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Review

Computational Models of Grid Cells

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Grid cells are space-modulated neurons with periodic firing fields. In moving animals, the multiple firing fields of an individual grid cell form a triangular pattern tiling the entire space available to the animal. Collectively, grid cells are thought to provide a context-independent metric representation of the local environment. Since the discovery of grid cells in 2005, a number of models have been proposed to explain the formation of spatially repetitive firing patterns as well as the conversion of these signals to place signals one synapse downstream in the hippocampus. The present article reviews the most recent developments in our understanding of how grid patterns are generated, maintained, and transformed, with particular emphasis on second-generation computational models that have emerged during the past 2-3 years in response to criticism and new data.

Introduction

The idea that behavior is guided by map-like representations of space can be traced back to Edward Tolman, who in the 1930s and 1940s proposed that animals learn about regularities by forming internal representations of the environment (Tolman, 1948). Based on studies showing that animals learn mazes without explicit reinforcement (Spence and Lippitt, 1940; Tolman and Honzik, 1930), Tolman proposed early on that animals discover relationships between places and events as they explore the environment and that exploration leads gradually to the formation of a "cognitive map." The map-like structure of this representation was thought to enable animals to navigate flexibly by making detours and shortcuts in the presence of obstacles (Tolman et al., 1946a, 1946b). The elements of the map were suggested to be linked to a wider knowledge structure based on the animal's own experiences in the environment. Tolman's ideas broke radically with classical behaviorism, which often treated complex behaviors as chains of stimulus-response relationships rather than spatial information structures. The departure from traditional stimulus-response associationism was not uncontroversial. Questions about what was actually associated remained unsettled, much because scientists did not yet have the right tools to investigate the neural mechanisms of behavior. Today, more than 50 years later, neuroscience has become a mature discipline, and we know that animals have specialized brain systems for mapping their own location in space, much like Tolman had predicted.

The characterization of map-like neural representations of the external spatial environment began with the discovery of place cells. In 1971, O'Keefe and Dostrovsky described neurons in the rat hippocampus that fire whenever the animal visits certain spatial locations but not anywhere else. These neurons were termed "place cells." Different place cells were shown to fire at different locations ("place fields"). Although there was no apparent topographic arrangement of place cells according to their firing location, the combination of activity across large ensembles of place cells was unique for every location in the environment, such that as a population, hippocampal cells formed a map-like structure reminiscent of the cognitive map proposed by Tolman in the 1940s (O'Keefe and Nadel, 1978). Already from the earliest days, however, O'Keefe (1976) acknowledged that maps based on place cells would not be sufficient to enable navigation on their own. Navigation has strong metric components that may depend on neural systems measuring distance and direction of the animal's movement. O'Keefe and others suggested that the metrics of the spatial map were computed outside the hippocampus (O'Keefe, 1976; Redish, 1999; Redish and Touretzky, 1997; Samsonovich and McNaughton, 1997; Sharp, 1999), and subsequent studies consequently searched for space-representing neurons in the entorhinal cortex, from which the hippocampus gets its major cortical inputs. However, evidence for strong spatial signals remained scarce (Barnes et al., 1990; Frank et al., 2000; Quirk et al., 1992).

The search for origins of the place cell signal received new inspiration in 2002, when it was observed that place fields persist in CA1 after disruption of all intrahippocampal input to this subfield (Brun et al., 2002). This finding raised the possibility that spatial information is transmitted to CA1 through direct connections from the entorhinal cortex, and as a consequence, the search for spatial maps was shifted to this brain region. The first of the new series of studies targeted the dorsal part of the medial entorhinal cortex (MEC), which provides a significant component of the cortical input to the most common recording regions for place cells in the hippocampus. Cells in the dorsal MEC were found to have sharply defined firing fields (Fyhn et al., 2004). These firing fields were similar to the place fields of hippocampal neurons, but the cells invariably had more than one field, and they showed a strikingly regular organization. Subsequent studies in large environments showed that in each cell, the activity points define a repeating triangular pattern tiling the entire environment covered by the animal almost like the holes of a Chinese checkerboard (Hafting et al., 2005). The firing fields formed a grid-like pattern, and the cells were referred to as grid cells (Figure 1). The size of each grid field and the spacing between them were found to increase progressively from small

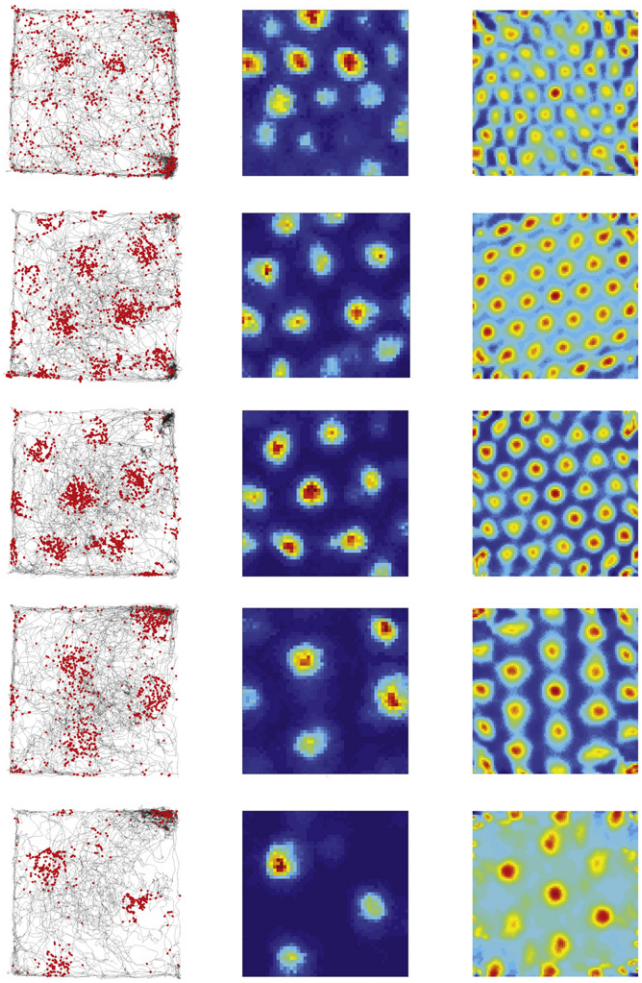

Figure 1. Examples of Grid Cells with Different Grid Spacing and Field Size

Left column: the rats walked in a 150 cm wide box. The trajectory of the rat is in gray, and each spike is plotted in red. Rate maps (middle column) and spatial autocorrelation maps (right column) are color coded (dark blue, minimum rate; dark red, maximum rate). The scale of the autocorrelation diagrams is twice the scale of the rate maps.

in dorsal to large in ventral MEC (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006). At the dorsal tip, the spacing was approximately 30 cm in the rat; at the ventral tip, it was more than 3 m (Brun et al., 2008). The position of the grid vertices in the x,y plane (their grid phase) appeared to vary randomly between cells at all dorsoventral locations, but each grid maintained a stable grid phase over time. The cells fired at the same x,y positions irrespective of changes in the animal's speed and direction, and the firing fields persisted in darkness, suggesting that self-motion information is used actively by grid cells to keep track of the animal's position in the environment (Hafting et al., 2005; McNaughton et al., 2006). This process, referred to as path integration, may provide the metric component of the spatial map.

Grid cells were soon found to colocalize with several other specialized cell types. A substantial portion of the principal cells in layer III and layers V and VI of the MEC were tuned to direction, firing if and only if the animal's head faced a certain angle relative to its immediate surroundings (Sargolini et al., 2006). Similar cells were already known to exist in other parahippocampal and subcortical regions (Ranck, 1985; Taube, 2007), but the entorhinal head direction cells were different in that many of them exhibited grid-like activity at the same time (conjunctive grid × head direction cells). In addition, approximately 10% of the active entorhinal cell population was found to fire selectively in the vicinity of geometric borders such as the walls of a recording enclosure or the edges of a table (Savelli et al., 2008; Solstad et al., 2008). We have referred to these cells as border cells (Solstad et al., 2008). Collectively, grid cells, head direction cells, and border cells are thought to form the neural basis of a metric representation of allocentric space (Moser et al., 2008).

The entorhinal spatial representation is different from the hippocampal map in that cell assemblies maintain their intrinsic firing structure across environments. If two grid cells have similar vertices in one environment, they will fire at similar locations also in another environment (Fyhn et al., 2007; Hafting et al., 2005). If two border cells fire along adjacent borders in one enclosure, they will do so in other boxes, too (Solstad et al., 2008). In the hippocampus, in contrast, different subsets of neurons are recruited in different environments (Muller et al., 1991), suggesting that the entorhinal network contains a single map, used universally across all environments, whereas the hippocampus contains a multitude of representations, individualized to include the unique features and experiences associated with every space experienced by the animal.

Grid cells have been reviewed in several recent papers (Derdikman and Moser, 2010; Giocomo and Hasselmo, 2008a; McNaughton et al., 2006; Moser et al., 2008; Moser and Moser, 2008; Witter and Moser, 2006). These papers described the initial experimental observations, the architecture of the grid cell network, and early theoretical attempts to understand the formation of grid cells as well as the transformation between grid signals and place signals. The focus of the present article is on the theoretical developments that have taken place more recently. We shall begin by describing strengths and limitations of the first generation of grid cell models—models for formation and transformation of grid signals that were proposed during the first 1–2 years after the discovery of grid cells in 2005. We will then show how limitations of these initial proposals, as well as new experimental data, have inspired the evolution of a second generation of models during the past 2–3 years. Assumptions and predictions of these new models will be discussed and compared with data, and key questions that remain to be answered will be identified.

Models of Grid Formation

A number of computational models have proposed mechanisms for grid-like firing patterns. These models have constrained the number of potential biological mechanisms for the grid pattern, and they have allowed the systematic investigation of parameters required for formation and maintenance of periodic spatial firing during irregular behavior. In this section, we shall summarize and compare these models and show how they have evolved in response to theoretical and experimental analysis.

Models of grid cells should capture cardinal features of grid cells such as the generation of a periodic spatial signal, the persistence of such periodicity in the presence of changing running speed and running direction, the variability of spatial periodicity within the cell population, and the presence of patterns of temporal structure such as phase precession. Models that satisfy all or most of these criteria historically fall into one of two classes, although some convergence has taken place more recently. The first class, referred to as oscillatory-interference models, uses interference patterns generated by multiple membrane-potential oscillations to explain grid formation. The instantaneous frequencies of the oscillators are determined by the running speed and running direction of the animal such that a spatial rather than temporal firing pattern is generated (O'Keefe and Burgess, 2005). The second class of models, referred to as attractor-network models, uses activity in local networks with specific connectivity to generate the grid pattern (Fuhs and Touretzky, 2006; McNaughton et al., 2006). Here, patterns of activity are moved across a network of recurrently connected, periodically active neurons in proportion to the speed and direction of the animal's movement. Thus, grid patterns emerge by path integration of speed and direction signals in both classes of models, but the mechanisms for obtaining triangular periodicity are different. Models of each class have now evolved beyond their first iterations, to address criticisms and integrate experimentally demonstrated features of the grid cell population.

Oscillatory-Interference Models

Oscillatory-interference models utilize changes in the frequency of membrane-potential oscillators to translate information about the speed and direction of motion into a periodic grid pattern. Their history can be traced back to an idea proposed by O'Keefe and Recce (1993) to explain temporal coding of position by hippocampal place cells. They found that, as an animal passes through the firing field of a place cell on a linear track, the spikes gradually shift in time to earlier phases of the EEG-captured theta rhythm. This phenomenon, termed "phase precession," was suggested to reflect interference between two membrane-potential oscillators operating at different frequencies and impinging on the same cell (Geisler et al., 2007; Lengyel et al., 2003; O'Keefe and Recce, 1993). One oscillator was suggested to keep a relatively constant frequency while the other increased or decreased in frequency based on input regarding the animal's velocity. If a threshold was applied to the resulting interference pattern, the spike times would reflect the phase difference between the baseline oscillator and the velocity-driven oscillator, and phase precession would fall out naturally if the frequency of the velocity-driven oscillator was higher than the frequency of the baseline oscillator. A side effect of this early hippocampal model was that it might generate repeating fields, which had not been observed at that time. However, with the discovery of grid cells, the proposal translated well into a model for spatial mapping in the entorhinal cortex (O'Keefe and Burgess, 2005). The model was extended to two-dimensional space by letting the baseline oscillator, thought to be in the soma, interact with several dendritic oscillators, each with a frequency determined by the projection of the animal's velocity in a specific direction (Burgess et al., 2007; Giocomo et al., 2007). If the direction modulation of the various linear oscillators differed in multiples of 60 degrees, a triangular grid pattern would form when the dendritic oscillation patterns were combined with the baseline frequency in the soma (Figures 2A and 2B).

The clearest strength of the oscillatory-interference model is that the experimental predictions are relatively easy to test, given the focus on individual cells rather than large ensembles. Predictions from the oscillatory-interference model have provided opportunities for experimental data to refute or support the original suggestions and drive them into their second and third generations. The original model predicted a decrease in the frequency of single-cell membrane-potential oscillations along the dorsoventral axis of MEC, in parallel with the decrease in the spatial frequency of the grid (O'Keefe and Burgess, 2005). Such a frequency change was subsequently demonstrated in whole-cell patch-clamp recordings of medial entorhinal layer II neurons (Giocomo et al., 2007). Moreover, consistent with the prediction that oscillations are key to generating stable grid cell representations, loss of the global theta rhythm by medial septum inactivation has been shown to result in loss of periodicity in the firing locations of grid cells (Brandon et al., 2011; Koenig et al., 2011). As predicted, the frequency of the field theta rhythm has been found to be more sensitive to changes in the rat's running speed in dorsal compared to ventral MEC (Jeewajee et al., 2008), and ventral MEC cells have been reported to fire only on every other theta peak (theta skipping) (Deshmukh et al., 2010), in agreement with an oscillatory-interference model implemented in a resonant network (Zilli and Hasselmo, 2010). It should be noted, however, that these experimental results can in principle also be obtained by mechanisms other than oscillatory interference.

Recently, multiple criticisms of the first generation of oscillatory-interference models have been raised. For example, several papers have criticized the oscillatory-interference approach for modeling biological oscillators as perfect sinusoids (Giocomo and Hasselmo, 2008a; Welinder et al., 2008; Zilli et al., 2009). In contrast to the modeled oscillations, in vitro slice recordings indicate that membrane-potential oscillations show a high degree of noise (Dudman and Nolan, 2009; Zilli et al., 2009), variance in frequency (Giocomo and Hasselmo, 2008a), and significant attenuation in high-conductance conditions, which may occur during realistic in vivo levels of synaptic input (Fernandez and White, 2008). Computational simulations indicate that accumulating noise interferes with the grid pattern. The rate at which a grid cell's spatial pattern drifts from its correct position can be calculated based on the variance of the oscillator (Welinder et al., 2008; Zilli et al., 2009). The measured variance in persistent spiking neurons and membrane-potential oscillations is not able to keep the grid pattern stable for more than a few seconds (Welinder et al., 2008; Zilli and Hasselmo, 2010), whereas the pattern is maintained for minutes in vivo (Hafting et al., 2005).

In addition, criticism has focused on the assumption that multiple, separate oscillations combine in the soma while maintaining independence in the dendrites (Remme et al., 2009). Successful implementation of models that rely on this assumption depends heavily on the ability of independent oscillations

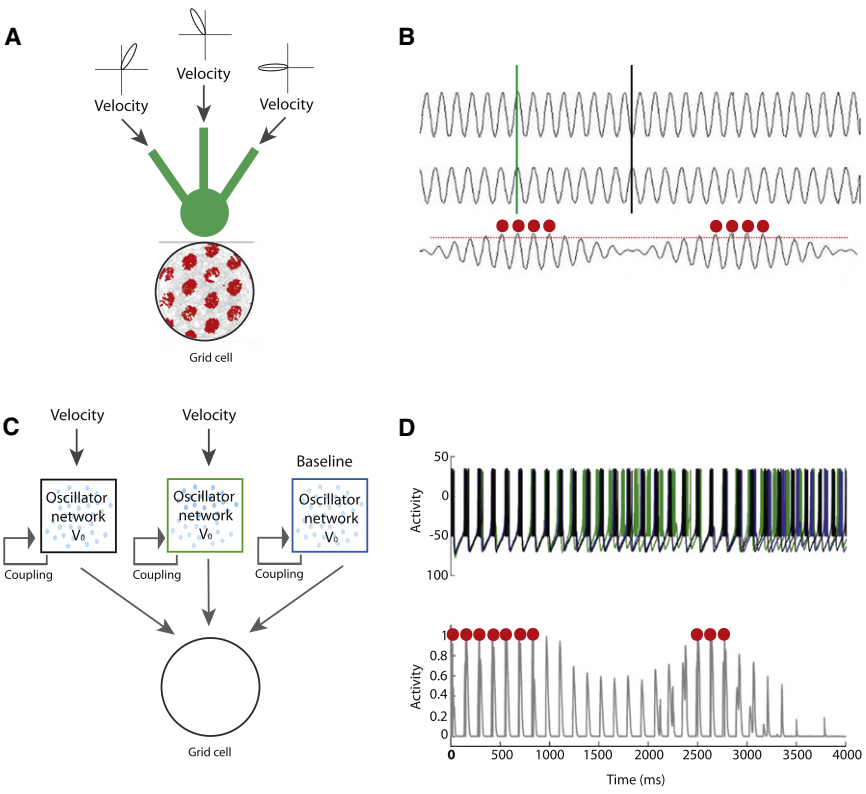

Figure 2. First- and Second-Generation Oscillatory-Interference Models

(A) Example of a first-generation oscillatory-interference model (Burgess et al., 2007; Giocomo et al., 2007). Top: speed-modulated head direction input influences the frequency of oscillations in three different dendrites. The three head direction inputs have preferred firing directions offset by 60 degrees relative to each other, as indicated by polar plots above each dendrite. An interference pattern is generated when the dendritic oscillations interact with the baseline soma oscillation. Modified from Hasselmo et al., 2007. Bottom: firing pattern produced by applying a threshold to the interference pattern evokes a grid cell firing pattern. The rat's trajectory is plotted in gray, and the spikes are plotted in red.

(B) Example of a single dendritic oscillation and soma oscillation generating an interference pattern. When the two oscillations are in phase (green line), the summation is large enough that the interference pattern will cross threshold and generate a spike (red dot). When the two oscillations are out of phase (black line), the summation is not large and the interference pattern will not cross threshold. Modified from Hasselmo et al., 2007.

(C) Example of a second-generation oscillatory-interference model (Zilli and Hasselmo, 2010). Top: two oscillator networks of internally coupled neurons receive signals about the rat's speed and direction (velocity inputs). A third network serves as a baseline and is insensitive to velocity inputs. The grid cell receives input from cells in all three networks and detects coincidental activity, which results in a grid cell firing pattern, as shown at the bottom, where the rat's trajectory is plotted in gray and spikes are plotted in red. Modified from Zilli and Hasselmo, 2010.

(D) Spiking activity of a coupled oscillatory network moves in and out of phase. Top: the output of a neuron from each network is in a different color (black, green, or blue). Bottom: when the activity of cells from all three networks is in phase, a spike occurs in the grid cell (red dot). Modified from Zilli and Hasselmo, 2010.

in different dendrites to unidirectionally influence the global, baseline oscillation. Using an idealized and detailed biophysical model based on sine waves, Remme et al., (2010) demonstrated that a biologically realistic bidirectional interaction between the local dendritic oscillations and global oscillations (in this case, soma oscillations) results in complete phase locking between all oscillations and a subsequent loss of the grid cell firing pattern. Phase locking occurred in the range of hundreds of milliseconds, even with parameters generously skewed toward promoting dendritic independence (Remme et al., 2010). Though not ruling out the potential importance of oscillatory and resonant properties, the detrimental effects of phase locking emphasize the importance of multicellular and network mechanisms in the generation of spatial periodicity.

Motivated by the challenges of dealing with noise and phase locking, the single-cell oscillatory model has evolved into several second-generation models. In general, oscillatory-interference models use oscillatory phase to perform a temporal integration of a rate-coded velocity signal (a rate-to-phase transformation). This transformation does not need to occur within a single neuron, and several models have simply moved the oscillators into clusters of different neurons. The velocity-driven oscillators can take the form of persistent-firing neurons (Hasselmo, 2008), single oscillatory neurons (Burgess, 2008), subcortical ring attractors generating velocity-modulated theta oscillations (Blair et al., 2008), or networks of coupled oscillatory neurons (Zilli and Hasselmo, 2010) (Figures 2C and 2D). However, persistent-firing models still suffer from the same noise problems as those encountered by the single-cell oscillatory models (Zilli et al., 2009), due to the variability in the frequency of persisting spiking.

One method for dealing with noisy oscillators is to assume that sensory cues frequently or constantly update the grid cell network. It has been proposed that memories of sensory configurations, supported by the hippocampus, can provide the needed updates to maintain a coherent grid pattern in the presence of noise (Burgess et al., 2007; Hasselmo et al., 2007; O'Keefe and Burgess, 2005). The frequency of the required updating has not been determined. Grid cells can maintain firing fields for up to ten minutes during foraging in complete darkness (Hafting et al., 2005), but the animals continue to receive tactile input from the walls of the recording box in such experiments, and the map may disintegrate with a much faster time constant on an open surface. Future studies must establish the accuracy of path integration over time, under conditions with no external sensory input, if we are to determine whether the limited persistence of grid representations in the oscillatory-interference models is biologically valid.

Another way to increase the stability of the grid is to couple the neural oscillators (Figures 2C and 2D) via excitatory or inhibitory connectivity (Zilli and Hasselmo, 2010). Coupled neurons

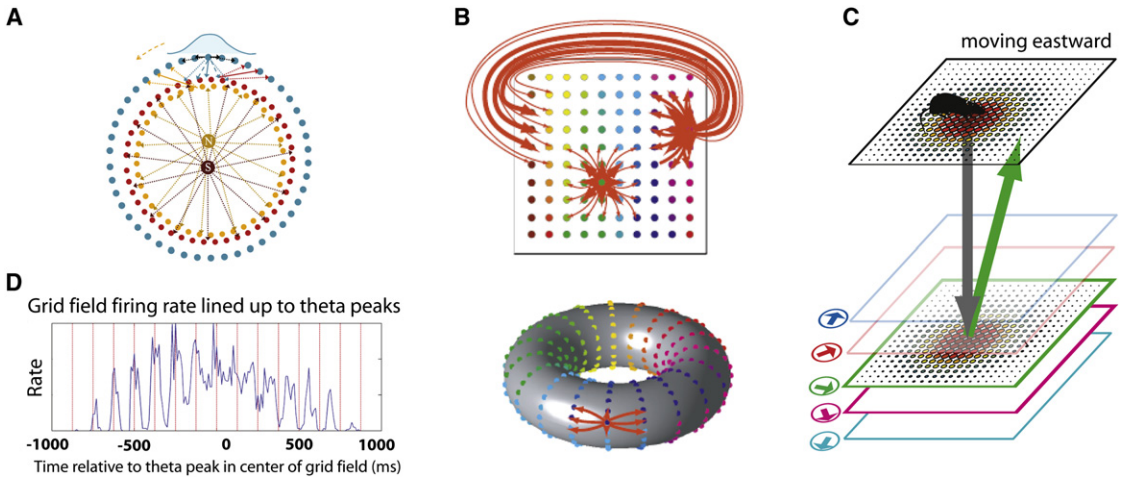

Figure 3. One-Dimensional and Two-Dimensional Continuous Attractor Models

(A) One-dimensional version of an attractor network. Grid cells (blue) form a ring of connectivity. Each cell has strong connections to nearby neighbors, with the strength of connections decreasing with distance, resulting in a "bump" of activity. Red and orange conjunctive cells, which receive input from head direction neurons, project to grid cells. When the animal moves south (for example), conjunctive cells with a preferred firing direction of south will asymmetrically connect to the grid cell layer and move the bump in the appropriate direction. Reprinted with permission from Navratilova et al., 2011.

(B) Two-dimensional version of the attractor network. Neurons arranged on a sheet have strong connections to neighbors that decrease in strength with distance. Neurons on one edge of the sheet connect to neurons on the opposite edge of the sheet (top), resulting in a toroidal shape of connectivity (bottom). Reprinted with permission from McNaughton et al., 2006.

(C) The bump in the two-dimensional network moves in a manner similar to the bump in the one-dimensional network, with a layer of conjunctive cells moving the network activity in the grid cell layer in the appropriate direction based on the rat's movement. Reprinted with permission from McNaughton et al., 2006.

(D) Network model with realistic spiking dynamics. The probability of spiking (blue) of simulated grid cells occurs at earlier time periods relative to the peak of theta (red lines), resulting in phase precession. Firing fields are aligned to the theta peak at the center of the field. Reprinted with permission from Navratilova et al., 2011.

produce network oscillations with less variability and have been shown to support stable grid representations for realistic trajectories lasting up to six minutes (Zilli and Hasselmo, 2010). It remains to be determined, however, whether the coupling required for such long-lasting performance is biologically valid. The coupled network must be very large in order to generate oscillations capable of long-lasting stability, implying that the rodent brain may only be capable of supporting a finite number of individual networks. If only a handful of coupled networks project to the grid population, many grid cells would receive input from the same set of coupled networks, resulting in discrete grid spacings and grid phases. The continuous distribution of spatial phase for grid cells at the same anatomical depth (Hafting et al., 2005) implies either that the brain contains tens to hundreds of velocity-coupled networks or that the coupled model makes biologically unrealistic assumptions.

Moving the oscillators to separate neurons may circumvent the phase locking that occurred within the single-cell oscillatory-interference models. In recent implementations, one of the external inputs is used as the baseline oscillator by simply making it insensitive to velocity signals (Blair et al., 2008; Zilli and Hasselmo, 2010) (Figure 2C). The grid cell then operates as a coincidence detector, firing when inputs arrive from the velocity-coupled oscillators at the same time (Zilli and Hasselmo, 2010) (Figure 2D). In this model, the velocity-coupled oscillators fire throughout the environment, with the phase of firing depending on the speed and direction of the animal. Such oscillator networks have not yet been identified, but they could hypothetically exist in any brain region projecting to the grid cells.

Attractor-Network Models

Another major class of computational models generates grid responses from local network activity. Single positions are represented as attractor states, with stable activity patterns supported by the presence of strong recurrent connectivity. A network can store many attractors (Amit et al., 1985, 1987; Hopfield, 1982), each of which might be activated by a specific set of input cues. In the event that the distribution of input cues is continuous, such as in a representation of direction or space, a continuous attractor emerges (Tsodyks and Sejnowski, 1995). If the individual neurons of the network have Mexican hat connectivity—i.e., the cells receive strong recurrent excitation from nearby neighbors, inhibition from intermediately located neurons, and little input from neurons located far away—then a bump of focused activity appears somewhere in the network, with the actual location of the bump influenced by incoming signals. The dynamics of head-direction cells can be modeled in a one-dimensional ring attractor where cells are arranged in a circle according to their directional preferences (McNaughton et al., 1991; Sharp et al., 1996; Skaggs et al., 1995; Touretzky and Redish, 1996; Zhang, 1996) and the activity bump is moved in accordance with changes in the animal's head orientation (Figure 3A). The dynamics of space-modulated cells can be modeled on a two-dimensional neural sheet where cells are arranged according to the location of their firing fields and the activity bump is moved in accordance with the animal's direction and speed of movement (Samsonovich and McNaughton, 1997; Zhang, 1996). The two-dimensional model was originally proposed as a mechanism for spatial representation by place

cells, but, like the oscillatory-interference model of O'Keefe and Recce (1993), the model implicitly predicted periodic firing fields. With the discovery of grid cells, this model could also be translated to entorhinal networks.

One of the earliest attractor models of grid cells used a self-organized pattern of activity that, if displaced across medial entorhinal neurons in concordance with the movements of the rat, imprinted a grid map to each of its neurons (Fuhs and Touretzky, 2006). Multiple "bumps" of activity emerged as a consequence of concentric ripples of positive and negative connections. To support translocation of the activity, each cell was assigned a preferred head direction. The bumps of activity were then displaced based on both velocity input to units with the appropriate head direction preference and asymmetric inhibition enforcing a single direction of movement (Fuhs and Touretzky, 2006). Navigation over small timescales resulted in the successful generation of grid cell patterns; however, population activity was constructed using biologically unrealistic piecewise trajectories. Spiking activity was plotted for a small sampled portion of the environment, and the network activity was then reset before the next sample. This resulted in the grid pattern falling apart when realistic trajectories over longer periods of time were used (for more detail, see Burak and Fiete, 2006). Another concern was that the initial connectivity used in the Fuhs and Touretzky model led to overwhelming excitation near the borders of the environment, causing neurons to fire over the entire environmental boundary. Disruption of path integration then occurred as avoiding these edge effects required significant attenuation of the recurrent activity near the borders, which caused distortions and rotations in the population pattern.

Edge effects in attractor networks can be avoided by supposing that neurons at the edges of the network connect with neurons on the opposite edges, resulting in periodic boundaries (Figure 3B). Periodic boundaries effectively turn the network into a torus shape of connectivity and naturally cause the firing fields of neurons on the attractor map to repeat at regular intervals (McNaughton et al., 1996; Samsonovich and McNaughton, 1997) (Figure 3B). The triangular pattern of the grid can be generated by assuming that the torus is twisted, with a rhombus as the repeating unit (Guanella et al., 2007; McNaughton et al., 2006). Attractors utilizing such periodic boundaries support accurate path integration for realistic trajectories and time periods without a loss of performance in the presence of neural noise (Burak and Fiete, 2009). It should be noted, however, that precise path integration can also be achieved with aperiodic boundaries if the network is appropriately structured (Burak and Fiete, 2009).

A common feature of attractor models that path integrate over a reasonably long duration of time is the inclusion of cells that are sensitive to direction and speed in addition to location. In the McNaughton model, for example, path integration was achieved by introducing a separate layer of direction- and speed-responsive cells (McNaughton et al., 2006; Navratilova et al., 2011) (Figure 3C). These cells were suggested to receive inputs from currently active grid cells and project back asymmetrically to cells that were next to fire on a trajectory along a particular direction at a particular speed of movement. In agreement with the predictions from the attractor models (Burak and Fiete, 2009; Fuhs and Touretzky, 2006; McNaughton et al., 2006), grid cells with conjunctive responses to direction, and to a lesser extent speed, have been observed in layers III to VI of the MEC of the rat (Sargolini et al., 2006).

The network models also make some predictions regarding the topography of the grid cell network. A dorsoventral organization in grid spacing can emerge from a topographical attenuation in the strength of the speed signal coming in to the spatial layer (Fuhs and Touretzky, 2006; McNaughton et al., 2006). However, because the bump of activity can only move at one speed through the interconnected continuous attractor network, the variance in the speed signal must occur in multiple, distinct attractor networks. This implicitly predicts the presence of discrete steps in grid spacing along the dorsoventral axis (Burak and Fiete, 2009; Fuhs and Touretzky, 2006; McNaughton et al., 2006). Emerging experimental evidence seems to support this prediction. Grid spacing appears to increase in a step-like manner along the dorsoventral axis of the MEC (Barry et al., 2007). The apparent discontinuity of the grid cell layer is matched by the organization of stellate cells into discrete patches of high cytochrome oxidase activity (Burgalossi et al., 2011). Whether these patches correspond to independent subpopulations of grid cells and whether the implied subnetworks operate as discrete attractor systems remain to be determined, however.

One major limitation of the initial attractor models for grid cell formation was the lack of temporal dynamics that could contribute to phase precession in grid cells (Hafting et al., 2008). To address this limitation, a recent model combines the torus-based attractor network of McNaughton et al. (2006) with intrinsic current dynamics to both achieve path integration and account for phase precession (Navratilova et al., 2011). This model consists of two interconnected networks, with the conjunctive cell layer receiving sine wave input to simulate the theta rhythm and the grid cell layer modeled as integrate and fire neurons with realistic after-hyperpolarization and depolarization conductances (Storm, 1987; Storm, 1989) (Figure 3D). When the animal moves, firing from the conjunctive cell layer moves the activity in the appropriate direction across the attractor manifold in the grid cell layer (look-ahead). At the trough of the simulated theta input, a decline of inputs and increased inhibition cause the bump to collapse. Rebound activity, determined by the after-spike and NMDA conductances, then helps to depolarize recently active cells, which contribute to the reformation of the activity bump (jump-back). The interplay of the look-ahead with the jump-back results in the activity of a single grid cell firing at successively earlier phases of theta over several theta cycles (phase precession) (Figure 3D). The addition of after-spike dynamics also provides a second possible mechanism for the dorsoventral organization in grid cell spacing. Increasing the time constant of the after-spike conductances causes the reinitiation (jump-back) of neurons active earlier in the theta phase, simultaneously reducing the rate of phase precession and increasing the grid period (Navratilova et al., 2011), and this jump-back could increase along the dorsoventral axis of the MEC. The validity of the model relies on several important assumptions, however. One is that the after-spike conductances generate reliable rebound spiking activity in grid cells. This has not yet been explored. Moreover, by integrating intrinsic

currents into the model dynamics, grid spacing becomes highly dependent on the time constants of these particular currents. In the case of NMDA and rebound conductances, some of the assumed time constants may not reflect the kinetics of entorhinal principal cells, as these currents have not been studied extensively in MEC. Even so, the model can tolerate a degree of heterogeneity in the current kinetics. Grid spacing does not depend on the individual, but rather on the average, time constant of the entire population of neurons within a given attractor module (Navratilova et al., 2011).

Finally, it is worth noting that the validity of the attractor models relies on the assumption of specific connectivity between grid cells with similar spatial phase. Whether entorhinal networks exhibit such connectivity remains a topic of investigation. Early studies in brain slices indicated a nearly complete lack of recurrent connectivity in layer II (Dhillon and Jones, 2000), whereas later photo-uncaging studies suggested that layer II neurons can be activated at synaptic latencies by stimulation within this layer (Kumar et al., 2007). Both of these studies are likely to suffer from the inevitable damage that the slice preparation imposes on axonal connections, especially in the outermost layers of the cortex, which may contain many of the intrinsic connections (Quilichini et al., 2010). Recent work in intact animals has indicated direct spike transmission between a small number of layer II neurons in MEC (Quilichini et al., 2010), suggesting that at least some of the principal cells in this layer must be strongly connected. However, quantitative connectivity estimates are still lacking, and the amount of recurrent wiring required to support bump formation and translation has not been determined. Future studies will likely show that attractor dynamics depend not only on the percentage of cells with direct connections but also on (1) whether the right cells—those with a similar spatial phase—are connected (Deguchi et al., 2011; Ko et al., 2011; Yu et al., 2009) and (2) whether sufficiently coincident activation can be achieved with indirect connections. Finally, should the layer II network not have the appropriate excitatory connectivity, attractors may nonetheless operate using more extensive recurrent connections in layer III (Dhillon and Jones, 2000) as well as rebound activation through interneurons (Witter and Moser, 2006). In support of the latter possibility, a recent attractor-network model of grid cells has shown that inhibitory recurrent connectivity is sufficient to support accurate path integration in the presence of excitatory feed-forward input (Burak and Fiete, 2009).

A Self-Organization Model

A recent model suggests that grid cells form by a self-organized learning process that naturally favors inputs that are separated by 60 degrees (Mhatre et al., 2010). Grid cells are suggested to receive input from "stripe cells," cells that fire in alternating stripes across the environment, very much like the band cells proposed as inputs to grid cells in some versions of the oscillatory-interference model (Burgess et al., 2007; Burgess, 2008). Path integration and grid formation occur in two steps in the Mhatre model. First, a one-dimensional ring attractor circuit is used to integrate velocity from incoming velocity signals such that the position of the moving activity bump in the stripe direction reflects the position of the animal along the stripe in the spatial environment. Then, in the second step, inputs from stripe cells self-organize in a competitive learning process to generate the hexagonal pattern of the grid cells. The self-organization is thought to take place as animals map environments for the first time postnatally. Initially, stripe cells with different orientations project nonspecifically to the target cells in MEC, but Hebbian learning mechanisms are then suggested to strengthen projections from cells that have orientations 60 degrees apart, at the same time as other orientations are weakened. No further velocity integration is needed in the second step.

The self-organization model borrows elements from both the oscillatory-interference and the attractor models but is unique in its emphasis on competitive self-organization as a mechanism for generating the grid signal. The model makes some clear predictions about this process. First, it depends critically on the existence of stripe cells. Cells in intermediate and deep layers of the MEC, as well as the parasubiculum, may occasionally fire more strongly along one of the grid axes than the two others, but nonperiodic band activity has not been reported in any of these regions so far. Furthermore, the model makes the clear prediction that a certain amount of spatial experience is necessary before grid patterns can be expressed. This suggestion is supported by simulations showing that inputs from stripe cells with randomized angular separations can generate stable hexagonal grid patterns after a few hours of exploration time. This is not incompatible with experimental data, as stable regular grid patterns only appear several days after developing animals start exploring spaces outside the nest (Langston et al., 2010; Wills et al., 2010); however, the limited data that exist suggest that grid formation is more dependent on the maturational stage of the MEC than the amount of experience (Wills et al., 2010). Finally, if stripe cells are identified in the future, it would be important to examine during development what happens to cells with nonpreferred orientations that lose the competition. Are these cells retuned to one of the three predominant orientations, or do they die out? Does the brain retain stripe cells that do not project to grid cells? If so, what would be their function?

A Path-Integration-Free Model

Whereas nearly all models for grid cells are based on path-integration mechanisms, one model stands out by suggesting that the formation of grid fields occurs with spatial rather than velocity-related inputs (Kropff and Treves, 2008). In this model, grid fields are formed by Hebbian self-organization in a competitive network, much like grid cells are suggested to emerge from stripe cells in the self-organized learning model of Mhatre et al. (2010). Neurons must include the crucial ingredient of an adaptation or fatigue dynamics, which makes the spacing of the resulting grid fields scale roughly like the average running speed multiplied by the time constant for adaptation. Although not explicitly evaluated in the model, the grid pattern could also be obtained with other kinds of temporal modulation of spike activity, such as changes in the time constants of spike repolarization, which are known to differ between dorsal and ventral MEC (Boehlen et al., 2010; Navratilova et al., 2011). A crucial prediction is a correlation between running speed and grid spacing, which is contrary to the apparent constancy of the grid scale when rats run at variable speed in an open

field (Hafting et al., 2005). However, a systematic test of this relationship has not yet been made. Finally, in contradiction with experimental findings, the grid fields of the model network have random orientations, but the authors suggest that grid orientations can be aligned locally by excitatory recurrent collaterals with ad hoc values of synaptic strength.

Cellular Mechanisms of Grid Formation

From the beginning, the oscillatory-interference models raised the possibility that grid patterns depend on properties of single cells such as membrane resonance and subthreshold oscillations (O'Keefe and Burgess, 2005). Such properties did not play a role in any of the network models until recently, when Navratilova et al. (2011) pointed to a possible role for after-spike conductances in the temporal dynamics of grid cells in the torus-based attractor-network model. Recent studies using in vitro whole-cell patch-clamp techniques have shown that several properties of individual cells correlate with the topographic expansion of grid scale along the dorsoventral axis of the MEC. Two sets of properties show such correlations, membrane resonance and temporal integration.

Resonant properties are highly topographically organized along the dorsoventral axis of MEC (Giocomo et al., 2007). The resonant frequency, which is the input frequency that causes the largest amount of membrane depolarization, changes from high in dorsal to low in ventral. Similarly, the frequency of sinusoidal and intrinsically generated membrane potentials changes from high in dorsal to low in ventral. A dorsoventral organization in resonant frequencies in vitro has now been observed across multiple ages (juvenile versus adult), different species (mice versus rats), and multiple entorhinal layers (layer V and layer II) (Boehlen et al., 2010; Giocomo and Hasselmo, 2008a, 2009; Giocomo et al., 2007), suggesting that oscillatory activity is closely associated with the formation of grid patterns. This possibility has recently received further experimental support from studies in behaving animals. Two concurrently published manuscripts demonstrated that pharmacological inactivation of the medial septum results in a complete loss of grid periodicity, correlating in time with the loss of theta rhythmicity (Brandon et al., 2011; Koenig et al., 2011). Whether the entire grid network or only a subset of grid cells depends on theta oscillations remains undetermined, however, as more than half of the grid cells in mouse MEC and in rat presubiculum and parasubiculum seem not to be significantly modulated by the theta rhythm (Giocomo et al., 2011; Boccara et al., 2010). Grid periodicity is likely dependent on input from the medial septum, but whether it is the theta rhythm itself that is important is still uncertain.

Membrane resonance is not the only electrophysiological property that changes along the dorsoventral axis of the MEC. The summation of excitatory postsynaptic potentials and the time window for the detection of coincidence inputs change from short in dorsal to long in ventral (Garden et al., 2008). These integrative properties depend on dorsoventral gradients in at least two ion channels, the hyperpolarization-activated cation current (Ih) and the leak potassium current (Garden et al., 2008). Complementing the change in the integrative properties of these neurons, the temporal dynamics of action potentials change along the dorsoventral axis, with the time constant of the spike after-hyperpolarization shifting from fast in dorsal to slow in ventral (Boehlen et al., 2010; Navratilova et al., 2011). The dorsoventral organization in spike repolarization time constants supports predictions from a recent attractor model including temporal dynamics to explain phase precession and grid spacing (Navratilova et al., 2011).

Both resonant and temporal-integrative properties depend on the presence of Ih (Giocomo and Hasselmo, 2009), which has a topographical organization in kinetics and density along the dorsoventral axis (Garden et al., 2008; Giocomo and Hasselmo, 2008b). Recent in vivo recordings indicate that properties dependent on Ih play a role in determining grid cell spacing (Giocomo et al., 2011). Mice that lack a subunit important for the conduction of Ih (HCN1) in entorhinal cortex show larger grid fields and larger grid spacing along the entire dorsoventral axis. The increase in grid scale is accompanied by an increase in the period of the theta modulation of the cells. Of crucial importance, the gradient in grid spacing is preserved in these HCN1 knockout mice in vivo (Giocomo et al., 2011), while the gradient in resonant frequency is abolished in vitro (Giocomo and Hasselmo, 2009). The previously reported correlation between in vitro resonant frequency and in vivo grid cell frequency along the dorsoventral axis supported predictions proposed by oscillatory-interference models; however, the continued presence of a grid scale in knockout mice that lack Ih currents is inconsistent with the idea that the frequency of intrinsic membrane resonance independently determines the spatial scale of grid cells (Giocomo et al., 2011). Instead, the increase in grid spacing and size along the dorsoventral axis in HCN1 knockout mice is consistent with changes seen in integrative properties with a reduction of Ih (Garden et al., 2008). The gradient in integrative properties systematically shifts with a loss of Ih in vitro (Garden et al., 2008), which is the exact same type of transformation as seen in grid spacing with the loss of Ih in vivo (Giocomo et al., 2011). Taken together, these observations identify HCN1-dependent variations in temporal integration properties as a candidate for the topographical organization in grid spacing. The mechanisms for the preserved gradient have not been determined, but other HCN subunits, such as HCN2 or the leak potassium current (Garden et al., 2008), might be critical.

Finally, it should be noted that the original oscillatory-interference model (Burgess, 2008; Burgess et al., 2007) used voltage-dependent changes in resonance, instead of the absolute frequency of the resonance, to generate a topographical organization in grid spacing. This version of the oscillatory-interference model predicted that any increase in grid spacing would be accompanied by a decrease in the modulation of the theta frequency and interspike interval by running speed (Burgess, 2008; Jeewajee et al., 2008). Consistent with this prediction, the loss of HCN1 results in a profound decrease in the modulation of the theta and intrinsic firing frequency by running speed (Giocomo et al., 2011); however, recent in vitro work demonstrating lack of systematic frequency changes in membrane-potential oscillations near theta frequency suggests that the voltage-dependent change must occur at the level of global, rather than single-cell, oscillatory processes (Yoshida et al.,

2011). The degree to which this in vivo reduction in the speed modulation of frequencies matches what would be predicted by the original oscillatory-interference models should be examined in future theoretical work.

Transformations between Grid and Place Signals

The strong direct projections from entorhinal cortex to the hippocampus implied from the beginning that place fields might be generated from the combined input of many grid cells (Fuhs and Touretzky, 2006; McNaughton et al., 2006; O'Keefe and Burgess, 2005; Solstad et al., 2006). Both computational and experimental studies have begun an attempt to parse out the mechanisms and nature of the interaction between space-responsive neurons in the hippocampus and entorhinal cortex.

The linear transformation of several grid fields can easily construct a localized pattern like the firing field of a place cell (Fuhs and Touretzky, 2006; Hafting et al., 2005; McNaughton et al., 2006; O'Keefe and Burgess, 2005; Solstad et al., 2006), and the hippocampal firing field would be expected to exhibit dorsoventral scale topography similar to that of the MEC (Brun et al., 2008; Kjelstrup et al., 2008). A mathematical model proposed by Solstad et al. (2006) mapped out the parameters required for the successful construction of a single place field. First, to avoid similar periodicity in the place signal as in the grid signal, it was suggested that the integration must occur across a moderate number of grid frequencies. Different frequencies then cancel out, and a single peak could be generated if the environment is not very large. The fact that dorsal hippocampal place fields decrease in size after lesions of the ventral and intermediate parts of MEC (Van Cauter et al., 2008) is consistent with the proposed convergence of input from grid cells covering a range of grid frequencies. Second, to produce multidirectional place fields and reduce extrafield place cell firing, most models integrate output from grid cells with more than one grid orientation onto each individual place cell (Molter and Yamaguchi, 2008; Savelli and Knierim, 2010; Solstad et al., 2006). The presence of variation in grid orientation in a single entorhinal hemisphere has not yet been experimentally demonstrated, but multiple orientations are not a critical feature for some of these models (Savelli and Knierim, 2010). Finally, it was emphasized in the Solstad model that the formation of a single firing location for a place cell requires alignment of the spatial phase of the contributing grid cells. While random grid cell inputs may in principle be sufficient to generate place-field responses (de Almieda et al., 2010), biological mechanisms exist that could support the mapping of MEC grid fields with similar spatial phases to a single hippocampal place field. Several computational models have applied classic Hebbian learning mechanisms to feed-forward networks in order to select inputs from grid cells that have overlapping spatial phases (Rolls et al., 2006; Savelli and Knierim, 2010; Si and Treves, 2009). Adding the precise temporal spiking characteristics of entorhinal and hippocampal neurons on top of Hebbian synaptic plasticity can further refine place cell selectivity. For example, the temporal code of entorhinal grid cells firing with theta phase precession provides a robust means to discriminate grid fields with perfect overlap from fields with partial overlap (Molter and Yamaguchi, 2008). The recent observation of hippocampal independent theta phase precession in grid cells (Hafting et al., 2008) suggests that the phase alignment required by the earliest grid-to-place transformation models is not completely unrealistic.

As an alternative to applying a threshold or modifying synaptic connectivity, a new model of grid-to-place cell transformations uses feedback inhibition within the place cell population to generate spatially specific patterns from periodic inputs (Monaco and Abbott, 2011). Correlated grid inputs form the basis of place cell activity in novel environments, which are refined by learning mechanisms as the environment grows more familiar. The model also parses the grid cell population into a modular spatial organization so that differently spaced grids project to place cells, which has the added benefit of providing a robust mechanism for global remapping in the hippocampus. Dramatic remapping was shown to occur with input from only two different grid modules, while more subtle remapping could result from changes in grid ellipticity or spatial rescaling. The model clearly demonstrates how a modular arrangement of grid cells would favor orthogonalization of representations in the hippocampus, which in turn could support the storage of large amounts of episodic information (Colgin et al., 2008). It will be a key objective for future experimental studies to establish the extent to which the grid map is modular, how many modules there are, and whether such modules operate independently.

Additional insight into the interactions between place cells and grid cells has recently been obtained from studies of the development of hippocampal and entorhinal functional cell types. When rat pups explore outside the nest for the first time, rudiments of grid cells and place cells are already present (Langston et al., 2010; Wills et al., 2010), suggesting that these spatial circuits may be at least partly hard-wired. However, place cells appear to have more adult-like characteristics than grid cells, which raises the possibility that grid cells are dispensable for the formation of place cells in young animals. A recent study with adult animals has shown that place cells can persist under conditions where the periodicity of grid fields is reduced as a result of medial septal inactivation (Koenig et al., 2011). However, because the grid cells and place cells were studied in different animals or, in one animal, in different hemispheres, it cannot yet be ruled out that a minimum of grid input was spared in those recordings that demonstrated intact place signals. It is not clear what alternative inputs could provide spatial signals to the hippocampus if no contribution is received from the grid cells; however, one possibility is that place cells obtain the necessary spatial information from entorhinal border cells (Savelli et al., 2008; Solstad et al., 2008), as proposed in early theoretical work (Hartley et al., 2000). Input from such cells may be sufficient to generate spatially localized activity. Another possibility is that grid patterns are present but difficult to visualize in time-averaged rate maps due to reduced spatial stability of neural activity in young and septum-inactivated animals. The jitter of firing may affect grid fields more than place fields, considering that the former are smaller. Finally, it is possible that the rudimentary periodicity of young grid cells, combined with Hebbian plasticity and phase precession, is sufficient to evoke localized firing in hippocampal target neurons.

The Extended Space Circuit

Following the discovery of grid cells in the MEC (Hafting et al., 2005), recent studies indicate the presence of a broader grid cell network in multiple parahippocampal structures. An abundant population of grid cells has now been reported in the pre- and parasubicular regions of the parahippocampal formation (Boccara et al., 2010). Compared to the MEC, pre- and parasubiculum have a higher percentage of grid cells conjunctive with a head direction preference, which may contribute to a slight reduction in the hexagonal periodicity of these grid cells compared to MEC grid cells. There are at least two possible mechanisms that could underlie the presence of grid cells in multiple parahippocampal cortices. First, the strong feed-forward projection from pre- and parasubiculum to MEC (van Groen and Wyss, 1990) gives rise to the suggestion that the MEC may inherit the grid signal from these input regions. This would require a complex wiring scheme based on minimal convergence between pre- and parasubicular cells with different grid phase, grid scale, or grid orientation. The transformation would also require a mechanism to enhance the hexagonal periodicity of inherited grids and to decrease the modulation by head direction for grid cells in the superficial layers of MEC. A more parsimonious explanation might be that different subregions generate grid cells locally. Medial entorhinal and parasubicular neurons share similar intrinsic properties such as persistent firing (Egorov et al., 2002; Yoshida and Hasselmo, 2009) and membrane-potential oscillations (Alonso and Llinás, 1989; Glasgow and Chapman, 2008), both of which have been used in computational models to generate grid cells (Burgess et al., 2007; Giocomo et al., 2007; Hasselmo, 2008).

Recent human work has raised the possibility that grid signals extend even further, beyond the parahippocampal cortex. Using fMRI, Doeller et al. (2010) reported direction-sensitive signals that are modulated in steps of 60 degrees, similar to the rotational symmetry of grid cells, in entorhinal cortex as well as parietal, temporal, and prefrontal regions. This six-fold symmetry was taken as indirect evidence for grid cells in these areas in humans. The extrapolation of grid patterns from rotationally symmetric blood oxygen level-dependent signals is based on some assumptions, however. For example, directional modulation of the signal would only be seen if the majority of the grid population shares the same spatial orientation and the preferred directional firing rate is aligned to one of the grid axes. This assumption receives experimental support from an analysis of conjunctive grid cells from rats in the same study (Doeller et al., 2010), but the data set is small, consisting of 18 grid cells. It remains unknown whether such directional alignment holds for the entire population of grid cells. Another assumption is that both speed and direction modulate activity. The rat data from the Doeller study support this assumption, but no work has yet been published indicating the presence of grid cells in the other cortical regions where six-fold rotational symmetry was inferred in the Doeller study. It is possible that the rotational symmetry in the fMRI scans instead reflects a periodic response in the population of head direction neurons, which are found in abundance throughout much of the posterior cortex (Taube, 1998), and perhaps also in humans (Baumann and Mattingley, 2010). No current evidence, however, indicates the presence of head direction cells with preferences tuned to 60 degree intervals (Boccara et al., 2010).

At the same time as several parahippocampal cortices have now been shown to contain strong spatial signals, the entorhinal cortex itself seems to be functionally divided. Compared to MEC, neurons in lateral entorhinal cortex (LEC) do not normally show strong spatial specificity (Hargreaves et al., 2005), even in contextually rich environments (Yoganarasimha et al., 2010). However, these nonspatial signals from LEC combine with spatial information from MEC in the hippocampus and contribute to environment-specific place representations there. In the dentate gyrus and CA3, inputs from MEC and LEC target different dendritic segments of single neurons, suggesting that these neurons form representations that include both location and events or features associated with the location (Leutgeb et al., 2005). In contrast, in CA1, the combination of spatial and nonspatial information is anatomically organized, with MEC projecting preferentially to proximal CA1 and LEC projecting preferentially to distal CA1 (Naber et al., 2001; Tamamaki and Nojyo, 1995; Witter et al., 2000). This results in a transverse organization of spatial firing, with the number of place fields and amount of dispersed firing increasing from proximal to distal CA1 (Henriksen et al., 2010).

Unlike the grid cells and the head direction cells, the border cells of the MEC may possibly extend into the subiculum. Studies of neural activity in this region have reported that approximately 25% of the cells fire in a single allocentric direction and at a specific distance from an environmental boundary (Lever et al., 2009). These cells were referred to as "boundary vector cells" based on prior theoretical work predicting such neurons. The existence of boundary vector cells was postulated after recordings of place cells demonstrated that when an enclosure is stretched, place cells remap to a new location but the firing field remains at the same distance relative to the stretched wall (O'Keefe and Burgess, 1996). This finding was explained by proposing that a population of boundary vector cells encodes the animal's distance from salient geometric borders and that inputs from such cells combine to generate place cells in the hippocampus (Hartley et al., 2000). The subsequent observation of boundary vector cells is consistent with this proposal. But are the boundary vector cells of the subiculum distinct from the border cells of the MEC (Savelli et al., 2008; Solstad et al., 2008)? Many border cells do have properties that differ slightly from the theoretical definition of boundary vector cells. For example, some border cells fire along only a portion of the environmental borders, while boundary vector cells would fire across the entire length. Regardless, boundary vector cells and border cells may serve similar functions by stabilizing grid cells and contributing to the formation of hippocampal place fields. The near absence of feed-forward connectivity from the subiculum to the hippocampus (Witter, 2006; Witter and Amaral, 2004) makes it plausible that entorhinal border cells play a more direct role in place cell formation, but border cells may inherit some of their spatial features from upstream boundary vector cells.

Functional Implications of the Grid Code

What is the encoding capacity of the grid cell network, and what is the spatial range that unique patterns of activity can

represent? The presence of many neural populations with different spatial periods (grid spacing) in dorsal MEC results in the capability of multiple grid cells to uniquely specify a precise location in the environment over a much larger range than any individual grid period (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Solstad et al., 2006). The precise capacity for spatial encoding and tolerance to encoding error (noise) can be investigated by interpreting the grid network as a two-dimensional equivalent of a modulo operator (Fiete et al., 2008). When active, the vertex of any given grid cell can be represented as a phase, which is calculated by integer division of the rat's position by the lattice (grid) period. The dorsoventral increase in grid spacing results in the presence of multiple neural subpopulations with different lattice periods. The current position of the rat can then be more precisely represented as the collective set of phases determined from the active set of neurons. Using this phase code to represent the grid cell network allows the theoretical demonstration that the grid code is vastly more efficient than a place code, resulting in a smaller number of neurons encoding a larger amount of space (Fiete et al., 2008). A modulo code of the grid network can uniquely represent 2000 m of environmental space with 6 cm resolution in each linear dimension (Fiete et al., 2008), an area well matched to the range covered by a rat during foraging (Recht, 1988; Russell et al., 2005). On the other hand, the place code in the hippocampal network would only be able to cover a maximum range of 20 m of environmental space. The excess capacity of the grid network, resulting from the extreme efficiency of periodic phase coding, can support the redundant expression of the same information. The redundant expression of spatial information reduces phase error and provides a high degree of tolerance to noise in the network (Fiete et al., 2008). In addition, representing location as a set of phases or remainders calculated from modulo division of a fixed set of lattice periods resembles a known encoding system, the residue number system (RNS) (Fiete et al., 2008). Mathematical properties of the RNS, or modulo code, allow a change in the location of the rat to update the phase code of all grid periods in parallel, reducing the computational complexity required by the network and facilitating efficient position updating. How precisely downstream networks could decode a modulo code remains undetermined, but future development of computational models may provide possible implementations of decoding schemes (Sun and Yao, 1994).

Additionally, very large spaces may be represented by mosaics of smaller spatial maps. Accumulating experimental evidence suggests that entorhinal maps consist of fragmented submaps instead of a single universal representation. In recordings of grid cells from animals running in a zigzag pattern through a square box broken into ten parallel corridors, grid cells did not exhibit the typical periodic hexagonal firing pattern observed in the open field (Derdikman et al., 2009). Instead, the grid pattern broke up into repetitive periodic representations generated in each corridor of the maze, resulting in repeating patterns across the alleys of the maze. Abrupt resetting of the pattern occurred at the turning point between each corridor, suggesting that salient landmarks or environmental features may reset the periodic pattern, resulting in a fragmented map. Based on the ability of the grid pattern to fragment in a complex environment, the encoding capacity of the grid network might also increase by representing environments as mosaics of smaller spatial maps (Derdikman and Moser, 2010; Derdikman et al., 2009). In large environments, smaller maps may split along salient environmental borders or features. Readout of location from multiple map fragments may then rely on a mechanism or brain system substantially different from the metric readout of grid and place cells.

Finally, a functional understanding of grid cells would need to incorporate the fact that natural environments have a three-dimensional topography that is very different from the flat, unconstrained surfaces that rodents explore in the laboratory. A recent paper probed how grid cells map to the vertical dimension by requiring rats to explore a helix-shaped track as well as a vertical surface lined with protruding horizontal pegs (Hayman et al., 2011). In these environments, grid fields appeared as vertical columns, suggesting that grid cells do not differentiate between x,y positions with different z coordinates. However, it cannot presently be ruled out that periodic fields would reappear if animals are allowed to move continuously in the vertical plane, in the same way that they move on horizontal surfaces. Another possibility is that the scale of grid cells is larger in the vertical plane and that the column structure simply reflects a stretched grid with a significantly larger field size. Testing these possibilities is challenging but may be possible in species other than rats and mice.

Future Directions

Our understanding of spatial representation in the hippocampal-entorhinal system has been strongly influenced by computational models. Models have proposed possible mechanisms for formation and transformation of spatial firing patterns, and they have constrained the ways in which such patterns can be generated in circuits with known properties. Each model that we have described makes a number of testable predictions, but verification and falsification have so far remained indirect in that the experimental evidence is mostly correlational and subject to multiple interpretations. With the development of more sophisticated experimental methods during the next few years, the interaction between theory and experiment will likely be strengthened. Direct testing of models of grid cells may require quantitative analysis of the intrinsic dynamics and connectivity of individual neurons, and it may be necessary to activate as well as inactivate specific inputs to these neurons. Detailed information about neural network structure, and manipulation of this structure, may be critical. While technology for such interventions is still under development, it is important that computational models spell out their predictions clearly to provide a fundament for definitive testing as soon as the methods are available.

Computational models have been particularly important in the search for mechanisms of grid cells. Theoretical models have for example highlighted the potential role of multiple single-cell properties, such as oscillations and after-spike dynamics, in grid cell formation. With the introduction of in vivo whole-cell patch-clamp and optogenetic methods, the role of these properties can be tested. Direct and controllable manipulation of intrinsic oscillation frequencies, the timing of synaptic inputs,

or the spiking dynamics of identified grid cells would provide paramount insight into what mechanisms contribute to the formation of spatially responsive neurons. Similarly, network models make strong assumptions about the architecture of the grid cell circuit, but whether the wiring has a Mexican hat pattern or whether connections are circular are examples of questions that cannot be tested until connections between functionally identified neurons can be traced at a large scale. It is possible that a combination of virally based tagging methods and voltage-sensing optical imaging approaches may get us to this point in the not-too-distant future.

Computational models have also offered potential mechanisms for transformation of spatial signals between subsystems of the entorhinal-hippocampal circuit. Current models provide a starting point, for example, for testing hypotheses of how a periodic entorhinal representation might transform into a nonperiodic hippocampal representation. With emerging technologies such as optogenetics (Yizhar et al., 2011) and virally based tagging (Marshel et al., 2010), it will soon be possible to address the functions of specific inputs to the hippocampus, for example by manipulation of specific spatial wavelengths of the grid signal. New studies will also improve our understanding of interactions that occur within individual brain regions. Anatomical evidence now strongly hints at a modular organization of entorhinal cortical neurons. But what physiological properties or cell types would the anatomical modules correlate with, and how would the individual modules interact to form a cohesive representation of the environment? Existing computational models consider only one or two cell types at most, and none of the current models integrate outputs from border cells, grid cells, and head direction cells. Are grid cells shaped by border cells or vice versa, and do border cells and grid cells provide parallel inputs to place cells? If so, are the same place cells influenced by the two entorhinal cell types; do properties of place cells depend on the source of the entorhinal input? What would the system be capable of in the absence of one but not the other cell type? It may be crucial for future models to consider the relative role that all spatially responsive cell types may have in supporting path integration and place responses.

Neural-code transformations may occur not only between grid and place cells but also between upstream cortical neurons and spatially responsive entorhinal neurons. One possibility is that, similar to other sensory cortices, the more complex grid pattern arises from the combination of several simpler inputs. Comparable to the transformation between concentric receptive fields in the retina and linear receptive fields in visual cortex, grid cells could result from the combination of elementary cells that fire in bands or stripes throughout the environment. These "band" or "stripe" cells have yet to be reported experimentally but have been predicted by computational models to exist in cell populations that project to entorhinal grid cells (Burgess et al., 2007; Hasselmo, 2008; Mhatre et al., 2010). If such simple cells exist, then the integration of inertia signals, optic flow, and proprioceptive cues might occur one step before the construction of the grid cell representation. Future work aimed at understanding the nature of the inputs to spatially responsive entorhinal neurons could begin to provide fundamental insight into the functional role and mechanisms of spatial representations.

Finally, while much work has focused on understanding the mechanisms underlying the physiological properties of entorhinal cell types and the transformation of these signals between brain regions, what are the computational benefits of these spatial properties? How is the hexagonal grid structure used for navigation and foraging? What is the advantage of a scaled representation? What is gained by transforming the grid signal in the entorhinal cortex to a place signal in the hippocampus? Can grid cells be used for additional computations, and are such additional functions more extensive in humans? Again, theoretical models have built a framework for testing ideas about the function of the various cells in the spatial network. However, experimental work has yet to nail down the precise function for the specific attributes of these spatial representations. Unfortunately, we may be limited in our answers to these functional questions until we reach a better understanding of how the spatial signals in the MEC and hippocampus are read out by downstream structures. The mechanism of readout from place cells and grid cells, and the transfer of positional information to circuits involved in planning of navigational movement, should be an important target for future computational models.

Understanding the brain's coding scheme for space may provide insight into the computational constraints and priorities of neural information processing in general. The reliability of the grid and place signals, and the relatively well-described connectivity between them, justifies the hope that general principles of pattern formation and pattern transformation can be extracted from studies of these cells in the years to come.

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