Computational Neuroscience: Hippocampus

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Abstract

Extensive computational neuroscience research has addressed the functional role of the hippocampus and associated cortical structures. In this field, computational models of the hippocampus have simulated physiological phenomena ranging from single cell membrane potential dynamics to the spiking activity of neurons relative to network field potential oscillations. Other models have focused on

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simulating specific behavioral functions of the hippocampus including episodic memory, classical conditioning, and spatial memory. Starting with influential papers by Marr and by McNaughton and Morris, many studies have focused on basic functions of hippocampus including pattern separation in the dentate gyrus and pattern completion in region CA3. This theoretical framework has been the focus of a number of experimental tests over the years, including neurophysiological studies of patterns of neuronal activity in behaving rats. Research has also addressed network dynamics in the hippocampus including theta rhythm oscillations, theta phase precession, and the patterns of grid cell firing in entorhinal cortex.

Keywords

Long-term potentiation · Theta rhythm · Theta phase precession · Place cells · Grid cells · Entorhinal cortex · Region CA3 · Region CA1 · Dentate gyrus · Medial septum · Pyramidal cells · Episodic memory · Spatial memory · Trace conditioning · Local field potentials · Spiking activity

Brief History

The hippocampal formation was an early focus of research in computational neuroscience, motivated initially by data showing a clear loss of episodic memory with lesions of the hippocampus (Scoville and Milner 1957) and distinctive physiological properties of hippocampus such as long-term potentiation (Bliss and Lomo 1973) and place cells (O'Keefe and Dostrovsky 1971). Many studies cite the groundbreaking study by David Marr (1971) as an influential first step in proposing computational concepts of memory encoding in the hippocampus, including the concept of pattern separation, to form distinct representations of different memories, and the concept of pattern completion, to complete missing elements of a stored memory during retrieval. These ideas were further developed and assigned to specific hippocampal subregions by McNaughton and Morris (1987) as well as Rolls (1987) and then developed into detailed computational models of separation of memories in the dentate gyrus (McNaughton 1991; O'Reilly and McClelland 1994) and completion of memories in region CA3 (Treves and Rolls 1992, 1994; Hasselmo et al. 1995). As reviewed here, many studies have also simulated physiological data in the hippocampus including the properties of place cells (O'Keefe and Recce 1993; Tsodyks et al. 1996) and the properties of long-term potentiation (Holmes and Levy 1990). This chapter provides an overview of the computational neuroscience of hippocampal function.

Anatomical Overview

The hippocampus is a three-layered cortical structure at the border of the neocortex that receives afferent input from cortical regions processing a range of sensory modalities. This cortical input arrives via the entorhinal cortex and other

parahippocampal regions. The hippocampus also receives GABAergic, cholinergic, and glutamatergic innervation from the medial septum and related subcortical structures as well as innervation arising from midbrain neurons containing norepinephrine, dopamine, and serotonin. The output of the hippocampus projects back to parahippocampal cortices primarily via the subiculum and projects to subcortical structures via the fornix. Models of hippocampus commonly include representations of neuron function within different subregions of the hippocampal formation, including the entorhinal cortex, the dentate gyrus, and cornu ammonis regions CA3 and CA1 as well as the regulatory inputs from subcortical structures. In recent years, there has been additional focus on region CA4 (consisting of cells in the hilus of the dentate gyrus) and CA2 (consisting of neurons receiving both Schaffer collateral and mossy fiber input).

Types of Models

Models of hippocampus range across many levels of abstractions. These include models of networks of biophysically detailed neurons using conductance-based models and compartmental models of membrane potential dynamics coupled with representations of voltage-gated conductances using the Hodgkin-Huxley model or other representations. Models also include spike time models of the hippocampus using mechanisms such as the integrate-and-fire neuron or other simplified spiking models. On a higher level of abstraction, researchers have developed firing rate models (or rate code models) of hippocampal function using simplified units with continuous values representing the firing rate per unit time. These include models using the Wilson-Cowan model or sigmoid input–output functions with winner-take-all dynamics. Firing rate models include a number of different classes of models addressing hippocampal dynamics and the role of the hippocampus in memory function and goal-directed behavior. On yet a higher level of abstraction, connectionist models of the hippocampus address memory function and goal-directed behavior with simplified learning rules based on Hebbian modification or error correction. Other functional models assume specific response patterns such as place cells and predict behavioral results such as goal-directed behavior on this basis. Some models of the hippocampus attempt to infer quantitative relations between structural and biophysical traits and parameters on the one hand and functional measures on the other, in domains not yet accessible to direct experimentation.

Models of Behavioral Functions of the Hippocampus

Human Memory Function

Models of hippocampus address the role of hippocampus in encoding and retrieval of information for a range of different memory-guided behaviors in humans and other animals. Many models were motivated by the effect of damage to the

hippocampus by the bilateral removal of the anterior hippocampus in patient HM (Scoville and Milner 1957) or by ischemia or encephalitis (Zola-Morgan et al. 1986; Eichenbaum and Cohen 2003). Damage to the hippocampus in human subjects causes severe impairments for encoding of new episodic memory. Episodic memory is defined as the memory for events occurring at a specific place and time (Tulving 1984). In humans, hippocampal lesions cause impairments of performance on memory tasks including free recall of lists of words and cued recall of the second word in a pair of associated words (Scoville and Milner 1957; Eichenbaum and Cohen 2003). Hippocampal lesions have little effect on priming or perceptual memory in which previous presentation of a stimulus increases the likelihood of subsequent responses using that stimulus as a response.

Models of hippocampus using rate code models of neurons have explicitly modeled performance on free recall of words from a list and cued recall of pairs of associated words (Hasselmo and Wyble 1997) as well as performance in recognition of stimuli based on recollection of the full episode of encoding (Norman and O'Reilly 2003). The definition of episodic memory includes a sense of reliving a series of events. This can be modeled as encoding and retrieval of a sequence of patterns (Jensen and Lisman 1996a,b; Tsodyks et al. 1996; Wallenstein and Hasselmo 1997; Lisman 1999) or of a complex spatiotemporal trajectory associated with specific items or events (Hasselmo 2009). Many early theories addressed the role of the hippocampus in tying together diverse sensory features of an episode (Teyler and DiScenna 1986; Teyler and Rudy 2007).

Models of hippocampus have also simulated temporally graded retrograde amnesia (Alvarez and Squire 1994; McClelland et al. 1995), in which only recent episodic memories appear to be impaired by hippocampal lesions. In these models, episodic associations are initially formed in a model of the hippocampal formation. These hippocampal associations are then reactivated during simulations of quiet waking or slow wave sleep, allowing training of long-term representations in the neocortex that allows the neocortex to encode and later retrieve memories that were initially encoded only in the hippocampus.

Rat Memory-Guided Behavior

In rats, hippocampal lesions cause impairments of memory-guided behavior in a range of different tasks. These include impairments in tasks requiring memory of previously encountered spatial locations, such as the Morris water maze, the 8-arm radial maze, as well as delayed spatial alternation and spatial reversal. These also include impairments in nonspatial tasks requiring relational memory such as the transitive inference tasks (Eichenbaum and Cohen 2003) and tasks requiring aspects of sequence memory such as the order of items in a list (Kesner et al. 2002) or the end of overlapping lists (Agster et al. 2002). Hippocampal lesions also impair trace conditioning in classical conditioning paradigms, in which a conditioned cue precedes an unconditioned response by an interval period without a cue.

Models of hippocampus using firing rate representations of neurons have been developed to simulate goal-directed behavior in rats. These models start with representations of place cell firing as a basis for goal-directed planning in a number of tasks, including the open field (Muller and Stead 1996; Touretzky and Redish 1996; Burgess et al. 1997), the Morris water maze (Redish and Touretzky 1998; Foster et al. 2000) as well as spatial alternation (Hasselmo and Eichenbaum 2005) and a multiple-T choice task (Johnson and Redish 2005). Some of the models of goal-directed behavior have used replay of previously experienced spiking activity to more rapidly build the representations of the environment for goal-directed behavior (Johnson and Redish 2005; Foster and Wilson 2006).

Other models have addressed the role of the hippocampus in trace conditioning (Rodriguez and Levy 2001) and other conditioning phenomena requiring memory of the specific timing of an input cue relative to a conditioned response (Grossberg and Schmajuk 1989; Schmajuk and DiCarlo 1992; Gluck and Myers 1993). Spiking models of hippocampus have also modeled rat behavior (Gerstner and Abbott 1997) though the complex dynamics necessary to generate realistic spiking behavior make these models more difficult to apply to the full behavioral output of the network.

Function of Hippocampal Subregions

Models of hippocampus have addressed the potential function of individual hippocampal subregions, including the dentate gyrus, region CA3, region CA1, the medial septum, and the entorhinal cortex.

Dentate Gyrus

In many studies, the denate gyrus has been proposed to enhance the encoding of new memories by performing pattern separation, the creation of distinct representations for similar memories. This reduces the interference between patterns when an incomplete cue triggers retrieval of a complete stored pattern. The mechanisms and role of this pattern separation was analyzed in many early studies (McNaughton and Morris 1987; Treves and Rolls 1994; O'Reilly and McClelland 1994; Hasselmo and Wyble 1997). This pattern separation was proposed to occur by an increase in sparseness of neural activity as patterns spread from about 250,000 neurons in rat entorhinal cortex to one million neurons in dentate gyrus (McNaughton 1991). The separation of patterns can also benefit from synaptic modification of inputs to dentate gyrus generating self-organization of distinct, random representations (Treves and Rolls 1994; O'Reilly and McClelland 1994; Hasselmo and Wyble 1997; Treves et al. 2008). The dentate gyrus has also been modeled as a latent attractor regulating remapping of place cell responses in different environments (Doboli et al. 2000). Neurogenesis in the dentate gyrus has been modeled as enhancing the pattern separation mechanisms (Becker 2005) but might also play a role in providing a temporal code for memories (Aimone et al. 2009).

Region CA3

Another component of many hippocampal models (McNaughton and Morris 1987) consists of autoassociative encoding of input patterns based on the extensive excitatory recurrent connections of the longitudinal association pathway arising from region CA3 pyramidal cells and terminating in stratum radiatum of CA3 on the dendrites of other CA3 pyramidal cells. Hebbian synaptic modification of excitatory recurrent synapses during encoding forms associations between the elements of an input pattern, allowing pattern completion during subsequent retrieval. During retrieval, a partial cue consisting of a subset of active neurons causes activity to spread across previously modified synapses to cause activity in other elements of the pattern, resulting in a pattern of activity more closely matching the originally encoded pattern. This basic mechanism of autoassociative memory function has been central to many models of region CA3. McNaughton and Morris (1987) described the role of recurrent connections for both autoassociative pattern completion as well as encoding of associations between a pattern at one time and the subsequent pattern at a later time step.

The encoding and retrieval of sequences in region CA3 has been extensively modeled with simplified spiking neurons (Levy 1996; Lisman 1999). Multiple cycles of the spread of excitatory activity can result in explosive activity unless it is balanced by inhibitory feedback, in which case the network can converge to an attractor state matching the initial encoded memory pattern. Attractor dynamics in region CA3 have been used for retrieval of encoded memory patterns in a range of hippocampal models (Treves and Rolls 1992, 1994; Hasselmo et al. 1995; Hasselmo and Wyble 1997; Norman and O'Reilly 2003). The modeling of attractor dynamics builds on extensive earlier analysis of the memory capacity of recurrent networks (Amit et al. 1987) that was applied to models of hippocampal function (Treves and Rolls 1992, 1994; Battaglia and Treves 1998), including models of multiple attractors (Battaglia and Treves 1998). The capacity limits of hippocampal circuits could constrain its role to holding intermediate term episodic memories that are eventually used to update neocortical representations.

As described in more detail below, attractor dynamics in CA3 have also been used to model the activity of place cells, which are neurons that selectively respond when a rat enters specific locations in the environment (Samsonovich and McNaughton 1997; Redish 1999). Similar attractor dynamics have more recently been used to model grid cell firing responses in the medial entorhinal cortex (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009).

Region CA1

In contrast to region CA3, region CA1 has little excitatory recurrent connectivity and receives primarily feedforward input from region CA3 and medial entorhinal cortex layer III. Some models have proposed that region CA1 functions as a comparator of the input from entorhinal cortex layer III with the output from region CA3

(Gray 1982; Hasselmo and Schnell 1994; Hasselmo and Wyble 1997). This comparator function was used to set the levels of acetylcholine to modulate the dynamics of encoding and retrieval in a simulation of region CA1 (Hasselmo and Schnell 1994) and in a network simulation of hippocampal memory function (Hasselmo and Wyble 1997).

The place cell responses in region CA1 have been modeled using arrays of sensory features linked to place cell responses by self-organization of afferent synapses from entorhinal cortex (Sharp 1991; Rolls and Treves 1998; Arleo and Gerstner 2000) or using error-based learning of associations with location (Shapiro and Hetherington 1993). Based on their clear differences in anatomical connectivity, region CA3 and CA1 have been proposed to have different roles in prediction based on prior experience (Treves 2004). Simulations show differences in this prediction property primarily when accompanied by intrinsic spike frequency adaptation of individual neurons.

Medial Septum

The activity of GABAergic and cholinergic neurons in the medial septum paces theta rhythm oscillations in the hippocampus and provides modulatory tone regulating intrinsic properties in the hippocampus. Models have addressed the role of medial septum in regulating theta rhythm oscillations (Denham and Borisyuk 2000) and in regulating the dynamics of encoding and retrieval within the hippocampus (Hasselmo and Schnell 1994; Hasselmo et al. 1995). In models (Hasselmo and Wyble 1997), the release of acetylcholine in the hippocampus enhances encoding in a number of ways: (1) increasing the spiking response to entorhinal input through depolarization and suppression of spike frequency adaptation, (2) enhancing synaptic modification, and (3) reducing recurrent excitation arising from region CA3 through presynaptic inhibition of glutamate release. The reduction of recurrent excitation prevents previously encoded associations from interfering with the encoding of new associations (Hasselmo and Schnell 1994; Hasselmo et al. 1995; Hasselmo and Wyble 1997). Acetylcholine levels are high during theta rhythm oscillations in active waking and decrease during quiet waking and slow wave sleep. Models show how low levels of acetylcholine could allow stronger transmission from CA3 to CA1 to drive neocortical consolidation (Hasselmo 1999).

Entorhinal Cortex

The entorhinal cortex provides the primary input to the hippocampal formation, with entorhinal cortex layer II projecting to dentate gyrus and region CA3, and layer III projecting to region CA1. Extensive modeling has addressed the mechanism and role of grid cells in medial entorhinal cortex of the rat. Grid cells respond in a regular array of locations in the environment falling on the vertices of tightly packed equilateral triangles. Grid cells have been modeled based on interference between

oscillations with frequencies shifted by the velocity of the rat (O'Keefe and Burgess 2005; Burgess et al. 2007; Burgess 2008; Hasselmo 2008). This model predicted (O'Keefe and Burgess 2005) that the difference in spatial frequency of grid cells at different positions along the dorsal to ventral axis of medial entorhinal cortex could arise from differences in the intrinsic oscillation frequency of entorhinal neurons. This prediction was supported by intracellular recording data showing a gradient of intrinsic subthreshold membrane potential oscillations and resonance (Giocomo et al. 2007; Giocomo and Hasselmo 2009). Other models have proposed that grid cells arise from attractor dynamics (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009) or self-organization of afferent input to the entorhinal cortex (Kropff and Treves 2008).

Physiological Phenomena

Computational neuroscience models of the hippocampus address several important physiological phenomena observed within the hippocampus. These physiological phenomena include long-term potentiation and long-term depression of synaptic strength, the intrinsic neuron properties including bursting and adaptation, the spiking activity during performance of behavioral tasks, local field potential dynamics, and the interactions of spiking and local field potentials.

Long-Term Potentiation and Long-Term Depression

The properties of synaptic modification in the hippocampus constitute an essential component of most hippocampal models, allowing changes in the strength of synaptic connections to mediate the storage of long-term memories. Neural network models of memory function demonstrated the importance of Hebbian synaptic modification (Anderson 1972; Kohonen 1972), in which strengthening of synapses depends on a combination of presynaptic and postsynaptic activity, allowing the selective encoding of associations between patterns of activity representing different behavioral stimuli, such as two words in a paired associate memory task.

Computational models of memory function motivated the experimental studies demonstrating that synaptic modification in the hippocampus has Hebbian properties using extracellular (McNaughton et al. 1978) and intracellular recording (Kelso et al. 1986). Activation of the NMDA (N-Methyl-D-Aspartate) receptor depends upon presynaptic glutamate release and postsynaptic depolarization and plays an important role in many forms of Hebbian long-term potentiation. The timing properties of the NMDA receptor appear to result in a requirement for a tight timing relationship between presynaptic spikes and postsynaptic activity (Levy and Steward 1983; Holmes and Levy 1990). This requirement has been shown in a number of subsequent studies (Bi and Poo 1998) and is referred to currently as spike timing dependent plasticity (STDP). Many synaptic models address the mechanisms of long-term potentiation and depression. Specific models address the role of molecular

pathways in regulating synaptic strength, including the role of bistability of autophosphorylation (Lisman 1989), or the role of different concentrations of calcium induced by different patterns of input. Many models have addressed the potential cellular mechanisms for spike timing dependent plasticity (Shouval et al. 2010).

Intrinsic Properties

Biophysically detailed models of cells in the hippocampal formation have explored the cellular mechanisms for spiking properties of the hippocampus, including phenomena such as bursting and spike-frequency accommodation or adaptation. Biophysically detailed compartmental models of single cells using Hodgkin-Huxley equations have demonstrated potential cellular mechanisms for bursting activity and adaptation (Traub et al. 1991). The dynamics of these intrinsic spiking properties have also been analyzed in simplified mathematical models of membrane potential dynamics (Izhikevich 2003).

Spiking Activity in Behaving Animals

Hippocampal models have addressed physiological data showing correlations between hippocampal spiking activity and a number of different variables of behavior. For example, models have addressed the appearance of place cells in the hippocampus (O'Keefe and Dostrovsky 1971; O'Keefe and Nadel 1978). Place cells are neurons that fire when a rat visits specific local regions within an open environment. Early models showed how place cells could arise from competitive self-organization of inputs from sensory cues (Sharp 1991; Arleo and Gerstner 2000) or from error-correcting rules guiding formation of place cells (Shapiro and Hetherington 1993). Later models simulated place cell responses based on path integration of self-motion information for self-localization (Touretzky and Redish 1996; Samsonovich and McNaughton 1997; Redish and Touretzky 1998; Redish 1999). These models also incorporated multiple different maps to account for the remapping of place cell responses based on changes in behavioral stimuli or task demands. The models of path integration for place cell responses were precursors to the models addressing the potential mechanisms for the generation of grid cell firing responses in the medial entorhinal cortex (McNaughton et al. 2006; Fuhs and Touretzky 2006; Burgess et al. 2007; Burgess 2008; Giocomo et al. 2007; Kropff and Treves 2008).

Recent models have addressed how place cells could arise from the properties of grid cells in the entorhinal cortex (Solstad et al. 2006; McNaughton et al. 2006). However, recent data suggests that place cells may not depend upon grid cell firing. The changes in place cell responses after movement of environment boundaries led to development of a model of place cells based on boundary vector cells (O'Keefe and Burgess 2005; Barry et al. 2006). The boundary vector cells predicted by the model were recently shown experimentally in the medial entorhinal cortex

(Solstad et al. 2008) and subiculum (Lever et al. 2009). Models have also demonstrated how context-dependent spiking activity can depend upon variables other than current location, including the presence of specific sensory stimuli, or on prior history (Hasselmo and Eichenbaum 2005). An important model of the effects of Hebbian synaptic plasticity (Blum and Abbott 1996) generated the experimentally verified prediction that the firing fields of place cells tend to shift backward with experience (Mehta et al. 2002).

Local Field Potential Dynamics

Hippocampal models have also addressed properties of the oscillatory dynamics of the hippocampal formation measured by electroencephalographic recordings of the local field potential. In particular, during active movement through the environment, the hippocampus shows prominent activity in the theta frequency band, with a peak in the power spectra around 6–8 Hz (Green and Arduini 1954; O'Keefe and Nadel 1978; Buzsaki et al. 1983; Buzsaki 2002). In anesthetized rats, some of the same mechanisms contribute to oscillations around 3–4 Hz that are also referred to as theta rhythm. The mechanisms of theta rhythm have been modeled as due to feedback interactions between the medial septum and hippocampus (Denham and Borisyuk 2000).

Current source density data shows a systematic change in magnitude of synaptic transmission in different layers during each cycle of the hippocampal theta rhythm (Brankack et al. 1993). Models have addressed the phase difference in different layers between stratum lacunosum-moleculare, stratum radiatum, and stratum pyramidale (Leung 1984). This difference in phase in different layers arises from different temporal dynamics of synaptic input to different layers. The difference in synaptic input to different layers at specific phases of theta rhythm could provide different dynamics appropriate for encoding versus retrieval of associations. The encoding of associations could take place on the phase of theta rhythm when there is a dominant influence of entorhinal input and the induction of LTP is strongest (Hasselmo et al. 2002). In contrast, the retrieval of associations could take place when there is a dominant influence of output from region CA3 and no induction of LTP (Hasselmo et al. 2002). This proposal is consistent with the region CA1 showing coherence at one phase of theta with high frequency gamma in entorhinal cortex and at a different theta phase with lower frequency gamma in region CA3 (Colgin et al. 2009).

Theta Phase Precession of Spiking Relative to Local Field Potentials

The spiking activity of the hippocampus shows clear relationships to local field potential oscillations. In particular, the firing of place cells on a linear track shows a systematic change in phase of firing relative to theta rhythm oscillations (O'Keefe and Recce 1993; Skaggs et al. 1996). When the rat first enters the field of firing of a

place cell, the spiking occurs at late phases relative to the theta cycle and then it shifts to earlier theta phases as the rat moves through the place field. This phenomenon is referred to as theta phase precession. A number of models have addressed theta phase precession using different mechanisms. These models can be grouped into three broad categories. In one category, phase precession is modeled as dependent on sequence readout. In these models, each location cues the retrieval of a sequence of place cell spiking activity due to Hebbian modification of associations between place cells firing to adjacent locations (Tsodyks et al. 1996; Jensen and Lisman 1996a,b; Wallenstein and Hasselmo 1997; Hasselmo and Eichenbaum 2005). In another class of models, phase precession arises from oscillatory interference. In these models, precession arises from interference between oscillators with different frequency. This can involve interference of intrinsic oscillations with network oscillations (O'Keefe and Recce 1993; Lengyel et al. 2003) or between oscillations in different groups of neurons (Bose et al. 2000). The same mechanism has been used to model theta phase precession in grid cells (Burgess et al. 2007; Burgess 2008; Hasselmo 2008). Finally, another class of models simulates phase precession based on a progressive change in depolarization relative to network theta. In these models, precession arises from a gradual change in depolarization that results in spiking at a different phase of theta (Kamondi et al. 1998; Mehta et al. 2002). Recent intracellular recordings from awake head-fixed mice running in a virtual world have tested predictions of these different models (Harvey et al. 2009). The intracellular membrane potential shows subthreshold oscillations that shift in phase relative to network oscillations, consistent with the oscillatory interference model rather than the sequence readout models. The data also shows a depolarization of membrane potential within the place field. These studies demonstrate how computational models of the hippocampus have consistently guided new physiological research.

Outlook

Computational neuroscience models of hippocampus have addressed experimental phenomena at levels ranging from the detailed membrane potential dynamics of hippocampal neurons to the spiking activity in awake, behaving animals, to the role of hippocampus in memory-guided behavior. These models have developed important hypotheses for testing in physiological experiments. Future models will focus on linking the data on these different levels to provide constraints for a complete model of the physiological mechanisms of hippocampal function.

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