodal distribution with a peak at the center of the sharp wave-ripple event. Furthermore, the subthreshold oscillation at the time of the read-out stimulus in the model could be fitted to experimentally observed subthreshold activity during sharp wave-ripple events. The resulting spike distribution in the model should then match the experimentally observed spike distribution during replay.

In addition to sequence replay also sequential place field activity corresponding to future place field crossings has been observed (Diba and Buzsáki, 2007). This ‘forward preplay’ can not be accounted for by the mechanism proposed here. For modeling aspects it would be essential to reveal whether forward preplay is really linked to planned future behavior. So far it has been demonstrated only on linear tracks on which rats run back and forth many times. Then, past and future place field sequences are inevitably similar.

In our model, sequence replay is used for the learning of temporal patterns. If something similar is performed in the hippocampal network, the prediction is that, through this learning, downstream neurons (e.g. in the subiculum) acquire response properties that conform to such patterns. For example, these neurons should be active throughout the corresponding sequence. For spatial behavior, this could be a cell which has a larger place field than single CA3 or CA1 place cells. Accordingly, the activity of subicular cells should match sequences of place cells and thereby subicular cells could be active throughout a whole arm of a maze or throughout a linear track. In fact, subicular neurons appear to have spatial firing characteristics, but fire over larger regions in the environment than place cells (Sharp and Green, 1994; Phillips and Eichenbaum, 1998; O’Mara et al., 2000). Furthermore, their activity is modulated by the running direction (Sharp, 2006), which is necessary to preserve information about sequences. Neurons representing sequences of events might be useful further downstream (e.g. in the striatum) to learn about the relevance of sequences of events. These sequences could be a path leading to a reward location, a sequence of auditory stimuli predicting a reward, or any sequence of arbitrary sensory stimuli, as required for mechanisms underlying episodic memory.

# Chapter 7

## Summary and Outlook

We found that phase precession in single trials has different properties than phase precession pooled over trials (Chapter 4). Phase-position correlations in single trials are stronger because in pooled data the overall variability is increased by trial-to-trial variability of e.g. the slope of phase precession. Furthermore, phase-time correlations in single trials are as strong as the phase-position correlations. This means that phase precession is well-suited to encode temporally structured events and may thereby play a role in episodic(-like) memory. We also found that the phase range of phase precession is smaller than suggested by pooled data. The phase range is an important property of phase precession because it provides a basic constraint for models of phase precession. Any functional role of phase precession is implemented by phase precession in single trials, not by data pooled over trials.

Phase precession in CA3 and CA1 occurs almost simultaneously, although the local CA3 and CA1 theta are out of phase (Chapter 5). Phase precession in CA1 occurs briefly after phase precession in CA3, in line CA1 phase precession being inherited from CA3.

Synaptic short-term facilitation can be used to model reverse replay in CA3 (Chapter 6). Through a decay of the facilitation on a timescale of seconds, a memory of the recent spatial behavior is maintained. Population activity patterns with reverse replay generated by the model can be learned by downstream structures through the tempotron learning algorithm. The model predicts synchronous activity in the dentate gyrus during sharp wave-ripple events. Furthermore, if structures downstream of CA3 learn temporal patterns, we predict e.g. the existence of subiculum cells that represent sequences of places.

The existence of strong trial-to-trial variability of phase precession has consequences for theories on hippocampal correlation coding. Through phase precession it is assumed that within a theta cycle the behavioral sequence

of place cells is maintained. However, this works only if phase precession is relatively similar in different cells. If the variability of e.g. the slope of phase precession is large across cells, the sequence compression feature is degraded. Therefore, it is of great interest to study not only the trial-to-trial variability, but also the variability across the whole cell population within the same trial. If all cells in the population undergo similar changes in e.g. the slope, the trial-to-trial variability that we observe does not affect the sequence compression. However, if there is substantial variability across cells in the same trial, it does affect the sequence of place cell activity within one theta cycle. Some preliminary evidence for variability across cells is provided in Section 8.1.5 (Appendix). This variability explains why theta sequences (Foster and Wilson, 2007) appear to be rather noisy. Future studies need to further determine the effect of the variability on the theta sequences.

There is currently no consensus on how to quantify phase precession. Even the determination of the phase-position correlation varies between studies because there is no standard way to correlate a circular variable (spike phase) with a linear one (animal position). Many studies treat the spike phase as a linear variable, but this can induce problems (e.g. underestimation of the slope or overestimation of the correlation strength). Therefore, a canonical method to analyze phase precession is required, which demands innovative analysis algorithms.

The presence of phase precession in several brain regions (e.g. CA3, CA1, and entorhinal cortex) raises the question about the relation of phase precession among different regions. Three aspects of this relation are of particular importance: (1) Is phase precession temporally coordinated among different brain regions? (2) Is phase precession in some regions inherited from other regions? (3) What function is implemented by the relation of phase precession in different regions? Current functional accounts on phase precession do not explain the use of phase precession outside the CA3 and CA1 regions. For example, the sequence learning hypothesis requires the recurrent network in CA3; it does not provide an explanation for phase precessing grid cells in the entorhinal cortex. However, it is likely that phase precession in various regions is the manifestation of a fundamental temporal organization principle in the brain.

# Chapter 8

## Appendix

### 8.1 Single-Trial Phase Precession

#### 8.1.1 Refined surrogate methods

In Chapter 4 we used a surrogate method as simple as possible. It ensured that the number of spikes, a basic single-trial property, was kept. Here, we refine our surrogate data method to take into account more intrinsic properties of single trials.

*'Bad' trials excluded.* Few 'bad' trials with no phase precession or, worse, a positive slope, may have had an undue effect on our surrogate data. Spikes from these trials, when distributed over several different surrogate trials, might weaken their phase-position correlations. Thus we removed all trials with a positive phase-position correlation from the place field. Still we found a significant difference between experimental and surrogate data ( $p = 1 \cdot 10^{-48}$ ; Figure 8.1).

*Similar running speed.* We tested whether the observed differences in the phase-position correlation in experimental and surrogate trials can be accounted for solely by running speed differences across trials. We tackled this problem by including only trials with similar running speed. For each place field, we calculated the mean running speed and its standard deviation. Then we included in the analysis only trials with a running speed within one standard deviation around the mean speed. In this subset of trials, the correlation between running speed and the phase-position correlation was rather weak ( $r = -0.04$  compared to  $r = -0.13$  in the whole data set). We still found a significant difference between surrogate and experimental trials ( $p = 3 \cdot 10^{-27}$ ; see 'Similar speed' in Figure 8.1).

*Spatial range.* Single trials do not always start and end at the border of the place field, and thus they cover only part of it (Figure 4.4A). We tested four

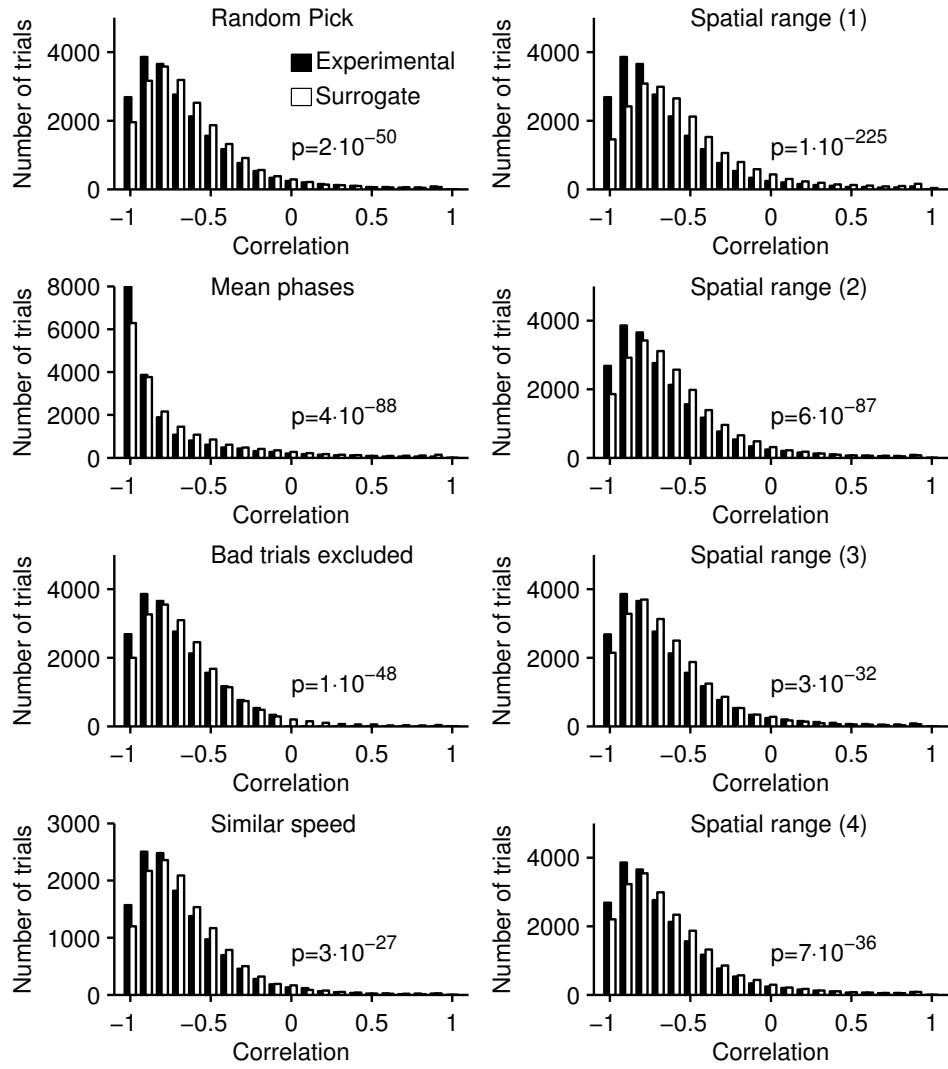


Figure 8.1: Comparison of surrogate data (white bars) and experimental trials (black bars) for eight different surrogate methods (described in section 8.1.1). All distributions show the phase-position correlation coefficient. ‘Random Pick’ is the standard surrogate method from Chapter 4. Inset numbers denote  $p$ -values for the corresponding Kolmogorov-Smirnov test.

variants of our surrogate method in which the spatial range of experimental trials was incorporated. Note that for the first three variants (but not the fourth) spikes were drawn with replacement, so that one spike from the place field could be picked for several surrogate trials. In these three variants, spikes were picked only from within the spatial borders of the experimental trial. So, if the experimental trial started at position 0.2 and ended at 0.7, only spikes between those borders were allowed in the surrogate trial. (1) In the first variant, which had no further constraints, we still found a significant difference between the two distributions of correlation coefficients from experimental and surrogate trials (Kolmogorov-Smirnov test:  $p = 1 \cdot 10^{-225}$ ; Figure 8.1). However, this first variant produced surrogate trials with a necessarily smaller spatial range than the experimental data. (2) To ensure that the spatial range was exactly the same, in a second variant we additionally kept the first and the last spike of the experimental trial for the surrogate trial, but randomly picked the remainder. We still found a significant difference between the two resulting distributions of phase-position correlation coefficients ( $p = 6 \cdot 10^{-87}$ ; Figure 8.1). However, a weakness of this second variant is that the last spike in the last cycle of a trial is biased towards higher phase values. (3) To avoid the resulting bias towards flatter slopes, we tested a third variant where the first spike in a trial and the first spike in the last theta cycle of that trial were kept. Still, this method produced a significant difference between experimental and surrogate single trials ( $p = 3 \cdot 10^{-32}$ ; Figure 8.1). (4) In the fourth variant, the animal position in the place field was divided into ten bins of the same size. For each spike in the experimental trial, the corresponding surrogate spike was drawn from the same position bin. This procedure led to similar spatial ranges in surrogate and experimental data; however, differences between experimental and surrogate phase-position correlations remained significant ( $p = 7 \cdot 10^{-36}$ ; Figure 8.1).

### 8.1.2 Correlation coefficients and the circular nature of spike phase

The quantification of phase precession with linear correlation coefficients can be problematic due to the circular nature of the spike phase. To exclude that our results were an artifact of an inappropriate approach, we determined phase-position correlations based on a circular-linear correlation coefficient and based on data mapping on a cylinder (similar to O’Keefe and Recce 1993), which both yielded significant differences between experimental and surrogate data ( $p = 9 \cdot 10^{-160}$  and  $p = 3 \cdot 10^{-54}$ , respectively). Because the differences persisted with all above quantification methods, we continued to

use the linear correlation coefficient because many other previous results are based on this measure.

In addition to the correlation coefficient, also fitting a line to the phase-position data is affected by the circular nature of the spike phase. In Figure 8.2 we illustrate some cases where circular-linear fits lead to different results than a linear-linear fit.

### 8.1.3 Mean phases

During phase precession, the cell often fires several action potentials within a single theta cycle (Figure 4.5 in Chapter 4). During such a burst with inter-spike intervals of a few milliseconds, the position of the animal does not change much. Thereby, spikes occur at different phases for the same position of the animal, decreasing the overall phase-position correlation. Instead of including all spike phase in the analysis, we also determined the circular mean phase (and mean position) of all spikes from the same theta cycle. Figure 8.3 shows several examples for single trials and pooled data.

### 8.1.4 Correlations between pairs of single-trial properties

There are two principal ways to analyze the relation between single-trial properties: (a) we can estimate the relation for each cell individually, e.g., by means of a correlation coefficient, and then average the correlation coefficient across the whole population of cells (Huxter et al., 2003) or (b) we can initially pool all single trials ( $n = 20602$ ) from all cells and animals, and then calculate correlation coefficients. As an example for method (b), we found a highly significant ( $p = 1.6 \cdot 10^{-73}$ ) but weak ( $r = -0.13$ ) correlation between the running speed and the phase-position correlation coefficient (Figure 8.4A; see also Figure 4.6 in Chapter 4).

A more extensive analysis of single-trial co-variability is shown in Figure 8.4B: Following method (a) from above, a correlation coefficient between each property pair was determined for each place field, and then the mean was calculated over all place fields and animals. We obtained a matrix of mean correlation coefficients with one value for each possible pair of single-trial properties. For example, the correlation between ‘running speed’ and ‘phase-position correlation’ is given as a number ( $-0.16$ ) in column 1 row 9 and color-coded in column 9 row 1. We reproduced previously reported correlations, such as the positive correlation between speed and firing rate (McNaughton et al., 1983; Czurkó et al., 1999; Huxter et al., 2003). We also examined

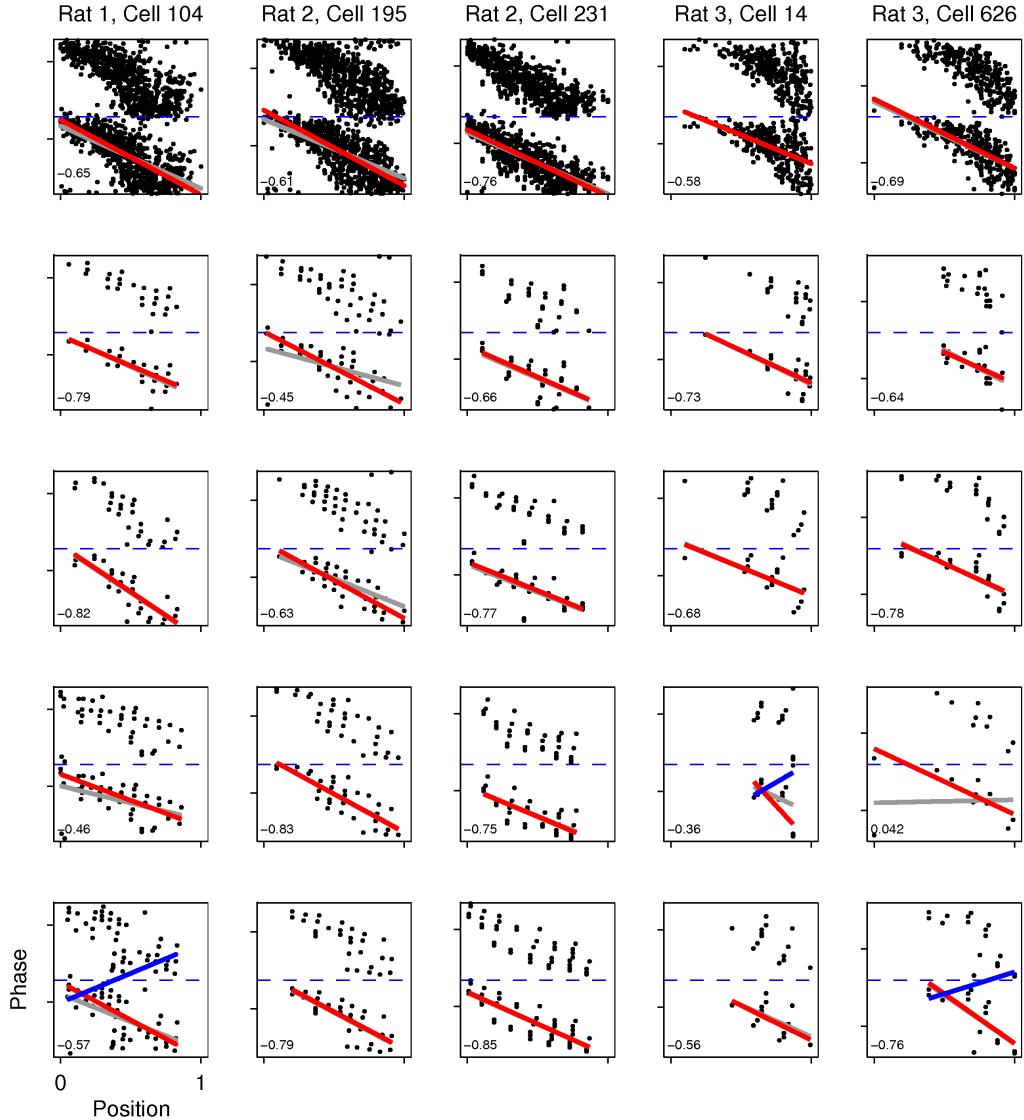


Figure 8.2: Different linear regression methods in examples for pooled-trial (**A**) and single-trial (**B**) phase precession. Similar illustration and notation as in Figure 4.1 is used, except that data points are drawn here on two cycles (ticks at  $0^\circ$ ). The red lines are circular-linear fits (described in Section 4.3.3), with slopes constrained to values within  $[-4\pi, 0]$ . The blue lines are also circular-linear fits, but constrained to slopes within  $[-4\pi, 4\pi]$ . In many cases, the blue lines overlapped with the red lines and are therefore not visible. However, in two cases (column 1, row 5; column 5, row 5) the two fits yielded very different results because the strong bimodal phase distribution in the corresponding trials favored a fit with a positive slope (see also Kjelstrup et al., 2008). The gray lines are linear fits, often not visible due to overlap with the circular-linear fit. The linear fit tended to underestimate the slope (e.g. column 2, row 2) and can even fail to detect phase precession (column 5, row 4).

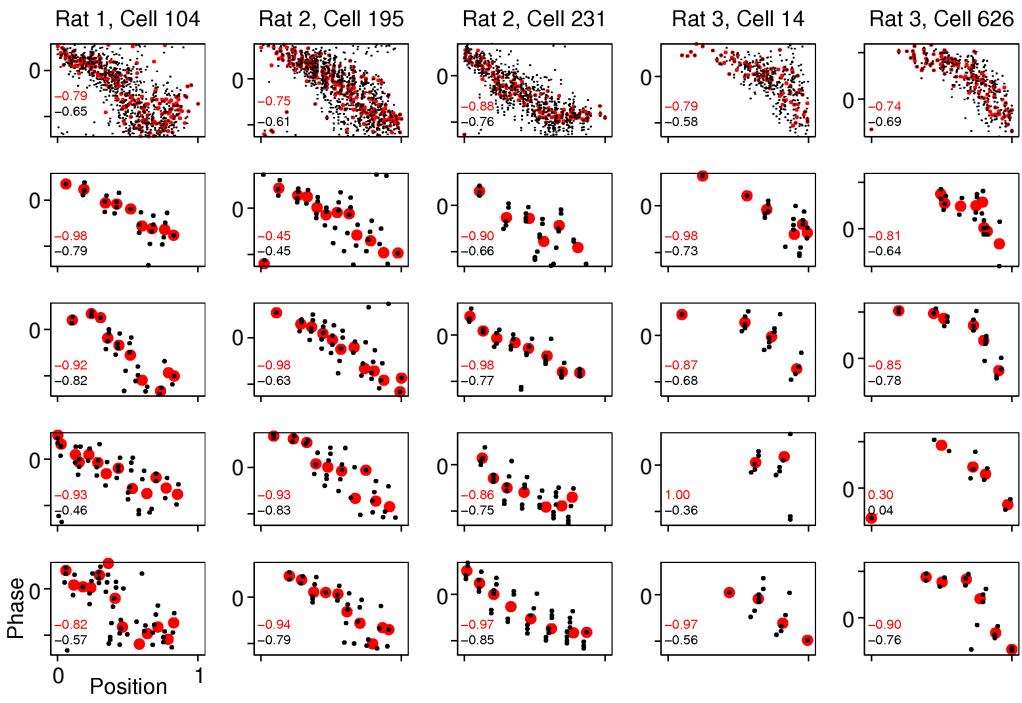


Figure 8.3: Comparison of phase precession derived from spike phases and from mean phases. Same notation, cells, and trials as in Figure 4.1 and Figure 8.2 are shown. In addition, here we include mean phases (circular mean phases of all spikes within the same theta cycle; red dots) as well as the corresponding phase-position correlations for mean phases (red numbers). Phase-position correlations for mean phases are stronger in both pooled-trial and single-trial phase precession due to the lack of variability introduced by bursts of action potentials.

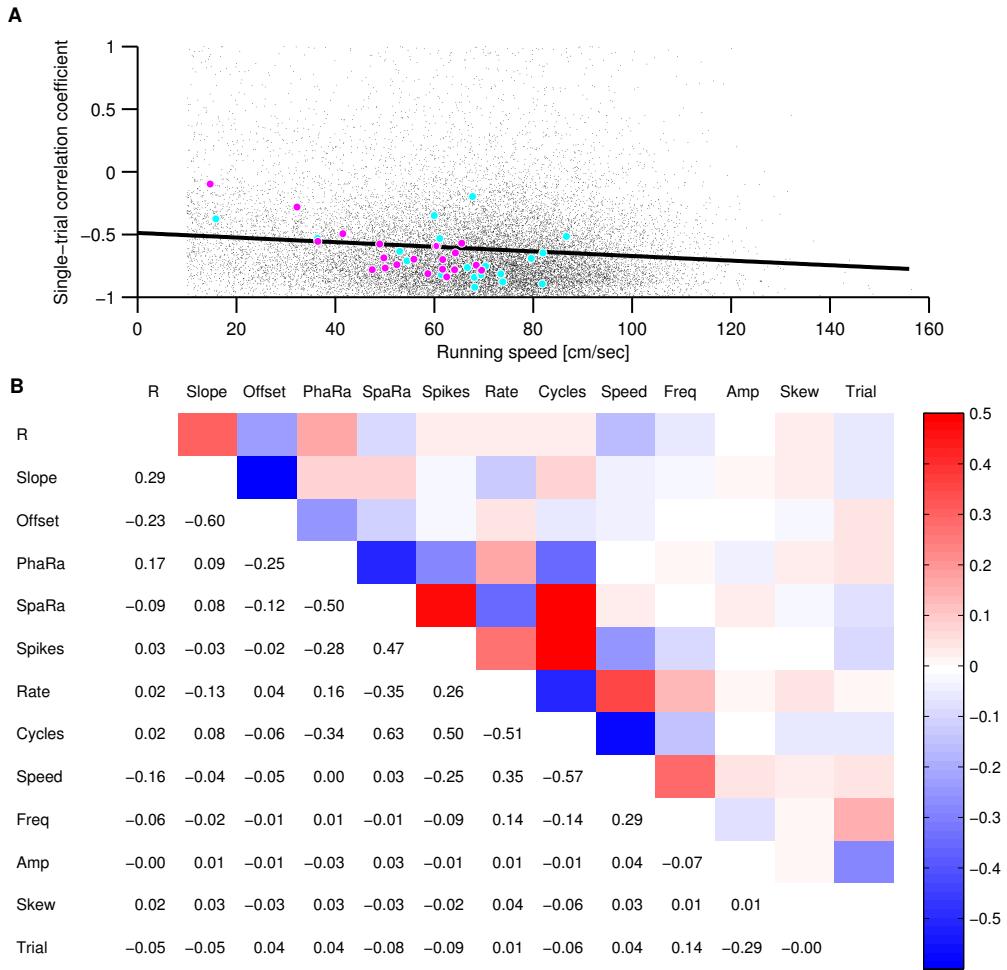


Figure 8.4: Correlations between pairs of single-trial properties. **(A)** Correlation between ‘running speed’ and ‘phase-position correlation’. Each data point corresponds to a single trial. The black line is a linear fit showing the negative correlation in the population ( $r = -0.13; p = 1.6 \cdot 10^{-73}$ ; calculated according to method (b), as described in Section 8.1.4). The cyan and magenta dots indicate data points from two single-cell examples. **(B)** Matrix of mean correlation coefficients of pairs of single-trial place field properties (method (a), see Section 8.1.4). In the upper right triangle, mean correlation coefficients are color-coded, in the lower left triangle numerical values are given. Abbreviations as in Figure 4.6.

single-trial skewness as it had been suggested to be a critical variable during phase precession (Mehta et al., 2002). However, although phase-position correlations become slightly stronger with more trials (column 1, row 13), this effect was not accompanied by an increase in skewness (column 12, row 13). To summarize, methods (a) (Figure 8.4A) and (b) (Figure 4.6, Chapter 4) gave similar correlation coefficients for most pairs of single-trial properties.

### 8.1.5 Correlations between cell pairs

In Chapter 4, we demonstrated the existence of substantial trial-to-trial variability in phase precession. Our analysis was restricted to single cells, i.e. we do not know whether this variability is also present on a population level. Here we present further results on how phase precession in pairs of cells is related. In general, there are three options.

First, it could be that the population of phase precessing cells follows a global dictation that determines e.g. the slope of phase precession in cells. Accordingly, even if there is large trial-to-trial variability, the variability across cells in the same trial could be small. In this case, we expect strong correlations between measures of phase precession of cell pairs from the same trial. Second, it could be that the variability in different cells is independent. In that case, we expect no correlations between measures of phase precession of cell pairs from the same trial. Third, not the whole population, but only a group of cells forming an assembly could show a common variability in measures of phase precession.

Analogous to Figures 4.6 and 8.4B, we correlated single-trial properties of cell pairs that exhibited phase precession in the same trial (Figure 8.5). For example, we determined whether the slope of phase precession in cell A correlates with the slope in cell B. As before, the correlations can be calculated before or after pooling over cell pairs (see above). Method (a) is applied in Figure 8.5, but method (b) yielded very similar results. Overall, we find that measures of phase precession are not correlated between cell pairs in the whole population. Therefore, a global dictation that adjusts phase precession in all hippocampal cells seems unlikely. Other global properties, such as running speed or theta frequency, do exhibit strong correlations, as expected. From this analysis alone it appears that phase-precessing cells might vary independently. Further analyses are necessary to find out whether cell assemblies with similar single-trial phase precession exist.

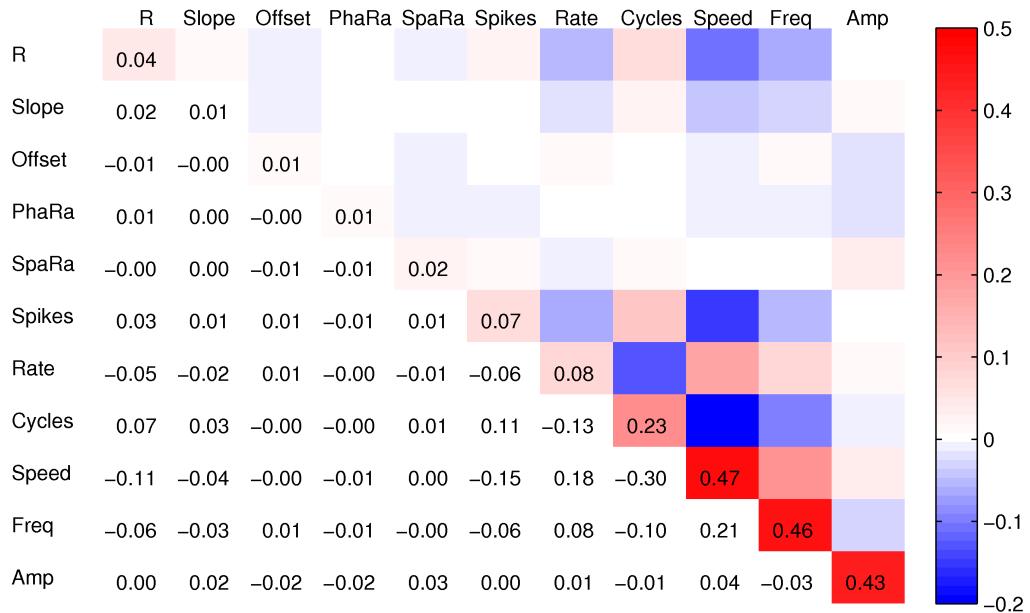


Figure 8.5: Correlations between properties of single trials in cell pairs. Notation and abbreviations as in Figures 4.6 and 8.4B. Numbers and color-code denote correlation coefficients between the single-trial property of one cell with the single-trial property of another simultaneously recorded cell. So the values on the diagonal indicate e.g. whether the slope of phase precession in one cell predicts the slope of phase precession in another cell in the same trial. All correlations between measures of phase precession are very weak.

## 8.2 Coordination of CA3 and CA1 Phase Precession

### 8.2.1 Phase-position correlations are stronger for CA1 than CA3 reference theta

Theta oscillations are present in both CA3 and CA1 pyramidal cell layer LFP (Figure 5.2C and D). In CA1, the power in the theta band relative to the whole spectrum was higher than in CA3. Thereby, the estimation of theta phases might be more accurate in CA1 than in CA3. To support this finding we compare distributions of phase-position correlations. We find that, in both CA3 and CA1 place cells, phase-position correlations are stronger for CA1 reference theta than for CA3 reference theta (Figure 8.6). Thus, CA1 seems to provide a ‘cleaner’ theta signal, reducing the noise in the phase estimation. So part of the noise in phase-precession originates from phase-estimation errors.

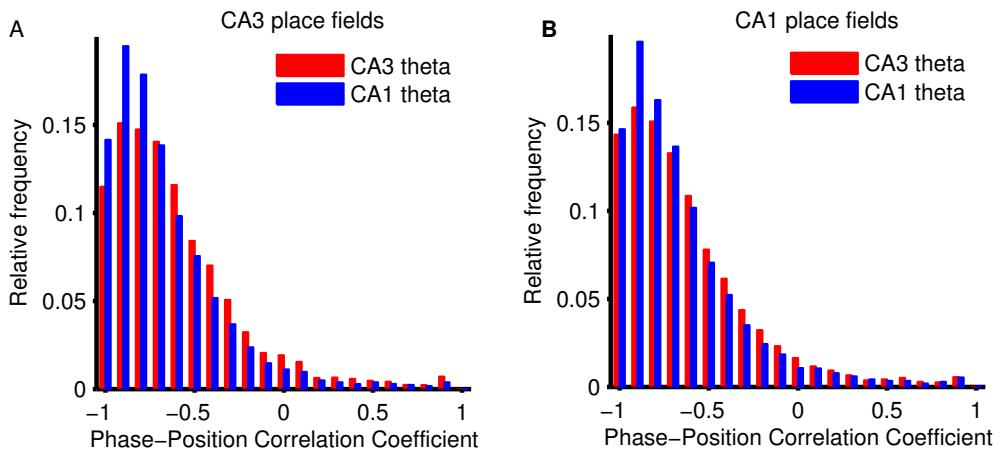


Figure 8.6: Phase-position correlation histograms with respect to CA3 and CA1 theta. Both CA3 place cells (**A**) and CA1 place cells (**B**) have stronger phase-position correlations with respect to CA1 theta compared to CA3 theta.

# Kapitel 9

## Deutsche Zusammenfassung

In dieser Arbeit untersuche ich Aspekte von Korrelationskodierung im Hippokampus. Insbesondere geht es um zwei Phänomene neuronaler Aktivität: Phasenpräzession und Sequenzwiederholungen in umgekehrter Reihenfolge.

Phasenpräzession bezeichnet eine bestimmte Relation zwischen der Aktivität von Pyramidalzellen im Hippokampus und einer Theta-Oszillation von ungefähr 8 Hz im lokalen Feldpotential. Pyramidalzellen im Hippokampus werden oft als Ortszellen beschrieben, weil sie in einem bestimmten Bereich der räumlichen Umgebung des Tieres mit einer Erhöhung ihrer Aktivität reagieren. Wenn das Tier durch diesen Bereich, das Ortsfeld, hindurchläuft, feuert diese Ortszelle mehrere Aktionspotentiale während mehrerer Oszillationszyklen. Die Phase dieser Aktionspotentiale relativ zur Theta-Oszillation ändert sich systematisch während der Durchquerung des Ortsfeldes: die Zelle ist in aufeinanderfolgenden Zyklen immer etwas früher aktiv; die Phase nimmt also ab oder ‘präzidiert’. Dadurch gibt es eine Korrelation zwischen der Phase des Aktionspotentials und der relativen Position des Tieres im Ortsfeld (Phase-Ort Korrelation). In der Population der Ortszellen, die den gesamten Bereich der räumlichen Umgebung abdeckt, führt diese Phasenpräzession zu einem Korrelationkode. Überlappende Ortsfelder sind innerhalb eines Oszillationszyklus in der Reihenfolge aktiv, die der Reihenfolge der Eintritte in die verschiedenen Ortsfelder entspricht. Die Sequenz der Ortszellaktivität, die durch den Weg des Tieres bestimmt ist, ist also in komprimierter Form in einem Oszillationszyklus repräsentiert.

Eine andere Form der Korrelationskodierung kommt in wachen Tieren während Ruhephasen nach bewegungsreichen Episoden vor. Vergangene Sequenzen von Ortsfeldaktivität werden in umgekehrter Reihenfolge wiederholt. Diese Episoden werden von auffälligen hochfrequenten Oszillationen im lokalen Feldpotential begleitet.

Die Mechanismen beider Formen von Korrelationskodierung sind unbe-

kannt. Da beide Formen eine wichtige Rolle in grundlegenden Gedächtnisprozessen wie z.B. episodischem Gedächtnis spielen können, ist es wichtig deren Mechanismen zu entschlüsseln. In den drei Ergebnisteilen meiner Arbeit (Kapitel 4 bis 6) untersuche ich Phasenpräzession mit Hilfe von elektrophysiologischen Messungen in Ratten (Kapitel 4 und 5) und entwickle ein Modell zur Generierung und zum Erlernen von zeitlichen Mustern, wie z.B. Sequenzwiederholungen im Hippokampus.

Kapitel 1 bis 3 enthalten eine allgemeine Einführung und Motivation der Arbeit, sowie eine Zusammenfassung der hippocampalen Physiologie und Funktion in Gedächtnisprozessen, Phasenpräzession, und Sequenzwiederholung.

In Kapitel 4 untersuche ich Phasenpräzession in einzelnen Versuchsdurchläufen, d.h. wenn die Ratte einmal das Ortsfeld einer Zelle durchquert. In bisherigen Studien wurden Daten zur Phasenpräzession immer über viele Versuchsdurchläufe zusammengelegt. Dies kann zu einer verzerrten Schätzung von grundlegenden Eigenschaften der Phasenpräzession führen und vernachlässigt eine mögliche Variabilität zwischen verschiedenen Versuchsdurchläufen. Durch vergleichende Analysen zeige ich, dass Phasenpräzession in einzelnen Versuchsdurchläufen eine stärkere Phasen-Ort Korrelation hat als in zusammengelegten Daten. In vorherigen Studien hat man auch eine Korrelation zwischen Phase des Aktionspotentials und der Zeit, die seit dem Eintritt in das Ortsfeld vergangen ist, gefunden (Phase-Zeit Korrelation). Die Phase-Zeit Korrelation war aber immer schwächer als die Phase-Ort Korrelation. Ich zeige, dass in einzelnen Versuchsdurchläufen beide Korrelationen gleich stark sind. Ein weiterer wichtiger Unterschied befindet sich im Phasenbereich. Während in zusammengelegten Daten der Phasenbereich von Phasenpräzession bis zu  $360^\circ$  umfasst, kommt in einzelnen Versuchsdurchläufen am häufigsten nur ein Phasenbereich von  $180^\circ$  vor. Weiterhin stellen wir fest, dass Phasenpräzession von Versuchsdurchlauf zu Versuchsdurchlauf variiert. Ich quantifiziere diese Variabilität bezüglich vier verschiedener Maße von Phasenpräzession: Phase-Ort Korrelation, Steigung ( $^\circ$  pro Ortsfeld), Anfangsphase und Phasenbereich. Es stellt sich heraus, dass es viel Variabilität innerhalb einer Zelle, d.h. in verschiedenen Versuchsdurchläufen, gibt und relativ wenig Variabilität zwischen verschiedenen Zellen. Andere Eigenschaften von einzelnen Versuchsdurchläufen, wie z.B. die Laufgeschwindigkeit der Ratte, können die gefundene Variabilität der Phasenpräzession nicht erklären. Zuletzt demonstrieren wir mit künstlich generierten Daten, dass durch die Variabilität zwischen Versuchsdurchläufen sich die Phase-Ort Korrelation verschlechtert, wenn man Daten von verschiedenen Versuchsdurchläufen zusammenlegt. Aus diesen Ergebnissen resultieren neue Beschränkungen für mechanistische Modelle der Phasenpräzession. Zusätzlich ziehen wir die Schlussfolgerung, dass

sich Phasenpräzession besser dafür eignet zeitlich-strukturierte Sequenzen zu lernen, als man aufgrund der zusammengelegten Daten vermutet hatte.

In Kapitel 5 untersuchen wir die Beziehung von Phasenpräzession in unterschiedlichen Teilen des Hippokampus. Wir zeigen, dass die extrazellulären Theta-Oszillation in der CA3 und CA1 Region außer Phase sind. Dennoch geschieht Phasenpräzession in beiden Regionen fast gleichzeitig, relativ zu einem gemeinsamen Referenz-Theta. Mehrere Analysen weisen darauf hin, dass Phasenpräzession in CA1 kurz nach (ca. 5 ms) Phasenpräzession in CA3 passiert. Die Interpretation dieses Befundes ist komplex - der Ursprung der Theta-Oszillation ist in verschiedenen Regionen des Hippokampus unterschiedlich und aktuelle Studien zeigen, dass auch die exakten Phasenbeziehungen innerhalb einer Region variieren. Wir ziehen die Schlussfolgerung, dass zumindest in bestimmten Subregionen von CA3 und CA1 die zeitliche Beziehung der Phasenpräzession eine direkte Vererbung von Phasenpräzession von CA3 nach CA1 erlaubt.

Kapitel 6 beschäftigt sich mit Sequenzwiederholungen, die z.B. auftreten, nachdem die Ratte einen Gang entlanggelaufen ist und sich in der Nähe einer Nahrungsquelle aufhält. In diesen Phasen gibt es keine Theta-Oszillationen im lokalen Feldpotential, sondern stattdessen episodenhaft auftretende hochfrequente Oszillationen (ca. 200 Hz) während sogenannter 'sharp wave-ripple' Ereignisse. Diese Ereignisse dauern ungefähr 100 ms an und beinhalten die Wiederholung vorangegangener Sequenzen in der Population der Ortszellen. Die Aktivität der Ortszellen spiegelt den gerade eben von der Ratte gelauftenen Weg wieder, diesmal jedoch in umgekehrter Reihenfolge. Wir zeigen, dass diese umgekehrte Sequenzwiederholung mit Hilfe von Kurzzeitfazilitierung z.B. in der Moosfasersynapse in CA3 erzeugt werden kann. Während das Tier durch verschiedene Ortsfelder durchläuft, führen die in der Synapse ankommenden Aktionspotentiale zu einer Kurzzeitfazilitierung, durch die sich die Amplitude der postsynaptischen Potentiale stark vergrößert. Diese Fazilitierung klingt ohne weitere Aktivität langsam, innerhalb einiger Sekunden, ab. Dies führt dazu, dass, wenn die Ratte sich z.B. am Ende eines gerade durchquerten Ganges ausruht, die Stärke der Fazilitierung davon abhängt, wie lange es her ist, dass die entsprechende Ortszelle durchquert wurde. Ein Stimulus der alle Ortszellen gleichzeitig erreicht, evoziert Aktionspotentiale zu Zeitpunkten, die von der übriggebliebenen Fazilitation bestimmt sind: stark fazilierte Synapsen evozieren in den Zielzellen früher Aktionspotentiale als schwächer fazilierte Synapsen. Dadurch wird in der CA3 Population ein Aktivitätsmuster erzeugt, dass der vorangegangenen Ortsfeldaktivität in umgekehrter Reihenfolge entspricht. Weiterhin demonstriere ich, dass diese zeitlichen Muster geeignet sind, um von nachgeschalteten Strukturen ausgelesen zu werden. Anhand eines kürzlich entwickelten Algo-

rithmus, dem Tempotron, untersuchen wir den Einfluss von verschiedenen Modellparametern auf die Lernperformanz. Es zeigt sich, dass zusätzliche Membranpotentialoszillationen für das Lernen notwendig sind. Das vorgestellte Modell zum Phänomen der umgekehrten Sequenzwiederholung sagt voraus, dass Zellen im Gyrus Dentatus kurz vor Sequenzwiederholungen in CA3 synchron aktiv werden.

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# Abbreviations

CA	cornu ammonis
CCG	cross-correlogram
EPSP	excitatory postsynaptic potential
EPSC	excitatory postsynaptic current
LFP	local field potential
PSTH	peri-stimulus time histogram
SEM	standard error of the mean
STDP	spike-timing dependent plasticity

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# **Selbständigkeitserklärung**

Ich erkläre, dass ich die vorliegende Arbeit selbstständig und nur unter Verwendung der angegebenen Literatur und Hilfsmittel angefertigt habe.

Berlin, den 6.10.2009

Robert Schmidt