Coding of space and time for memory function.

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Abstract

Data from rodents shows neuronal activity that may code specific intervals of space and time, as revealed by recordings in structures implicated in episodic memory function. These data are relevant to modeling of episodic memories as spatiotemporal trajectories. The review will include data on neuronal actitivy that disambiguates overlapping spatiotemporal trajectories, as well as neurons that change firing rate and rhythmicity based on running speed and head direction. These data support the model of episodic memory as a trajectory that includes speed and direction, in contrast to Tulving's initial definition of episodic memory as a series of snapshots. Spatial behavior requires coding in multiple coordinate frames, and recent data supports the idea that space could involve neural coding of environmental boundaries in egocentric coordinates, as well as neural coding of transformations between egocentric input and memory that could be mediated by neurons coding allocentric location. These data will be discussed in the context of a more recent model of the transformation between coordinate systems. The egocentric input can be used both for coding the location along spatiotemporal trajectories and for retrieving specific viewpoints of the environment. The chapter will also include a brief discussion of the importance of mathematical models to move beyond verbal definitions.

Introduction

Multiple cortical structures are implicated in episodic memory function. This review will present data on the neuronal activity that codes space and time in cortical structures. These data have been used in models of episodic memory that involve the encoding and retrieval of spatiotemporal trajectories. This review will also present data and modeling of the transformation between egocentric and allocentric coordinate systems.

Episodic memory was defined as memory for events that occur at a specific place and a specific time (Tulving, 1984; Eichenbaum et al., 1999). Episodic memory was described as "snapshots whose orderly succession can create the mnemonic illusion of the flow of past time" (Tulving, 1984). A neural model of episodic memory (Hasselmo, 2009; Hasselmo, 2012) proposed that episodic memory must contain more than a sequence of snapshots, but instead include a continuous representation of time and space as a spatiotemporal trajectory, that includes the speed and direction of movement of an agent or other objects (Hasselmo et al., 2010; Hasselmo, 2012), the agent's viewpoint of an event (Conway, 2009), and the coding of prior context for disambiguation of memories (Hasselmo and Eichenbaum, 2005; Hasselmo, 2009). This chapter will review relevant neural data relevant to modeling of episodic memory, as well as briefly reviewing models and emphasizing approaches that include modeling of the transformation between egocentric and allocentric coordinate systems. Finally, there will be a section emphasizing the importance of mathematical models to move beyond verbal definitions.

Coding of time (time cells)

Episodic memory can be succinctly defined as “What did you do at time T in place P” (Tulving, 1984). The neural coding of time and space is important for this definition, and many cortical neurons code both time and space (Pastalkova et al., 2008; MacDonald et al., 2011; Kraus et al., 2013; Kraus et al., 2015). Neurophysiological data shows neurons, termed “time cells,” that code time intervals relative to task events, such as the onset of a delay period. In many tasks used to study time cells, a rodent runs around a loop of elevated track, and then remains in a consistent single location and direction while running for 10-20 seconds on a running wheel (Pastalkova et al., 2008) or a treadmill (Kraus et al., 2013; Kraus et al., 2015). During this delay period of running in one location, individual neurons fire at specific intervals after the onset of the delay. Running is not essential as time cells can also appear during delay periods of a delayed matching task performed without running (MacDonald et al., 2011) or even during a delay period in stationary head fixed animals (MacDonald et al., 2013; Heys and Dombeck, 2018). Time cell responses have been shown in a wide range of different structures, including hippocampal region CA1 (Pastalkova et al., 2008; Kraus et al., 2013; Mau et al., 2018), hippocampal region CA3 (Salz et al., 2016) as well as the entorhinal cortex (Kraus et al., 2015; Tsao et al., 2018; Heys and Dombeck, 2018). These data show that time cell responses can be important for disambiguating events that occur at one time point versus another on a time scale of seconds.

More recent data shows that neurons also show a difference in calcium activity across the trials within a given day (Mau et al., 2018), and show consistencies across days supporting coding of time on the time scale of minutes (MacDonald et al., 2011; Liu et al., 2022). This supports a model of multiscale coding of time developed by Marc Howard and colleagues (Howard et al., 2014). Calcium imaging of the same population of hippocampal neurons over several days (Mau et al., 2018) also shows that time cells drop out or appear slowly over days, resulting in a change in correlation across the population on time scales of days (Mau et al., 2018). This slow drift in ensemble membership could provide a differential coding of memories on different days (Howard et al., 2014; Mankin et al., 2015; Rubin et al., 2015; Cai et al., 2016; Rule et al., 2019; Kinsky et al., 2020; Ziv et al., 2013; Levy et al., 2021). Models show that changes in the correlation of a population of cells on multiple longer temporal scales are essential for the capacity to differentiate episodic memories occurring at different time points on the scale of seconds, minutes, and hours (Howard et al., 2014; Liu et al., 2019). This multi-scale representation provides an efficient representation for memory on different scales, but it is also possible that time coding involves different mechanisms at different scales (Phillips, 2014), particularly for long scales on the order of weeks, months or years. The focus on disambiguating different time points motivated the use of the term "time cell" (Howard and Eichenbaum, 2013; Eichenbaum, 2014; Kraus et al., 2013; MacDonald et al., 2011). However, these cells could be coding sequences of assocations of internal and external features making up the events in an episode (Buzsaki and Tingley, 2018) consistent with the initial description of these neurons as 'episode cells' (Pastalkova et al., 2008).

One experiment compared time versus running distance by recording as a rat ran on a treadmill at different speeds during different delay periods (Kraus et al., 2013). This experiment showed that neurons could respond on the basis of either time or running distance during the delay (Kraus et al., 2013) as predicted by previous models (Hasselmo, 2008; Burgess et al., 2007). Neurons that fire as time cells also code other dimensions related to episodic memory, consistent with evidence of mixed selectivity in other regions (Rigotti et al., 2013). Some cells that fire as time cells during running on the treadmill might also fire as place cells during running off the treadmill on the return arms (Kraus et al., 2013; Mau et al., 2018) indicating that these cells do not only code time. Coding of both space and time was also shown for single grid cells in the entorhinal cortex (Kraus et al., 2015). These grid cells fired in an array of spatial locations when animals foraged in a two-dimensional environment, but also fired as time cells at different time points during a 16 second delay as the rat ran in a single location on the treadmill. Interestingly, a recent study showed that the overall population of space-encoding neurons and neurons coding time during immobility in entorhinal cortex form anatomically distinct sub-populations (Heys and Dombeck, 2018; Heys et al., 2014). The coding of episodes as spatiotemporal trajectories only requires a population code containing both space and time, so this model can function whether the representation is shared across individual neurons or appears in different populations (Hasselmo, 2012). Human imaging data shows neural activity associated with disambiguating the retrieval of overlapping trajectories in virtual mazes (Brown and Stern, 2014; Brown et al., 2010; Brown et al., 2014).

Time cells code time not only by overall firing rate, but also by the phase of firing of cells relative to rhythmic oscillations at theta frequency in the local field potential. Time cells show theta phase precession within their firing fields (Pastalkova et al., 2008; Terada et al., 2017; Ning et al., 2022). A a time cell starts firing, its spikes appear at late phases of theta, and as time evolves the spiking shifts to earlier phases of theta cycle before spiking ends. The coding of space by place cells shows a similar shift in phase as an animal runs through a place field. This phase coding appears important for the temporal specificity of time cell firing as time cells are lost during inactivation of the medial septum (Wang et al., 2015), which reduces theta rhythm in the hippocampus (Brandon et al., 2014; Rawlins et al., 1979). The same inactivation of medial septum also removes spatial specificity of grid cell firing (Brandon et al., 2011; Koenig et al., 2011). Theta phase coding has the advantage that it could allow a single neuron to code a continuous dimension of time or space, which might allow a broader range of transformations on the level of single neurons that might be difficult to implement across a full population.

Coding of spatial location

A range of studies show that damage to the hippocampus causes impairments in two-dimensional spatial navigation tasks such as the Morris water maze, in which the animal learns a specific goal platform location and must then navigate to that location from a range of different starting locations (Morris et al., 1982; Eichenbaum et al., 1990). Models have addressed how different neural subtypes could underlie planning of spatiotemporal trajectories to generate the correct trajectory to the goal location from a new start location (Erdem and Hasselmo, 2014; Erdem and Hasselmo, 2012; Redish and Touretzky, 1998). Early models focused on the role of place cells and head direction cells (Redish and Touretzky, 1998), but those models would require dense representation of spatial locations by place cells. Later models address the additional role of grid cells and speed cells in planning trajectories to a goal location without needing to form a place cell code for each location (Erdem and Hasselmo, 2014; Erdem and Hasselmo, 2012; Kubie and Fenton, 2012). Impairments of goal-finding in the Morris water maze are also observed after lesions of the entorhinal cortex (Steffenach et al., 2005) or the dorsal presubiculum (Taube et al., 1992), consistent with a role of different neuronal subtypes such as head direction cells and grid cells from these regions. Further data shows neural coding of position along a trajectory in structures such as the retrosplenial cortex (Alexander and Nitz, 2017; Alexander and Nitz, 2015), and human imaging data shows coding of arc length along a trajectory in addition to coding of euclidean distance, translation and rotation (Chrastil et al., 2016; Chrastil et al., 2015). This section will briefly review some data on coding of spatial location.

Place cells in hippocampus

Neurophysiological recording in the hippocampus revealed place cells that fire based on spatial location (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971). The relationship of these place cell responses to philosophical questions about the a priori representation of space were addressed extensively in the influential book by O’Keefe and Nadel on coding of space as a cognitive map (O'Keefe and Nadel, 1978). Further studies showed place cell responses when animals were in specific locations during foraging an open field environments (Muller et al., 1987; O'Keefe and Burgess, 1996; Huxter et al., 2008; Lever et al., 2002), and in local areas of linear tracks (O'Keefe and Recce, 1993), the 8-arm radial maze (McNaughton et al., 1983), or a spatial alternation task (Ainge et al., 2007; Wood et al., 2000; Kinsky et al., 2020). The firing of place cells can vary dependent on many factors including direction through the place field (Fenton and Muller, 1998) and cells can have more than one firing field (Fenton et al., 2008). The position of an animal can be effectively decoded from the firing activity of hippocampal place cells (Brown et al., 1998), supporting their role in guiding behavior in spatial memory tasks. In more recent studies, hippocampal cell firing has been shown to code informaton about the direction and distance of a goal location (Ormond and O'Keefe, 2022).

In addition to coding location by firing rate, place cells also code location by their phase of firing in a phenomenon called theta phase precession (O'Keefe and Recce, 1993). This discovery preceded the finding of phase precession by time cells described above. As the animal enters the firing field of a place cell, spiking occurs at late phases of theta and then shifts to earlier phases as the animal runs through the firing field and exits (O'Keefe and Recce, 1993; Skaggs et al., 1996; Maurer et al., 2006; Schmidt et al., 2009; Zugaro et al., 2005). Theta phase precession is associated with sequential spiking of neurons coding sequential places on different phases (Foster and Wilson, 2007), but theta phase precession appears on the first trial of running on a novel linear track, whereas theta sequences only appear on later trials (Feng et al., 2015). These data further emphasize the potential role of spike timing and phase for the coding of space and time.

Grid cells in entorhinal cortex

Neurophysiological recording in the entorhinal cortex demonstrates different types of coding of spatial dimensions. The most striking form of coding involves the response of entorhinal grid cells, which respond when a foraging animal visits an array of spatial locations in the environment that appear in a hexagonal pattern (Hafting et al., 2005). Different grid cells fire with different size and spacing between firing fields, allowing a population of grid cells to code a single location (Sargolini et al., 2006; Barry et al., 2007; Stensola et al., 2012; Heys et al., 2014). Many grid cells code both for the animals location and the current head direction of the animal (Sargolini et al., 2006).

Entorhinal grid cells also exhibit phase coding in the form of theta phase precession as an animal runs on a linear track (Hafting et al., 2008), or as an animal forages in two-dimensions in an open field (Climer et al., 2013; Jeewajee et al., 2014). Consistent with this, the intrinsic rhythmicity of entorhinal neurons differs with spatial scale (Jeewajee et al., 2008) and shifts with running speed (Hinman et al., 2016; Jeewajee et al., 2008). The potential role of theta rhythm in generation of grid cell responses is supported by the fact that inactivation of the medial septum causes both a dramatic reduction of theta rhythm in the entorhinal cortex (Mitchell et al., 1982; Jeffery et al., 1995), and a loss of the spatial selectivity of firing of grid cells (Brandon et al., 2011; Koenig et al., 2011). Inactivation of the medial septum or lesions of the fornix also cause impairments in the memory of goal locations (O'Keefe et al., 1975; Chrobak et al., 1989; Brioni et al., 1990). The specific population of medial septal neurons involved in regulating grid cell firing has not yet been demonstrated. However, recent studies show that inactivation of glutamatergic neurons causes a decreased specificity in grid cell firing activity, and inactivation of GABAergic neurons in the medial septum results in the loss of grid cell spatial firing along with a reduction in theta rhythm oscillations (Robinson et al., 2019).

Coding of prior context

The performance of tasks such as delayed spatial alternation or delayed non-match to position requires the capacity to distinguish (disambiguate) spatial location on different trials, as described in previous modeling work (Levy, 1996; Hasselmo and Eichenbaum, 2005; Hasselmo, 2009). Lesions of the hippocampus cause impairments in these types of tasks (Ainge et al., 2007; Aggleton et al., 1986; Aggleton et al., 1995; Hallock et al., 2013) that require memory of both spatial location and the specific time of the prior trial to disambiguate it from other previous trials. Neurophysiological data in these tasks show context-dependent activity appropriate for this behavioral disambiguation based on memory. For example, when a rat runs on the stem of spatial alternation task, individual neurons will fire selectively based on the past or future turning response. These “splitter” neurons have been observed in the hippocampus (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Kinsky et al., 2020; Levy et al., 2021) and entorhinal cortex (Frank et al., 2000; Lipton et al., 2007; O'Neill et al., 2017). The separation and disambiguation of overlapping spatiotemporal trajectories is a challenge for any model of episodic memory, particularly when considering the large number of memories that can be generated in a single familiar environment (Robins, 2015). This raises questions of the relative overlap of representations, which could range from the extreme case of an index model, in which a small number of non-overlapping neurons code each memory, to the alternate case of a broadly distributed representation in which most neurons are involved in every memory, which is more amenable to cueing of memories, but less amenable to prevention of interference (Robins, 2015). The nature of the amount of overlap and capacity to cue less overlapping memories remains an empirical question for both simulations and neurophysiology (Hasselmo, 2015).

The context-dependent neuronal responses in a spatial alternation task can appear at specific times during training and are more stable than place cell responses in the task, possibly because the splitter responses are more necessary for accurate task performance (Kinsky et al., 2020). The left-right discriminability of splitter cell responses correlates significantly with accurate behavioral performance (Kinsky et al., 2020). Context-dependent activity can also distinguish the sample versus test trials in delayed non-match to position (Griffin et al., 2007; Levy et al., 2021), and during the course of learning the task shows a gradual shift from coding both turn direction and task phase, to showing more coding of turn direction or task phase alone (Levy et al., 2021). The separation of representation could also include the dentate gyrus, as neural activity associated with turning to one side of the maze differs from the representation associated with turning both directions (Wilmerding et al., 2023).

Both the guidance of behavior and the learning-dependent shift in context-dependent representations over time may depend upon mechanisms of sequence retrieval during theta rhythm. Theta sequences appear to reflect planning of future trajectories, as sequences appear at choice points (Johnson and Redish, 2007; Kay et al., 2020), and the length of theta sequences increases with greater distance of future goals (Wikenheiser and Redish, 2015). The phase of firing relative to theta rhythm also appears to shift based on the novelty of individual cues (Manns et al., 2007) or the novelty of the environment (Wells et al., 2013; Douchamps et al., 2013), consistent with proposals for encoding and retrieval on different phases of theta rhythm cycles (Hasselmo et al., 2002; Hasselmo, 2006). If encoding and retrieval processes occur on different phases of theta, then the ability to discriminate a retrieved memory from current sensory input could depend upon an intact theta rhythm (Hasselmo, 2005). Loss of this phase coding could result in confabulation of imaginary memory with real memory, which has been shown to occur after damage to the medial septum (DeLuca and Cicerone, 1991). The different phases of encoding and retrieval could include a neural signal associated with phase that distinguishes the memory of a real event from the memory of an imagined event (Boyle, 2021).

Coding of trajectory speed and direction

In contrast to the model of episodic memory as a series of snapshots, the model of episodic memory as a continuous spatiotemporal trajectory includes dimensions beyond spatial location and time interval (Hasselmo, 2012; Hasselmo, 2009). The fact that one can remember a specific viewpoint of a scene (Conway, 2009), or changes in speed of movement indicate that direction and speed are available in episodic memories.

In addition to the importance of speed and direction for episodic memory, many models of grid cell firing use path integration of self-motion to code location. This standard mechanism could function in parallel with coding of location by transformation of sensory input. Grid cells retain their spatial firing pattern in darkness, suggesting a role for path integration of self-motion in the absence of visual cues (Hafting et al., 2005; Dannenberg et al., 2020). However, sensory input is important as grid cells rotate with visual cues in a circular environment (Hafting et al., 2005), and spatial coding by grid cells is lost when all sensory cues are lost or obscured including visual, auditory, somatosensory and olfactory input (Chen et al., 2016; Pérez-Escobar et al., 2016). The role of sensory input is further supported by evidence that grid cells lose spatial coding during inactivation of regions providing head direction input (Winter et al., 2015). The subsequent sections will review data on the potential role of memory for spatial location based on path integration versus the transformation of sensory input.

Coding of speed

The running speed of animals has been shown to be coded by neurons in the hippocampus (O'Keefe et al., 1998; McNaughton et al., 1983) and medial entorhinal cortex (Sargolini et al., 2006; Wills et al., 2012; Buetfering et al., 2014; Kropff et al., 2015; Hinman et al., 2016). Some cells appear to selectively code running speed (Kropff et al., 2015), but others show mixed selectivity as grid cells and head direction cells that also code running speed (Sargolini et al., 2006; Wills et al., 2012; Buetfering et al., 2014; Jeewajee et al., 2008; Hinman et al., 2016).

Coding of running speed also appears in retrosplenial and parietal cortex (McNaughton et al., 1994; Alexander et al., 2020; Clancy et al., 2019; Carstensen et al., 2021) and sensory responses are modulated by running speed in visual cortex (Niell and Stryker, 2010) and auditory cortex (Nelson and Mooney, 2016). The direct coding of speed could occur without requiring the computation of distance over time, as neurons also show responses to acceleration guided by the vestibular system, such that integration of acceleration could generate a speed response independent of the ongoing perception of distance or time.

This speed coding could be important for episodic memory of spatiotemporal trajectories. In contrast, the data on speed coding does not uniformly support the use of speed for path integration of 2-dimensional spatial location. Models of path integration require linear coding of running speed by firing rate, as found in many speed tuning curves, but many speed-modulated cells show non-linear responses that saturate at moderate speeds (Hinman et al., 2016; Dannenberg et al., 2019). Surprisingly, neurons represent speed by firing rate over intervals of several seconds, but over shorter periods than a second, the firing rate code is too inaccurate for effective path integration (Dannenberg et al., 2019). This calls into question the use of coding of location based on integration of a firing rate code for running speed.

Coding of direction

In addition to coding of running speed, both models of episodic memory as spatiotemporal trajectories and path integration models of grid cells require coding of movement direction. Many place cells show sensitivity to movement direction on a one-dimensional linear track (McNaughton et al., 1983; Huxter et al., 2003), and hippocampal cells also appear to code the direction of a goal on a honeycomb maze (Ormond and O'Keefe, 2022). Outside the hippocampus, there are many neurons that show responses to the current allocentric direction of an animal’s head (Taube et al., 1990). These head direction cells do not depend on current location or movement direction. A systematic analysis of neurons in entorhinal cortex during periods when movement direction differed from head direction demonstrated numerous head direction cells but no cells that exclusively code movement direction (Raudies et al., 2015). Researchers have proposed that movement direction could instead be coded by rhythmic firing of theta cells (Welday et al., 2011) or spiking in theta sequences (Zutshi et al., 2017). However, the broad evidence for head direction cells in the absence of movement direction cells suggest that path integration of self-motion might be less important than the coding of sensory feature angle provided by head direction cells (Raudies et al., 2015).

Head direction cells could instead be vital for accurate transformation of egocentric coordinates into allocentric coordinates, as allocentric head direction is needed if one is to transform egocentric coordinates of sensory feature angle into allocentric location (Byrne et al., 2007; Touretzky and Redish, 1996; Bicanski and Burgess, 2018). Head direction cells have been found in a range of structures including dorsal presubiculum (Taube et al., 1990), anterior thalamus (Taube, 1995) and entorhinal cortex (Sargolini et al., 2006; Brandon et al., 2013; Brandon et al., 2011; Giocomo et al., 2014). Lesions of the dorsal presubiculum or anterior thalamic nucleus, which both provide head direction input to cortex, cause destablization of hippocampal place cells (Goodridge and Taube, 1997) and loss of spatial coding by entorhinal grid cells (Winter et al., 2015). Head direction cells usually do not show theta rhythmicity, but in the entorhinal cortex show theta rhythmic firing that falls on alternate cycles of the theta rhythm (Brandon et al., 2013), consistent with place cell readout of trajectories on alternate theta cycles in the hippocampus (Kay et al., 2020).

Coding based of different coordinate systems

The above data indicates that path integration of self-motion may not be the most important mechanisms for updating the memory of spatial location. In contrast, the influence of sensory feature angle could be used to update the memory of spatial location, as supported by the influence of visual cue rotation on the firing of place cells (Muller and Kubie, 1987), and grid cells (Hafting et al., 2005) and the loss of grid cell firing when darkness is combined with removal of auditory and somatosensory cues (Chen et al., 2016; Pérez-Escobar et al., 2016). Understanding the influence of sensory input on place cell firing requires understanding of coordinate transformations. The coding of spatial location by place cells is commonly described in allocentric coordinates (i.e. allocentric coordinates describe the position of an animal relative to environment boundaries). This requires a coordinate transformation from the egocentric coordinates of sensory input such as visual feature angle (i.e. egocentric coordinates describe the position of a feature relative to an animal). This may correspond to the philosophical descriotion of a perspectival view of an object compared to a constant representation of an object (Green and Schellenberg, 2017). Studies of neural activity in the human brain have demonstrated differences in neural activity associated with viewing a navigation task from a first person, egocentric perspective, compared to performing the task from a third-person overhead perspective (Sherrill et al., 2013; Sherrill et al., 2015). The following sections will review further data relevant to this topic.

Allocentric boundary cells

The important influence of sensory cues for location coding was shown in experiments in which the distance of environmental barriers relative to other barriers (i.e. allocentric position) was changed (i.e. changing a 1x1 meter square environment to a 1x2 meter rectangle) and this was shown to alter the position of the firing fields of place cells (O'Keefe and Burgess, 1996). This data motivated the theoretical proposal of boundary vector cells that code animal position relative to boundaries (Burgess et al., 2000; Hartley et al., 2014; Hartley et al., 2000). This theoretical prediction was supported by data demonstrating boundary vector cells that fire when boundaries are at a specific distance and allocentric angle in allocentric coordinates (Solstad et al., 2008; Lever et al., 2009; Savelli et al., 2008; Barry et al., 2006). These boundary responses can occur at a distance from the boundary (Lever et al., 2009), indicating a role of visual sensory cues, and they show responses to insertion of new barriers in the environment (Lever et al., 2009). A related population of neurons, termed object vector cells, respond when the animal occupies specific allocentric angles and distances from non-boundary objects (Hoydal et al., 2019; Deshmukh and Knierim, 2011; Deshmukh and Knierim, 2013). Grid cells also respond to the allocentric positions of environmental boundaries, showing compression or expansion of the distance between firing fields (Barry et al., 2007; Stensola et al., 2012; Munn et al., 2020), and changes in coding of velocity with wall movement (Munn et al., 2020).

Models have demonstrated how allocentric spatial location can be generated from egocentric visual coding of boundaries (Byrne et al., 2007; Bicanski and Burgess, 2018; LaChance and Taube, 2023; O'Keefe, 1990). Models have demonstrated how allocentric boundary vector cells could be generated from egocentric sensory coding of environment boundaries combined with head direction (Burgess et al., 2000; Hartley et al., 2000; Byrne et al., 2007; Bicanski and Burgess, 2018). These latter models predicted the existence of neurons that code the egocentric position of boundaries. Influences of boundary location on grid cells and allocentric boundary cells has also been modeled based on the angle and optic flow of visual features (Raudies and Hasselmo, 2015; Sherrill et al., 2015).

Egocentric boundary cells

The prediction that allocentric boundary cells could be generated from egocentric boundary cells was supported by data showing egocentric boundary cells in a range of structures, including the retrosplenial cortex (Alexander et al., 2020; van Wijngaarden et al., 2020), the postrhinal cortex (LaChance et al., 2019; Gofman et al., 2019), the entorhinal cortex (Wang et al., 2018; Wang et al., 2020) and structures receiving output from these regions such as the dorsomedial striatum (Hinman et al., 2019) and parietal cortex (Alexander et al., 2020). As animals forage in an open field environment, egocentric boundary cells fire selectively when the barriers or boundaries of the environment are at a specific angle and distance to the animal (Hinman et al., 2019; Alexander et al., 2020). They are therefore most efficiently described by plotting the position of the barrier for each spike in egocentric polar coordinates. The sum over all spikes shows how neurons respond to a barrier at a specific distance of a few to many tens of centimeters. Different neurons respond selectively for barriers at a specific range of angles and distances relative to the animal itself, with most right hemisphere neurons responding to barriers directly to the left of the animal, and most left hemmisphere neurons responding to barriers directly to the right (Alexander et al., 2020). Other neurons respond to angles to the front or behind the animal. Many egocentric boundary vector responses are invariant to the appearance of environmental boundaries indicating that the response property is not driven by high-level visual features (Hinman et al., 2019). While some papers focus on the egocentric response to barriers, others focus on the coding of position relative to the center of the environment or specific objects or goals (Wang et al., 2018; Wang et al., 2020). The neurons show tuning to barriers at a number of distances, including distances well outside the range of whisker contact, as well as at a number of angles, including positions behind the animal.

Egocentric coding of the environments has also been shown in several other cortical regions, including posterior parietal cortex, secondary motor cortex, and postrhinal cortex (LaChance et al., 2019; Gofman et al., 2019; Alexander et al., 2020). In the postrhinal cortex egocentric boundary responses persist in darkness (LaChance et al., 2019), supporting the computational theory of their generation by some mechanism of path integration based on prior contact with the barrier. In the postrhinal cortex, egocentric bearing was found to be anchored to the center of the environment rather than the boundaries (LaChance et al., 2019).

The theta phase coding shown for place cells and grid cells reviewed above suggests that theta phase coding might occur for egocentric and allocentric boundary cells. Retrosplenial neurons show phasic firing relative to hippocampal theta rhythmicity (Alexander et al., 2018) and some egocentric boundary cells show theta phase locking (Alexander et al., 2020). Consistent with the proposed separation of encoding and retrieval on different theta phases in the hippocampus (Hasselmo et al., 2002), allocentric boundary cells fire on different phases of theta during direct experience of boundaries versus trace responses to boundaries that are no longer present (Poulter et al., 2021). Theta phase coding could provide a component of spatial representation that can contribute to the transformation from egocentric coordinates to allocentric coordinates and the encoding of egocentric information in spatiotemporal trajectories for episodic memory.

Brief review of hippocampal models

The above sections reviewed some of the data on neural representations for time and space that are relevant to episodic memory. This section will provide a brief review of some existing models of episodic memory and the internal representations used in those models. Historically, both psychological and neural models of episodic memory have focused on the representation of the world as a set of vectors, usually with an arbitrary mapping of environmental features (such as words in a verbal memory task) to individual vectors. This mapping was used in many memory models in mathematical psychology (Murdock, 2005), and the vector representation carried over into neural network models of episodic memory (McNaughton and Morris, 1987) that focused on encoding of an array of vectors representing individual memories (McNaughton and Morris, 1987). These memories were proposed to undergo orthogonalization (later called pattern separation) in the dentate gyrus (McNaughton and Morris, 1987; Hasselmo and Wyble, 1997; Treves and Rolls, 1994), and then to be stored in a recurrent auto-associative memory in region CA3 that could mediate pattern completion (McNaughton and Morris, 1987; Hasselmo and Wyble, 1997; Treves and Rolls, 1994). Finally, region CA1 would map the stored patterns back to the input.

One major criticism of these early models is their relatively small capacity relative to the number of neurons, and also the lack of a representational structure to match space and time in the world. Another concerns the simple nature of the arbitrary vector representation, which does not reflect any hierarchical representation of information, though that could be feasible in a vector representations such as those generated by convolution (Eliasmith et al., 2012; Plate, 1995). These models also lack many of the elements of neural dynamics, such as network and cellular oscillations and dendritic subthreshold dynamics.

Other neural models of memory focus on the role of neurons with specific functional properties, such as place cells, grid cells and head direction cells. These models have address the potential functional role of these subtypes in representing a spatial environment. Models of this type have focused on a number of functions, including: 1.) guidance of behavior to a specific goal location from a variety of start locations using place cells (Redish and Touretzky, 1998; Burgess et al., 1997; Arleo et al., 2004), or using grid cells (Erdem et al., 2015; Erdem and Hasselmo, 2014; Erdem and Hasselmo, 2012; Kubie and Fenton, 2012), 2.) the encoding and retrieval of previously encoded trajectories in episodic memory (Hasselmo and Eichenbaum, 2005; Hasselmo, 2012; Hasselmo, 2009), or 3.) the transformation between egocentric and allocentric representations of environmental features (Byrne et al., 2007; Bicanski and Burgess, 2018; Alexander et al., 2023; Sheynikhovich et al., 2009). Merging these different functions in a single model would be desirable.

Models that contain functional subtypes will automatically resemble those properties of the biological data, but their function for practical behavior tends to be somewhat limited. In particular, many of these models require input that has already been coded in terms of specific aspects of spatial location or velocity, though a few have been designed to respond on the basis of direct egocentric sensory input (Sheynikhovich et al., 2009; Arleo et al., 2004). The model of episodic memory as a spatiotemporal trajectory effectively encodes and retrieves continuous trajectories through an environment and associated features of events at different positions along the trajectory. However, this model must be modified to account for later data, as the initial version of the model used grid cell input to generate place cells and also used speed-modulated direction cells that depend on movement direction rather than head direction (Hasselmo, 2012; Hasselmo, 2009).

The models that start with functional cell types such as place cells and grid cells often do not account for detailed biophysical dynamics of individual neuronal conductances. More biophysically detailed models simulate the membrane conductances and single cell membrane potential dynamics of neurons (Traub et al., 2022; Kelley et al., 2021; Wallenstein and Hasselmo, 1997; Traub et al., 1992; Sutton and Ascoli, 2021). However, the computational demands of these biophysical models make it very difficult to simulate a wide range of functional cell types or to simulate the guidance of complex behaviors.

A different class of models uses large multi-layer systems of neuron-like elements with an implementation of an error-correcting learning rule such backpropagation of error in deep learning (Banino et al., 2018) or contrastive Hebbian learning (O'Reilly and Munakata, 2000; Naud and Sprekeler, 2018). These models have the advantage of not using an a priori representations of functional cell types, but instead generating these functional cell types within the model (Banino et al., 2018). These models also have the advantage of using a more realistic egocentric input of visual input from the environment, rather than a pre-coded neural representation. Because these models generate behavioral output that usually exceeds the capabilities of most hand-wired models, this approach is considered to have great potential for advancing the understanding of neural representations. However, so far the internal dynamics of these models have not been easily interpretable to yield guidance concerning the internal dynamics that allow for the function of the models. The distributed code is difficult to decipher and does not seem to exhibit features of symbolic representations such as compositionality and productivity, that would allow breaking down their functional processes into interpretable rules and elements (Do and Hasselmo, 2021).

In summary, the models that best simulate behavior using error-correcting learning rules do not provide interpretable internal dynamics, the models that directly simulate a range of functional cell types are more limited in their behavioral function and still do not address the complex dynamics of membrane potentials and membrane currents, whereas the models containing the biophysical detail of membrane currents have not been used to guide behavior or to generate simulations of most functional cell types.

Need to explore broader variety of models

There is a need for better models of neural circuits. Given the limited ability of existing models to demonstrate the computational relevance of many aspects of biophysical data, one can consider the question of what would a more effective model look like? What modifications could result in a revolution in neural memory models. The dimensions of possible models are actually enormous, and existing models have only explored a tiny fraction of this space (Hasselmo et al., 2021). Some ideas are presented here for exploring different areas of model space.

1. Phase coding. The use of temporal coding by the phase of spiking activity could provide advances over the dominant use of firing rate as the neuronal code. Most of the models described above use vectors with a continuous change in value that represents a continuous change in firing rate. These models do not directly account for the temporal coding of space and time that appears in multiple studies as theta phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996; Hafting et al., 2008; Climer et al., 2013), nor do they account for the rhythmic coding of running speed (Hinman et al., 2016; Dannenberg et al., 2020). Place cells and grid cells have been effectively modeled with phase coding based on oscillatory interference (Burgess, 2008; O'Keefe and Recce, 1993), but these models have not been the focus for most researchers.

2. Dendritic processing. Another underexplored area concerns the dynamics of dendritic processing, including the potential role of phase shifts within dendritic compartments (Vaidya and Johnston, 2013; Kelley et al., 2021), which could be modulated by synaptic activation of metabotropic receptors. Previous models of dendritic H current have focused on how these currents normalize timing of synaptic potential peaks (Magee, 1999; Vaidya and Johnston, 2013), but these currents could instead play a role in generating heterogeneity of phase based on interaction with other phase shifting inputs and matching to other dendritic inputs (Alexander et al., 2023). For example, one set of phase shifts could represent the relation between two features within an object (angle and distance) and an external phase shift could represent current object angle and current viewing angle.

3. Dendritic coding of transformations. Dendritic processing via phase shifts could allow transformations to be coded at a single neuron level rather than a network level. Many models of coordinate transformations use gain modulation (Bicanski and Burgess, 2018), in which different

populations of neurons code different transformations and a gating input (such as head direction) modulates the selection of different populations, requiring large numbers of neurons. In contrast, coding of transformations by individual neurons could allow coding of a broader range of transformations, and more flexible modulation of individual neuron transformations (Alexander et al., 2023).

4. Transmission of memory representations. Another appealing feature would be to have memory representations that can be easily transmitted between neurons, so that instead of requiring a long-term synaptic modification they could instead be rapidly transmitted. One possible way of doing this would be to have neural phase codes that can be transmitted between different neurons to activate cellular mechanisms that regulate phase within individual neurons. For example, neural activity could phosphorylate the H current or potassium currents in such a manner to change their time constant (Chen et al., 2001). The H current has been shown to shift the frequency and the phase of neural activity in dendrites (Vaidya and Johnston, 2013; Kelley et al., 2021). Changes in these currents could underlie alterations in neuronal responses such as those contributing to place cell firing (Bittner et al., 2015).

5. Analogy with computer animation. Beyond the details of cellular representations, there could be more focus on the nature of neural representations for flexibly representing all elements of an existing world. There could be inspiration from the framework used in computer animation. For example, the use of matrix implementations of two dimensional bezier surfaces (Sederberg, 2012) or non-uniform rational beta-splines (NURBS) (Liu and Wang, 2002) to generate the elements of an allocentric scene and the projection transformation into an egocentric view.

Words versus equations: verbal hypotheses versus computational models

This chapter has focused on a review of neural data and computational models. However, inspired by the interaction of neuroscientists and philosophers at the meeting in Tucson that prompted this edited volume, this section will venture out of the neuroscience expertise to discuss verbal hypotheses versus computational models.

The conference in Tucson was titled Time, Space and Memory, similar to elements of many other conferences and the title of this chapter. However, one could argue that neuroscience must eventually outgrow verbal terms such as memory and associated terms such as episodic memory, semantic memory, and working memory, and to develop more sophisticated representations for words such as space and time.

Science is ultimately a quest to create new symbolic languages of description that transcend prior verbal descriptions. Mature scientific fields such as Physics have a mathematical language of theories that completely supplant and transcend verbal descriptions. Words can be used to communicate and teach about physical theories, but they are in no way a component of the theory itself. The accepted scientific theories are identical regardless of the inexact words or even variations in mathematical notation being used to describe it. Multiple theories ranging from Newtonian mechanics to the Schrodinger equations for atomic structures can be described entirely in equations that accurately guide. In most cases, the attempt to describe these theories in words alone usually introduces inaccuracies or misunderstandings. Similarly, the structure of molecules ranging from simple compounds to functional proteins to the genetic code in DNA can be described with a sequence of letters that need no words from natural language. The sequence and quantitative characteristics of each the sequence of amino acids in a protein and their structure and interaction with other proteins or small molecules can be functionally modeled, again without words.

At this point, systems neuroscience and psychology are still too immature as fields to have many accepted theories that transcend words. Theories at the single cell level can do this, using the mathematical framework of Rall and others to describe the membrane potential interactions across the structure of dendrites and axons, and using the Hodgkin-Huxley framework to describe the dynamics of voltage-sensitive and calcium-sensitive channels. Cellular neurophysiology is a mature science with theories that transcend words. However, systems neuroscience and behavioral neuroscience still suffer from the promiscuity of words to have multiple overlapping or nonoverlapping meanings.

In an immature field such as neuroscience, words can describe experimental results for which there is not yet a quantitative theoretical framework. And the names of researchers can provide another type of symbolic representation for forming an interlocking web of collaborations and dates that give some structure to the broad mass of neuroscience data. But sometimes scientific questions become overshadowed by disagreements over definitions of terms.

In the history of science, many domains of inquiry were initially domains of natural philosophy. Then, as empirical scientific inquiry grew more sophisticated within individual fields, the empirical components of individual fields of inquiry sequentially separated from philosophy and became independent disciplines. In some cases, the split seems to occur when the empirical data from experiments and the scientific theories about this data took a form that was independent from the verbal description of questions in the field. The philosophical questions remain in many areas of science, but the empirical theories in physics, chemistry and molecular biology have moved beyond verbal descriptions.

Replacing words

How do we replace words in systems neuroscience? Based on examples from other fields such as physics, astronomy, chemistry and engineering, the answer is to develop mathematical theories that quantitatively account for the full range of data being addressed. What we currently inaccurately call episodic memory and semantic memory and working memory could eventually be addressed with a broad continuum model with multiple time scales and spatial scales that cannot be differentiated into these primitive terms. Or conversely, a theoretical framework might allow quantization of the dynamics of neural substrates that results in precise mathematical definitions of a specific number of memory elements that have no clear relationship to our current primitive terms. Terms like episodic, semantic and working memory could be like the terms of air, water, fire and earth used in early science, and could be replaced by an orderly periodic table of neural memory dynamics that predicts and guides quantitative research on memory.

How do we defined the structure of knowledge addressed in neuroscience? Unfortunately, this is a daunting task as the scope of neuroscience is not just the empirical data, but also the scope of knowledge represented in the human brain. These internal representations include everything that we can understand about the universe. In the simplest terms, the field addresses how the nervous system guides behavior. On the one hand, we can at least focus on a single system in the body, the nervous system, so we have a physically contained substrate. On the behavioral side, we could focus like a behaviorist on only the physical manifestations of behavior – our movements in the world. However, this immediately expands into a description of everything, because we can utter words and write mathematical equations that attempt to describe our understanding of everything in the known universe. Thus the domain of neuroscience is not everything in the universe, but the domain does include our human understanding of everything. In order to model how the nervous system guides behavior, we need to model how the nervous system represents everything an individual can know about the universe, including a representation of the conscious self as a discrete entity interacting with the external world and planning future behavior based on past memories (Hasselmo, 2010). Ultimately, a model of memory function in cortical neural circuits must provide a framework for understanding how neurons can encode a memory representation of everything that a human can think about and remember. This is clearly a challenge, but an exciting challenge.

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