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COMMENTARY

Grid Cells: The Position Code, Neural Network Models of Activity, and the Problem of Learning

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ABSTRACT: We review progress on the modeling and theoretical fronts in the quest to unravel the computational properties of the grid cell code and to explain the mechanisms underlying grid cell dynamics. The goals of the review are to outline a coherent framework for understanding the dynamics of grid cells and their representation of space; to critically present and draw contrasts between recurrent network models of grid cells based on continuous attractor dynamics and independent-neuron models based on temporal interference; and to suggest open questions for experiment and theory. © **2008 Wiley-Liss, Inc.**

KEY WORDS: grid cells; place cells; navigation; encoding/decoding; theory; entorhinal cortex; hippocampus

INTRODUCTION

The surprising and delightfully geometric nature of the response of grid cells in the dorsocaudal medial entorhinal cortex (dMEC) to rat position, as reported by Hafting et al. (2005) and summarized below, has sparked numerous intriguing questions for both experiment and theory: What do grid cells encode? What properties make the grid cell code useful for downstream readouts and behavior? What are the roles of hippocampus and grid cells and their interactions in performing spatial computations? What kinds of neural systems can generate regular firing patterns as a function of rat position? How robust is the phenomenon: that is, how finely must parameters be tuned to produce stable grid responses? During development or through learning, how is the requisite network connectivity established? What, if any, is the role of gamma and theta oscillations in all of the above?

Behaviorally, rats have a rich navigational repertoire. They forage for food over 50–100 m per linear dimension per day before returning to a well-defined home base, and their range can extend over 100 m^{-1} km (Jackson, 1982; Stroud, 1982; Recht, 1988; Miller and Clesceri, 2002; Russell et al., 2005). To locate themselves in such large environments, they must have the ability to form mental representations of a large set of positions distributed over great distances. In small enclosures, rats are able to perform straight-line homing following random outbound paths (Whishaw and Maaswinkel, 1998; Maaswinkel et al., 1999; Etienne et al., 1998, 2000; Etienne and Jeffery, 2004), even in the absence of external sensory cues. Similarly, they can compute the straight path home following an outbound journey in a covered L-shaped passage (Etienne et al., 1996). This homing ability implies that rats can cumulatively sum idiothetic (self-motion) cues to estimate their instantaneous location relative to a home base, and construct a vector pointing from their instantaneous location to home. Grid cells may form an important piece of the neural substrate for these navigational computations (Parron and Save, 2004; Steffenach et al., 2005).

The list of questions given above may be divided into the broad categories of "Why?" and "How?." The "Why" question asks why the rat's brain might represent information about its position in space using the grid cell code rather than some other encoding strategy. To rephrase the question less ontologically, what properties of the grid cell code make it useful for the representation of position and for the computation of position-related quantities? In principle, the peculiarities or features of a code can shed light on the computational priorities of the encoder and on the possible downstream uses of the encoded information. In fact, various unique features of the dMEC code suggest, independently of dynamical considerations, that grid cells may be the primary repositories of abstract positional information in general environments, and that they may constitute the idiothetic path integrator.

The "How" question addresses mechanism: how must the network be wired to generate grid cell responses, how do the dynamics emerge from such connectivity, and how might such connectivity be established in the first place. Because the properties of the grid cell code, explored in response to the "Why" question, strongly suggest that a central function of grid cells is to integrate idiothetic cues, and because rats are capable of dead-reckoning or path-integrative behaviors, we explore whether under biologically realistic conditions different mechanistic schemes for grid cell activity can produce appropriately accurate location estimation based on velocity inputs.

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The review begins with a brief summary of grid cell responses, as measured by experiment. We then summarize results on the computational properties of the grid cell code, and the implications of these properties for computations that may be performed within dMEC and in readout areas. Next, we describe different dynamical models of the grid cell response and discuss whether they are consistent with and explanatory of known properties of grid cells and rat navigation under biologically plausible assumptions. We compare the requirements and predictions of the different models with each other and with biological reality. It is our hope that a critical review will spark more thorough investigations of biological plausibility across models and between models and experimental data. We conclude with a brief, high-level view of the relative roles of hippocampus and grid cells in representing space, and some open questions for experiment and modeling.

BACKGROUND AND EXPERIMENTAL OBSERVATIONS

We begin with an overview of the experimentally measured grid cell properties (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006; Barry et al., 2007), which are particularly relevant for the computational work reviewed here. At present, the typical behavioral protocol for neurophysiological recordings involves rats running freely in enclosures, foraging for randomly scattered food pellets. In most experiments, the enclosure measures 1–2 m per side, and a cue-card attached to the wall provides a global orienting cue to the rat. Recordings are made in dMEC by tetrodes that capture multiple single-unit extracellular neural responses. Grid cells have also been found in mice (Fyhn et al., 2008) and are likely to be found in other animals as well (Bingman and Sharp, 2006; Ulanovsky and Moss, 2007; Kahn et al., 2008).

Individual grid cells fire when the rat is at multiple locations, corresponding to every vertex of a virtual triangular lattice overlaid on the floor of the enclosure, Figure 1A. The periodicity of the cell's response appears to be independent of the size and shape of the enclosure (Hafting et al., 2005): thus the scale of the neural grid response is set by intrinsic, rather than extrinsic, parameters. Barry et al. (2007) find that when an environment is suddenly expanded, a grid cell's period changes, but the change occurs when familiar enclosures are suddenly re-sized, and is temporary.) The rat moves at variable speeds with decelerations near walls or food pellets, and it frequently revisits the same locations following different paths, while the locations of a neuron's firing fields in space remains regular and unvarying. Thus, rat velocity does not greatly affect the placement of the grid vertices, and the grid response is independent of the rat's path. Neurons in layer II have relatively little sensitivity to the speed or head direction of the rat (Hafting et al., 2005), while the grid firing of neurons in layer III and deeper layers is significantly modulated by the rat's speed and heading direction (Sargolini et al., 2006). The lattice response is not distorted

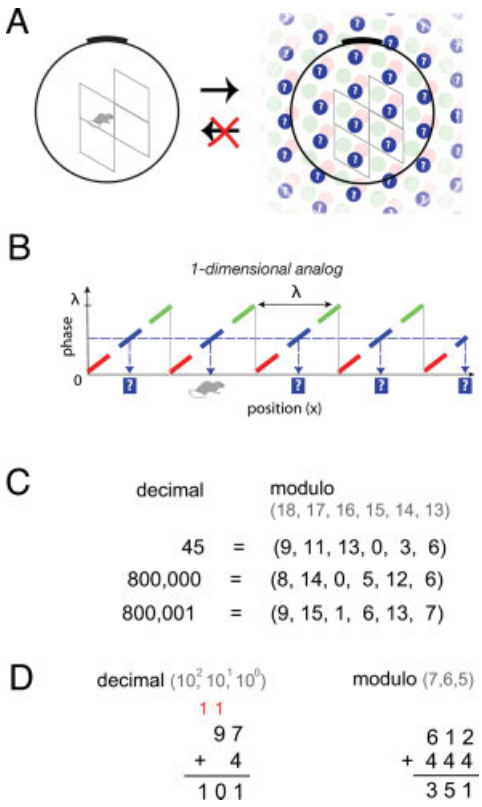

FIGURE 1. Coding of position by grid cells. (A) When the rat explores the enclosure (left, with the top thick bar representing the cue card) its instantaneous position corresponds to the firing of one set of neurons (blue) in dMEC (right), for each grid population. The active (blue) set of neurons defines the phase of the rat position in the lattice unit cell, as opposed to other phases (red and green), but cannot specify which unit cell the rat is in. (B) shows the 1-d analog of (A) the blue cell fires when the rat is at location x_0 or any location $m \cdot \lambda + x_0$, separated by an integer number m of lattice periods λ. The phase of the blue cells differs from those of the red and green cells. Thus, each grid population represents rat position as the modulo remainder following integer division by the grid period. (C) In the modulo system, the periods (registers) can be of similar sizes without sacrificing the combinatorial representational capacity. All registers are important for representing numbers at all scales: the number 45 and the number 800,000 involve all the registers: in this sense, the representation is "whitened." When the number 800,000 is incremented by one, all the registers increment; in fact, the modulo representation is maximally distinct for similar locations, providing a highly decorrelated representation of position at nearby locations. (D) Parallel, carry-free position updating. Register-based representations like the fixed-base number systems (including decimal and binary) require carry operations when two numbers are summed and a register wraps around (left). The same two numbers summed on the right in the modulo representation also produce wrap-arounds in the registers; however, no carry operation is needed, and it is easy to verify that the result is indeed 101, represented in the modulo basis. Thus, different lattices do not need to pass information between themselves when incrementing their estimate of position based on movement updates. Adapted from (Fiete et al., 2008). The colors green, red and blue refer to light, medium, and dark gray respectively in the printed issue. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

near the enclosure boundaries, suggesting that the grid should exist in roughly unchanged form in much larger enclosures, if not indefinitely. The orientation of a neuron's grid response relative to the fixed external world can be rotated by moving the cue-card in the enclosure to another angular position on the wall (Hafting et al., 2005).

The period and orientation of the grid responses of neurons situated close to each other in the dorsolateral MEC strip are identical, up to the resolution of present experiments. Their responses differ from each other only in their spatial phases, that is, by translations of the grid along the plane (Hafting et al., 2005). Neurons that are farther apart have different lattice periods, with the period increasing monotonically toward the ventral end of dMEC. The periods, as measured in 2-d enclosures, increase from ~30 cm (dorsal end) to <1 m (halfway along the length of the strip) (Hafting et al., 2005). Extrapolating to the ventral end, we might expect periods of 1–10 m (Brun et al., 2008a). The firing field width at the grid vertices scales directly with the lattice period. It is unknown whether the gradation in the lattice period along dMEC is continuous or discrete.

Finally, the activities of grid cells are strongly modulated by a theta oscillation. Some grid cells (layer III) emit their spikes at a fixed phase relative to the oscillation (Hafting et al., 2006b), while others (layers II, and to some extent layers III and V) display prominent phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996; Hafting et al., 2008), firing at successively earlier phases of the theta cycle as the rat moves through a firing field.

Moser and Moser (2008) provide a more comprehensive overview of the physiological responses of grid cells and other cells in the entorhinal cortex.

POSITION CODING BY GRID CELLS

Hippocampal place cells have long been viewed as the primary encoders of the rat's location in space (O'Keefe and Dostrovsky, 1971). The firing of single place cells is tightly correlated with specific locations, and responses in 2-d enclosures are largely independent of the rat's path or the direction and speed of its motion (O'Keefe and Nadel, 1978). Moreover, the hippocampus plays a major role in various spatial learning and memory tasks (Eichenbaum et al., 1999; Sharp, 1999; Frank et al., 2000; Brun et al., 2002, 2008b), in which an intact hippocampus is critical (Morris et al., 1982; Moser et al., 1993, 1995). Yet, the hippocampus is also involved in a number of nonspatial tasks, including declarative memory, which need not include a spatial component (Eichenbaum et al., 1999; Sharp, 1999; Kishimoto et al., 2006; Broadbent et al., 2004; Parsons and Otto, in press) (but see (O'Keefe, 1999) for an opposing viewpoint). Consistent with the observed involvement of the hippocampus in nonspatial tasks, hippocampal place cells also possess more complex properties than simply representing space in an abstract (i.e., divorced from the particulars of specific locations) sense. Place field firing frequently depends not only on rat location, but also on context, with place cells failing to fire at the same location if the context under which the location is visited changes (Quirk et al., 1990; Anderson and Jeffery, 2003; Jeffery et al., 2003; Smith and Mizumori, 2006; Hayman and Jeffery, 2008). Context changes can include changes in distal landmarks or sensory cues, the color of the enclosure, and the behavioral paradigm or reward contingencies under which the space is visited. Place cell allocation within a space can also be nonuniform, or bunched around behaviorally salient locations (Hollup et al., 2001). As a population, place cells do not undergo a simple transformation (e.g., a coherent translation, shift, or expansion of all their fields) when context is varied or when an enclosure is re-sized. These and other observations have led some to propose (Eichenbaum et al., 1999; Sharp, 1999) that hippocampal place cells may not constitute the primary, abstract map of space in the brain, if such a map exists.

The entorhinal cortex is the primary gateway of cortical information flow to the hippocampus, including the major sensory inputs. Grid cell firing appears to be a considerably more invariant representation of space than place cell firing. Like many place cells, layer II grid cell responses are correlated with the rat's location, and are largely independent of the rat's path, direction, and speed. Unlike place cells, grid cell firing is independent of context, up to global (population-wide) phase shifts (Hafting et al., 2005; Fyhn et al., 2007). Environmental conditions like enclosure size do not typically affect the grid cell response, and changing global orientation cues produces coherent rotations in the responses of all grid cells (Hafting et al., 2005; Fyhn et al., 2007). These invariances suggest that grid cells may form the basis of an abstract, general-purpose representation of location in space. Yet from the perspective of neural coding, the grid cell code begs the question of why a variable (position in 2-d space) that can be fully described by just two numbers or coordinates is broken up by the brain into a set of periodic patterned responses using as many as 100,000 neurons (Amaral et al., 1990; Mulders et al., 1997).

This question is addressed by Fiete et al. (2008), by mathematically characterizing the relationship between the simultaneously recorded variables of rat position and grid cell firing, and using the characterization to observe that the encoding scheme has notable advantages for representing and incrementing rat position in the neural context.

The population response of all cells with the same period is invariant to translations of the rat in 2-d space by any integer multiple of the period along the primary axes of the grid, Figure 1A. In a 1-d analogue, the population represents the rat position x as a phase within a unit cell of the grid response or modulo remainder of x with respect to the grid period (Burak et al., 2006; Fiete et al., 2008), Figure 1B. This population code, in which a population of neurons of grid period 35 cm represents as identical rat positions of 10, 80, . . . , $(35m + 10)$ cm (where m is any positive integer), appears highly nonunique and thus wasteful. However, because dMEC contains neural populations with different periods, it is possible to use

the phases from different grids to uniquely specify different locations over a much larger range than any of the individual grid periods (Fuhs and Touretzky, 2006; Fiete et al., 2008). The total range of positions that can be uniquely represented by dMEC—its coding capacity—grows combinatorially (exponentially) with the number of different periods, and is vast even when knowledge of the actual phases is assumed to be uncertain (Fiete et al., 2008). Thus, viewed as a code over multiple independent populations of grids, the dMEC code is compact and combinatorial, even though the usage of neurons in single grid populations seems wasteful.

But beyond the qualitative insight about coding capacity that the characterization of dMEC as a modulo code affords, why is it useful? For instance, it may be tempting to instead view the dMEC code as analogous in some way to a 'Fourier transform'. Yet there are many reasons why the Fourier analogy is inaccurate: Instantaneous rat position in 2-d space is fully specified simply by a pair of numbers (scalars). A Fourier decomposition, on the other hand, is a decomposition of an entire 2-d function in space (e.g., a detailed image of a rat sitting in its environment), rather than merely a periodic decomposition of a number. (Straight away, the possibility of this type of encoding seems implausible because from whose vantage point would a rat obtain an image of itself in space?) Even if hypothetically, the brain were to encode rat position as an image of the rat in its environment, to specify a single object of a size L_{rat} in a space of size L_{range} using a Fourier basis, requires periods that range in size from L_{rat} to L_{range}. Yet the largest dMEC grid, estimated to be $\sim$10 m in period (Burak et al., 2006), is significantly smaller than rat ranges in the wild, with L_{range} of about 100 m (Stroud, 1982; Jackson, 1982), or even up to 1 km (Recht, 1988; Miller and Clesceri, 2002; Russell et al., 2005), per linear dimension per day. Blair et al. (2007) propose that the role of dMEC may be to serve as a periodic function basis set for general function representation. For the reasons just given, we do not believe that dMEC represents Fourier decomposition for use in position representation. It also seems unlikely, given that dMEC is not in the main visual processing pathway, and given that the grid phases are determined by rat position and increment with rat movement, that dMEC is providing a Fourier basis for the representation of viewed images and scenes.

By far the most important objection to the Fourier analogy is that it does not shed light on the specific computational features of the grid cell code, with respect to position representation. Yet, such properties do become apparent on considering the code as a modulo code. The resulting properties can be contrasted, for context, to the properties of a similar and more apt hypothetical alternative (compared to the Fourier analogy) for position representation: the fixed-base numeral systems (e.g., decimal or binary). The fixed-base numbers operate using a similar principle as the modulo code: they decompose the represented scalar into the remainders or phases of a small set of periodic registers of different sizes. In both modulo and fixed-base systems, the representation is compact because the largest representable number scales exponentially with the number of registers (periods). However, in a modulo code, all the registers or periods may be of similar size, instead of spanning the full dynamic range (L_{range}/L_{rat}) of the represented variable, as required in the fixed-base systems. Biologically, this means that no underlying parameter in dMEC need vary over several orders of magnitude, and explains why the range of periods in dMEC can be relatively small compared to the rat's behavioral range. It also means that the representation of position across grids is "whitened" or shared equally, so that all grids contribute equally to position representation at all scales, instead of one set being dedicated to large scales only, and another set to small scales only, Figure 1C, as in the fixed-base systems. Second, position increments may be performed by each register (or grid) without keeping track of whether and when any other grid phase has wrapped around. This is possible because modulo arithmetic is completely parallel across registers, and unlike the fixed-base systems does not require carry operations, Figure 1D. Biologically, despite the fact that one position variable is represented piecewise in many grids, the carry-free property means that there is no need for information passing between grids, and that each grid can perform its own share of position representation and updating independently, based on feed-forward inputs about rat motion.

These properties are characteristics of the position code measured in dMEC, and are independent of dynamical models of dMEC activity. Nevertheless, they do hint at the role of dynamics in dMEC. Ideal characteristics for a system intended to integrate and represent an analog variable with a large range include high capacity, and efficiency in performing the arithmetic computation of addition. A high capacity is important not only to encode the full range of the variable, but to do so with high resolution, a necessary condition for minimizing the inevitable rounding-off errors that result from any finite-resolution representation, which in an integrator will accumulate over every time-step and rapidly swamp the integrated variable. Efficient arithmetic is defined as the existence of algorithmic and computationally fast rules for incrementing the integrator state in response to input. The dMEC modulo code possesses both these properties, hinting, without considering dynamics, that dMEC may be the neural path integrator and the primary locus of abstract position representation in the rat brain.

Even though the observation, that the dMEC code is a modulo code for position, cannot be "wrong" because the modulo operation is simply the mathematical name for the observed relationship between rat position and grid cell firing, it could certainly be deemed relevant or irrelevant. The rest of the rat brain may not utilize any of the modulo properties of the dMEC code. For example, the multiple grids may not be exploited to distinguish or uniquely represent locations separated by a greater distance than the size of a single grid, as possible with the modulo code. Instead of the responses of grid cells of different periods being read out in parallel, they may be read individually, with each grid individually specifying rat position in a separate small (e.g., one grid period in diameter or smaller), disjoint, subregion of space. Another alternative is that the grids are all used in parallel, but merely to redundantly

represent position in the same small region of space, at different levels of resolution for each grid, where the overall region size is comparable to the scale of individual grid periods.

Ultimately, the characterization of the dMEC representation of position as a modulo code is relevant if it is shown that many grid scales simultaneously play a role in position representation at all scales, and that multiple grids are used simultaneously and cooperatively by the brain to uniquely specify location at scales much larger than any single grid period. The question of whether the brain exploits the modulo properties of the code, when considered in the context of specific possible downstream readout schemes, leads to predictions that may be tested by experiment (Fiete et al., 2008).

DYNAMICS

Here, we address what is known about the "How" question. Existing models fall into two classes: recurrent network models based on continuous attractor dynamics (Fuhs and Touretzky, 2006; Burak and Fiete, 2006; McNaughton et al., 2006; Guanella et al., 2007; Burak and Fiete, 2008), and essentially single-cell feed-forward models based on temporally interfering waves (O'Keefe and Burgess, 2005; Burgess et al., 2007; Burgess, 2008; Hasselmo, 2008; Blair et al., 2008; Giocomo and Hasselmo, 2008). Both classes of model rely on precise established patterns of velocity-modulated inputs to the network, and produce position-coded responses. Thus, they are built on the premise that the grid cell network is the idiothetic path integrator, which converts motion cues into position estimates. However, the model classes differ on essentially all other fronts. We will focus on continuous attractor models, and discuss the temporal interference model to contrast its requirements and predictions with the vastly different set of requirements and predictions of the continuous attractor models.

Although we will not describe it in detail in this review, we mention for completeness that a companion article in this issue contains an altogether different model for grid cell dynamics (Kropff and Treves, 2008). The model is not based on the premise of path integration. Rather, it takes as a primitive the position-coded activity of place cells, and assumes that this position-coded information is the primary input to dMEC. Using competitive network-level inhibition and a neuron-level adaptation (fatigue) mechanism, Kropff and Treves (2008) demonstrate how a broad position-coded input (the sum of many place fields with different preferred locations) may be converted into a periodic output. This model is intriguing in its distinctness from existing models, but a conceptual problem with understanding dMEC response within its framework is that it suggests no obvious functional role for dMEC. A motivation for this alternative model is that attractor models require a large number of neurons to perform path integration. However, this model requires more neurons than the independent-neuron (temporal interference) models, and unlike any of the models whose primary inputs encode the animal's velocity, the model network does not appear to compute anything "new" in the sense that its inputs are already position-coded. A major model premise is that place fields are primitive to grid cells. This premise is in contrast to most other models of dMEC, in which place cells are proposed to be formed by summing grid cells (O'Keefe and Burgess, 2005; Fuhs and Touretzky, 2006; Solstad et al., 2006; Rolls et al., 2006; McNaughton et al., 2006; Molter and Yamaguchi, 2007), and to some existing studies of the hippocampal formation suggesting that place cells inherit many of their response characteristics from grid cells and other subcortical structures (Vertes and Kocsis, 1997; Vertes et al., 2001; Pan and McNaughton, 2004; Hafting et al., 2008), rather than the other way around. The relative primacy of grid vs. place cells can be tested by lesion and perturbation studies, in the absence of highly spatially informative external sensory inputs.

We now return to consider in more detail the models based on the premise of path integration. The maximum range of accurate dead-reckoning behavior has not been determined, and it is likely that over long distances, rats use external sensory cues to correct their integrator state. However, rats are known to perform accurate dead-reckoning without the help of external sensory cues over trajectories of at least a few meters (Maaswinkel et al., 1999). Models of dMEC based on the premise of path integration must therefore be able to accurately integrate velocity inputs over at least this range, without the help of external positional resetting inputs. It's possible that rats can perform idiothetic integration over larger distances, and under the path integration premise of both classes of models, as well as the fact that in the models, the velocity inputs are exact reflections of rat motion, means that the range of demonstrated idiothetic path integration in rats is a strict lower bound on how accurate these models must be. The sharpness of the $\sim$1 m-sized features (blobs, periods) in the observed single-neuron grid patterns, which are visualized after summing over several hundred meters of cumulative trajectory length, provide additional clues on the accuracy of the grid cell phase update mechanism. As described below, different mechanistic models of the grid cell response involve assumptions of varying levels of biological plausibility, and explain grid cell activity with significantly varying degrees of success.

CONTINUOUS-ATTRACTOR MODELS

Recurrent network models of grid cells (Fuhs and Touretzky, 2006; Burak and Fiete, 2006; McNaughton et al., 2006; Guanella et al., 2007; Burak and Fiete, 2008) are based on two elements: (1) strong recurrent circuitry within the network which drives the formation of a set of steady-state activity patterns, and (2) a velocity coupling mechanism, whereby velocity inputs generated by rat motion drive transitions between different steady-state patterns.

If each neuron has sufficiently strong Mexican-hat interactions with its neighbors, inhibiting a local set of surrounding neurons, the steady state of the network is a regular triangular lattice pattern of activity, with groups of active neurons on every vertex of the lattice (Murray, 1993; Fuhs and Touretzky, 2006; Burak and Fiete, 2006; McNaughton et al., 2006). If connectivity throughout the network follows the same rules, then all translations (phases) of the pattern are equivalent steady-states or "attractors" of the network dynamics. Thus, the steady states of the network include one pattern and all its translations. This set constitutes a low-dimensional continuous manifold of attractor states, depicted in Figure 2. In the absence of any perturbations, the network stays in the attractor state in which it begins. Perturbations that distort the pattern are unstable, and the pattern will rapidly relax to the closest point on the attractor manifold, Figure 2. Next, if rat velocity inputs are coupled to the network dynamics to drive a flow of the formed population pattern, the network state will move to another point on the continuous attractor manifold when the rat moves, Figure 2. Because motion inputs drive pattern flow, placing the network on another stable point in the continuous attractor manifold, an inherent feature of such networks is that they are capable of path integration (Seung, 1996), as long as the velocity-driven phase updates are accurate.

These two basic ingredients—the formation of a manifold of steady-state responses due to recurrent interactions, and a shift mechanism driven by velocity inputs for transitioning between steady states—form the basis for models of diverse neural integrator systems. These include the oculomotor integrator, which integrates velocity-proportional saccade command inputs or vestibular head movement inputs to produce the appropriate drive to eye muscles to stabilize the gaze (Lopez-Barneo et al., 1982; Robinson, 1986; Pastor et al., 1991; Seung, 1996; Seung et al., 2000); the head-direction system, which uses vestibular signals generated as the animal moves around to update an internal estimate of the direction in which the animal's head is pointing (Taube et al., 1990; Skaggs et al., 1995; Taube, 1995; Zhang, 1996; Goodridge and Touretzky, 2000; Sharp et al., 2001; Stringer et al., 2002; Xie et al., 2002; Taube, 2007), see Figure 3A; and models of hippocampal place cells, based on the hypothesis that the hippocampus is the locus of idiothetic path integration, in which a single local bump of neural activity is moved around by velocity inputs (Tsodyks and Sejnowski, 1995; Samsonovich and McNaughton, 1997; Tsodyks, 1999). Continuous attractor grid cell models are direct generalizations, from one dimension to two (Tsodyks and Sejnowski, 1995; Samsonovich and McNaughton, 1997; Tsodyks, 1999), and from a single-bump pattern to a multi-bump pattern, of the head direction cell model networks (Skaggs et al., 1995; Zhang, 1996; Goodridge and Touretzky, 2000; Xie et al., 2002; Stringer et al., 2002), Figure 3.

Although conceptually sound, existing models based on continuous attractor dynamics and the integration of velocity inputs have fared poorly under actual computational efforts to model grid cell responses. The first published recurrent network model of grid cells, by Fuhs and Touretzky (2006), contains

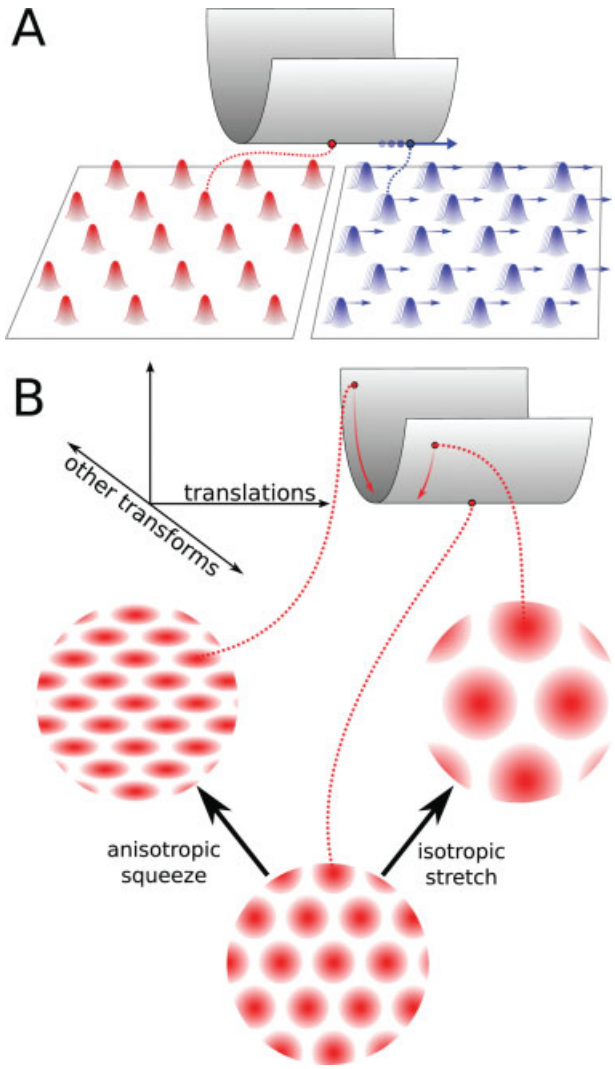

FIGURE 2. The state of activity in a neural network can be viewed as a point in a high dimensional state space. Under certain conditions, the state space may be represented by an energy surface. (A) The state space of a continuous attractor manifold. The set of steady or long-lived states forms a low-dimensional manifold, represented by the trough in the higher dimensional manifold (Seung, 1996). Other states decay rapidly, by flowing to the nearest point in the trough. In the context of grid cells, the ravine consists of a population activity grid pattern stabilized by the pattern formation process, and all its translations, (A) Points not in the trough include stretches, squeezes, or other global deformations of the pattern, as well as noisy corruptions, added local defects, or other local deformations of the pattern, (B). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the conceptual elements described above. The instantaneous population response of the network has clear triangular grids, and over short time-scales the population pattern does translate in response to velocity inputs. Nevertheless, the responses of single neurons, when simulated with the recorded trajectory of a rat (Hafting et al., 2006a) as input, do not display discernible spatial periodicity or patterning (Fuhs and Touretzky, 2006; Burak and Fiete, 2006; Touretzky and Fuhs, 2006). This is

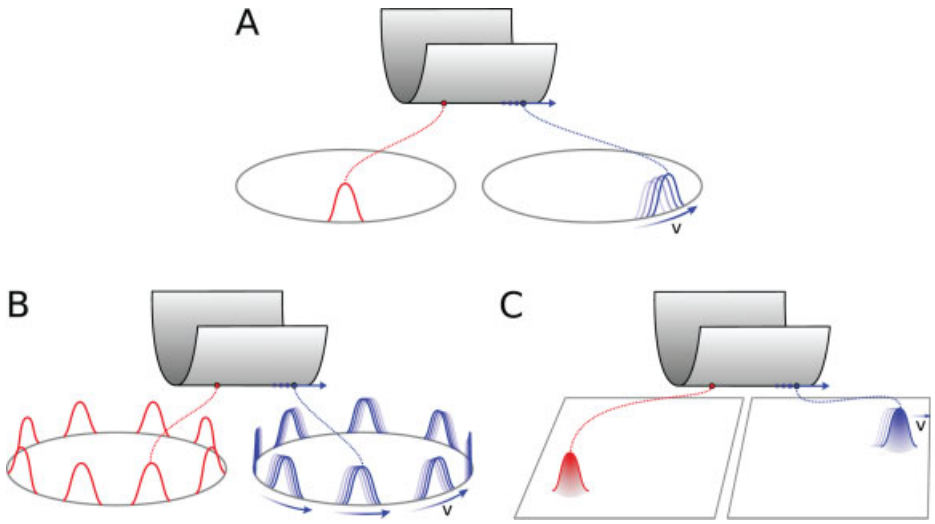

FIGURE 3. Shown are three examples of possible continuous attractor networks in the brain, all operating on the same principle. The primary differences in the examples are the shape of the stable pattern (unimodal (A, C) vs. multimodal (B)), and the dimensionality of the space in which the pattern is formed and of the associated attractor manifold (1-d (A, B) vs. 2-d (C)). A The head direction cells in the limbic system in rats can be modeled as a periodic 1-d continuous attractor network. The ring represents a "ring" of neurons, where the outlined red bumps represent the activity of the neurons. B An analog of the head-direction network but with each steady state pattern consisting of multiple bumps, which would result if lateral inhibition were local instead of global. C The idea in A can be generalized into two dimensions, creating a single two-dimensional bump of activity (Touretzky and Redish, 1996; Tsodyks and Sejnowski, 1995; Samsonovich and McNaughton, 1997). Translations on the plane are stable states along the bottom of the ravine of the high dimensional manifold. The grid cell network may be realized from C by restricting the range of the inhibitory connections to nearby cells, or from B by generalizing to two dimensions (Fuhs and Touretzky, 2006). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

because the pattern also rotates in response to velocity inputs, and because the velocity of pattern translation is not linearly proportional to the input velocity (Burak and Fiete, 2006). Next, Burak and Fiete (2006) and McNaughton et al. (2006) concurrently proposed that continuous attractor models of grid cells can be based on a simple Mexican-hat connectivity rather than the more complex, multi-modal weight profiles used by Fuhs and Touretzky (2006). However, neither of those works involved actual simulation of the dynamics of such networks, and therefore did not generate results on whether single-neuron responses would be grid-like. Thus, despite being labeled as models of path integration, some existing proposals do not demonstrate path integration ability, while some have explicitly been shown to not be able to path integrate (Fuhs and Touretzky, 2006; Burak and Fiete, 2006). More recently, a model by Guanella et al. (2007) uses periodic boundary conditions on the dMEC sheet, but finds that a modest amount of noise in the network destroys single-neuron grid responses, and requires frequent corrective input assumed from external sensory inputs. This failure of existing continuous attractor network models to produce periodic single neuron responses through path integration has contributed to enhanced interest in alternative explanations for the emergence of grid cell responses (O'Keefe and Burgess, 2005; Burgess et al., 2007; Hasselmo et al., 2007). But to discount continuous attractor dynamics as the explanation for grid cell activity is premature.

A very recent modeling effort (Burak and Fiete, 2008) provides the proof of principle that it is actually possible to reproduce sharp single-neuron responses with a clear grid structure purely through the integration of velocity inputs, even under realistic assumptions about network size and stochasticity. These results and the accompanying list of predictions, which are fully consistent with existing results on dMEC, argue that continuous attractor dynamics is likely to underlie grid cell activity.

What made it possible for Burak and Fiete (2008) to produce grid cell responses through the integration of velocity inputs, where other efforts did not succeed? First, they showed that obstacles to obtaining single neuron grids are fundamental in origin, in the sense that they are due to two generic structural properties of the attractor manifold: (1) In a network with aperiodic boundaries (i.e., where neurons at an edge are not near neighbors of neurons on the opposite edge), the attractor includes pattern rotations, not just translations. Unfortunately for the single neuron grid response, if the population pattern is allowed to rotate during rat movements, the single neuron response will not be patterned or periodic. (2) The attractor manifold is not truly continuous for all translations; the network boundary, interacting with the lattice period, produces a ripple in what would have been a continuous attractor manifold, meaning that some phases of the pattern are at a slightly higher "energy" than others; as a result, velocity inputs that are too small to overcome the energy barrier do not drive translation of the pattern, and do not result in a phase update. This means that small velocities are not integrated to reflect rat position updates. Either of these two effects, which are due

simply to the existence of boundaries and therefore cannot be eliminated in any finite-sized aperiodic network, will obliterate single neuron grids if they are large enough.

Once armed with the understanding that the network boundary plays a critical role in determining whether the network will have a linear and rotation-free response to velocity inputs, it became possible to greatly ameliorate the problem by selecting appropriate boundary conditions (Burak and Fiete, 2008). In particular, smoothly fading all inputs to the network near the network boundaries in a specific manner causes activity in those neurons to fade to zero without inducing significant distortions in the lattice pattern anywhere in the network. Such boundaries minimize the influence that boundary neurons exert on the bulk network dynamics, and dramatically improve the ability of the network to produce single-neuron grids. With appropriately smooth boundaries, aperiodic networks can accurately path integrate over ~10 min and ~100 m. It was also found that networks with periodic boundaries do not suffer from the problems inherent to aperiodic networks: namely, pattern rotations are not part of the attractor manifold, so the pattern does not tend to rotate; also, there are no barriers to pattern translation, meaning that the network responds with correct phase updates to arbitrarily small velocity inputs. As a result, the periodic network is quite robust over a wide range of parameters, and produces clean single neuron grids through the integration of velocity inputs (Burak and Fiete, 2008). Stochasticity leads to accumulating errors in the path integrated estimate of position even in periodic networks and the eventual destruction of single-neuron grids, but again, stochastic networks can integrate accurate velocity inputs over ~10 min and ~100 m without external corrective input to produce coherent single-neuron grid responses.

Contrary to concerns that in a periodic networks, the activity pattern representing the rat's location might "fall off" the network edge (McNaughton et al., 2006; Witter and Moser, 2006), we note that in any network with aperiodic boundaries but with a periodic activity pattern formed through dynamical pattern formation mechanisms involving local connectivity—this includes the network and simulations described originally in (Fuhs and Touretzky, 2006)—the grid automatically regenerates itself at the boundaries as the pattern flows by any amount. The regeneration occurs through the same purely local competition-based pattern formation dynamics that drove the initial patterning of the aperiodic sheet of neurons. In short, is not necessary to invoke periodic boundaries, where neurons on one edge of the sheet connect to neurons on the opposite end, to explain how the pattern would regenerate at the edges to potentially tile all 2-d space explored by the rat. Rather, the real problems introduced by network boundaries, as described above, are subtle but important for accurate path integration of trajectories of any length, and are an important part of the reasons why the network of Fuhs and Touretzky (2006) is unable to faithfully path integrate, even though the pattern automatically regenerates near one boundary as blobs of activity flow off the opposite boundary (Burak and Fiete, 2006). Periodic boundaries simply produce a more linear and rotation-free response to velocity inputs, enabling more accurate path integration (Burak and Fiete, 2008).

NETWORK TOPOGRAPHY

In the networks described above, nearby neurons have similar grid phases. But in experiments, nearby neurons recorded on the same tetrode do not necessarily display similar grid phases, suggesting that neurons in dMEC are not arranged topographically by phase (Hafting et al., 2005). If in the recurrent network models above, neurons and their pairwise connections were to be labeled by the indices i, j and weights W_{ij}, and if the locations of the neurons on the cortical sheet were randomly shuffled while retaining all labels and weights, the pattern of population activity, if viewed using wide-field cellular-resolution imaging techniques, would appear random instead of grid-like. Nevertheless, the single-neuron responses would remain grid-like, exactly as in the unshuffled network, because the network connectivity or weight matrix is unmodified. Clearly therefore, the nontopography observed in the neuron population in experiments is not a problem for the dynamical models themselves, per se. Instead, the problem is one of explaining how the connectivity required in these dynamical models may have been formed (discussed below, under 'Learning and the development of grid cell networks').

PREDICTIONS OF THE CONTINUOUS ATTRACTOR MODEL

One of the most basic predictions of the continuous attractor models is that the underlying network must display recurrent connectivity. Lateral inhibition is the key feature of connectivity because it is responsible (both necessary and sufficient) for the pattern-forming instability that generates a manifold of steady states (Burak and Fiete, 2008), while lateral excitatory connectivity is not necessary but can be included in models without qualitative modifications of the results. Although the exploration of microcircuitry in the entorhinal cortex is in its infancy, there is anatomical and functional evidence for extensive recurrent connections in dMEC (Dickson et al., 2000; Witter and Moser, 2006; Kumar et al., 2007). In layer II, where cells have grid responses, recurrent excitatory connectivity appears sparse (Dhillon and Jones, 2000); however, layer II neurons innervate layer III inhibitory interneurons, which influence the activity of the layer II principal cells (Jones and Buhl, 1993). This is in contrast to connectivity in layers III and V, where lateral excitatory connections are in abundance (Dhillon and Jones, 2000), and where grid cells with conjunctive head-direction and speed-modulated sensitivity are found (Sargolini et al., 2006).

In continuous attractor networks, all cells in the same network (i.e., connected neurons that share the same period) must

have exactly the same orientation (Fuhs and Touretzky, 2006; Burak and Fiete, 2008), but differ from each other in their preferred spatial phase. In fact, all phases must be exactly equally represented. Furthermore, any local defects or global distortions in the grid patterning of one cell should be exactly replicated in the responses of all cells of the network up to an overall phase shift (Burak and Fiete, 2008). These observations follow from the fact that in continuous attractor models, the response of any cell in the network is generated by translations of the same underlying population activity pattern. Existing experiments, in which neurons recorded on the same tetrode share grid spacing and orientation, but represent different phases with apparent statistical uniformity (Hafting et al., 2005), are consistent with these predictions. However, more detailed properties remain to be studied: for example, if a grid cell can be found with a clear defect in its response, then if all its neighbors display the same defect, it would constitute strong evidence in favor of the continuous attractor hypothesis (Burak and Fiete, 2008).

The essential signature of attractor networks is the firing relationship between neurons: A steady-state pattern or attractor is defined by the coactivations of groups of neurons. The dynamics of the network stabilize the patterns, maintaining the firing relationships between neurons even with stochastic inputs or network activity. Thus, in the continuous attractor model, the phase relationships between pairs of neurons should be stable over long periods, even in the absence of sensory inputs, and should not drift: two neurons with a difference in their spatial phase of x_{shift} should stably maintain that difference relative to each other (for any value of x_{shift}) (Burak and Fiete, 2008).

Because of the fact that all cells in a continuous attractor network will share the same period (and orientation), any two recorded cells with periods (or orientations) differing from each other must belong to distinct networks. The prediction is that dMEC consists of several subnetworks of cells, with each subnetwork having a particular period (and orientation) and all cells within the subnetwork sharing that period (and orientation). Thus, the different periods (orientations) that can be recorded from cells in dMEC must form a discrete set, not a continuum (Fuhs and Touretzky, 2006). In fact, given the number of neurons in each continuous attractor model grid cell network (Fuhs and Touretzky, 2006; Guanella et al., 2007; Burak and Fiete, 2008), and the estimates of the total number of neurons in dMEC (Amaral et al., 1990; Mulders et al., 1997), the total number of different lattice periods is likely to be no greater than 10–100 (Burak and Fiete, 2008).

COMPARISON WITH TEMPORAL INTERFERENCE MODELS

The second class of mechanistic models for grid cells is based on single neurons and temporally interfering oscillations (O'Keefe and Burgess, 2005; Burgess et al., 2007; Burgess, 2008; Hasselmo, 2008; Blair et al., 2008; Giocomo and Hasselmo, 2008). Examples of this class of model, the original of which is based on subthreshold membrane potential oscillations (MPOs) (O'Keefe and Burgess, 2005; Burgess et al., 2007), as well as numerous variants (Burgess, 2008; Hasselmo, 2008; Blair et al., 2008; Giocomo and Hasselmo, 2008), are discussed in detail in several other articles of this issue, so our goal is instead to briefly summarize the idea behind the temporal interference models and then focus on the differences in the requirements and predictions of the two model classes, the continuous-attractor based recurrent network models, and the single-cell temporal interference models. This section focuses on the MPO-based temporal interference models, although much of the discussion applies to temporal interference models in general.

Briefly, in the MPO version of the temporal interference model (O'Keefe and Burgess, 2005; Burgess et al., 2007), subthreshold MPOs of different frequencies in the soma and dendrites of a postsynaptic neuron interfere to produce a temporally periodic response. The temporal responses acquire the spatial characteristic of grid cells when two conditions are met: (1) The oscillation frequencies in each of the two or more major dendritic branches increase linearly with how fast the rat is moving in principal directions associated with each dendrite. When the temporal oscillation is viewed as an oscillation in space, the modulation of temporal frequency with rat speed keeps the spatial periodicity of the dendritic oscillation from varying with rat speed. (2) The principal directions of the dendrites are separated by 60 degrees. Each dendrite sums its MPO with the common somatic MPO, and the resulting dendritic signals multiplied together in the soma to produce a triangular grid pattern in space (Burgess et al., 2007). Spikes are produced whenever the somatic membrane potential reaches the firing threshold.

The temporal interference model is attractive, because it proposes an explicit role for the pervasive oscillations found in entorhinal cortex (Alonso and Llinas, 1989; Chrobak and Buzsaki, 1998). It also makes the interesting prediction that the theta oscillation frequency should decrease along the length of dMEC toward the ventral end, as a function of the increasing grid period (Burgess et al., 2007). This prediction has recently been verified by intracellular recordings from dMEC layer II stellate cells, which indeed show a systematic change in their MPO frequency along the length of dMEC (Giocomo et al., 2007).

But the temporal interference model in its present form has serious gaps. Most fundamentally, all temporal interference models (O'Keefe and Burgess, 2005; Burgess et al., 2007; Burgess, 2008; Hasselmo, 2008; Blair et al., 2008; Giocomo and Hasselmo, 2008) rely on an idealized conception of the interfering signals as pure, single-frequency coherent phase sine waves or otherwise perfectly phase-coherent periodic signals. Because of the dependence on the precise phases and frequencies of the input oscillations for formation of a spatial grid, the consequence of deviations from the ideal can be disastrous. Ex-

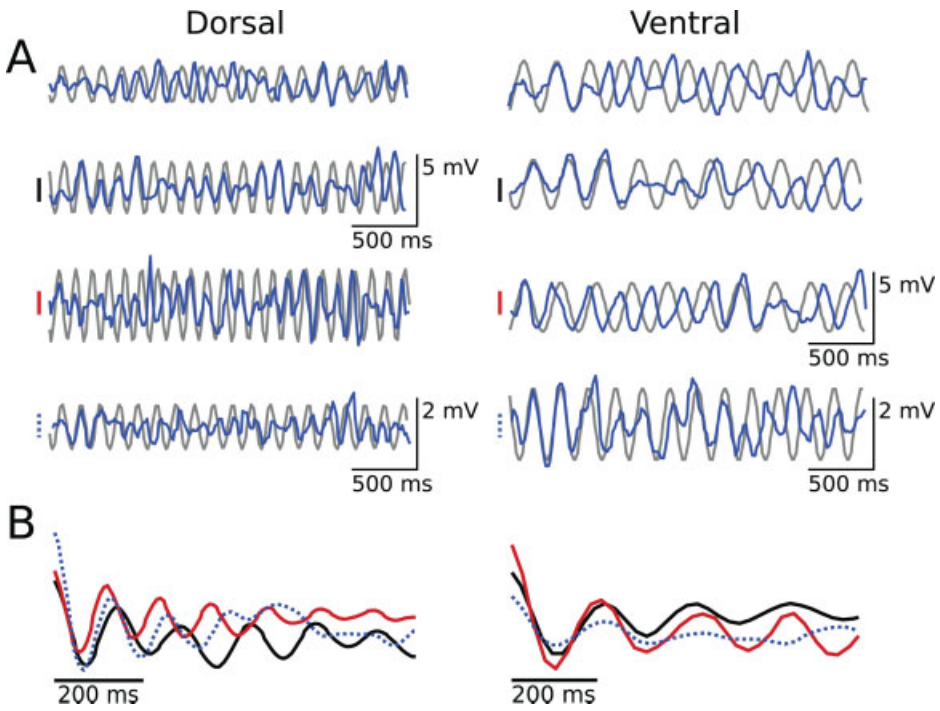

FIGURE 4. Instability of subthreshold membrane potential oscillations (MPOs) in dorsal and ventral dMEC. (A) Subthreshold MPO traces (blue) recorded by Giocomo et al. (2007) (adapted from (Giocomo et al., 2007)) displayed on top of pure sinusoidal signals (gray). The frequency of the sinusoids is derived in each case from the maximum in the Fourier spectrum of the corresponding recorded signal. The phase of the sinusoids is chosen by eye to match that of the first few periods of the experimental recording. It is clear that the MPO is unstable, with poor phase coherence: the frequency and phase change in less than a second. (B) Corresponding autocorrelations for the bottom six traces in A. Notice how most of the autocorrelations fade out after only 3–4 periods, quantifying the instability in A. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

perimental recordings of subthreshold MPOs in entorhinal cortical stellate cells show that the oscillation frequency and phase of the signal are far from ideal (see also the discussion of noise in the MPOs in (Giocomo and Hasselmo, 2008)). Figure 4 compares experimental intracellular recordings of subthreshold MPOs from Giocomo et al. (2007) with pure sinusoidal signals. Both the direct examination by eye, and the corresponding autocorrelation plots in Figure 4B show that the frequency and phase change over less than 10 periods (less than 2 s). In fact, the phase of the theta (and gamma) rhythm throughout the hippocampal formation tends to display skips and jumps, so that the temporal cross-correlation of the oscillation signal decays in only 3–4 periods, or less than 1 sec (Chrobak and Buzsaki, 1998). It does not appear plausible therefore that in the absence of external resetting cues, cells in the model network with realistic theta oscillations could produce a spatially periodic response over a path of length greater than 0.5 m (corresponding to $\delta t \cdot 1$ m/s, where $\delta t = 0.5$ s, and 1 m/s is the assumed maximum sustained rat running speed), a distance smaller than most of the grid periods. This problem arises from the inherent incoherency of the phase of the theta oscillation in the entorhinal cortex, even in the absence of any noise in neural responses or any deviation from the perfectly tuned relative angular velocity inputs to different dendritic branches of each neuron.

In defense of the temporal interference models, intracellular recordings to measure the MPO in grid cells have only been performed in vitro, and the poor phase-coherence of the oscillations may be a result of the preparation. In vivo MPOs may be significantly more phase-coherent. For the temporal interference model to remain a viable candidate mechanism for path integration and the generation of grid responses without external inputs, the In vivo MPOs would have to remain phase-coherent over the time-scale of a minute (or more), which corresponds to more than 360 cycles of the theta oscillations.

In addition to the dependence on idealized sine-wave theta oscillations, the temporal interference models are subject to essentially all the same tuning requirements as continuous attractor models. For instance, continuous attractor models of grid cells require specific input wiring that pairs neurons with outgoing weights shifted by θ° relative to each other with velocity inputs that have a similar angular separation (Fuhs and Touretzky, 2006). The temporal interference models require two or more sets of dendritic inputs to each neuron that are separated by 60° (Burgess et al., 2007). In both classes of models, these wiring constraints require learning mechanisms that have neither been analyzed computationally nor observed in experiment. Next, continuous attractor manifolds require that statistically speaking, connectivity within the network be trans-

lationally invariant: that is, the outgoing weight profile of all neurons of a given type in the network should be statistically similar, regardless of the location of the neuron within the network. Once translation invariance is satisfied, the network will automatically have a manifold of attractor states consisting of all translations of one attractor state, and the responses of all cells in the network will share the same period and orientation (Fuhs and Touretzky, 2006; Burak and Fiete, 2008). The temporal interference models based on interference within dMEC (rather than in inputs to dMEC, as in (Blair et al., 2008)) provide no reason why cells should share the same grid orientation, even if they share the same period. To ensure that cells with the same period share the same orientation would require including an additional ingredient that constrains all cells to receive exactly the same absolute angular inputs, rather than each cell receiving any set of three angular inputs separated from one another by 60°. It is not clear what biological process might guide such cross-cell coordination in the absence of recurrent circuitry.

From a high-level view, the conditions needed to ensure equi-orientation across independent cells (assuming that the temporal interference takes place within dMEC rather than in its inputs, as in (Blair et al., 2008)) are equivalent to assuming the existence of some translation-invariant pattern-forming attractor dynamics, as in the continuous attractor models. Because of stabilizing network interactions, continuous attractor models require only statistical invariance across cells, with room for fluctuations in local regions, to nevertheless produce and maintain exact equi-orientation across all cells (Fuhs and Touretzky, 2006; Burak and Fiete, 2008). The cell-to-cell invariance in the temporal interference model is more stringent than in continuous attractor grid cell models due to the lack of dynamical forces, because there must be exact invariance to produce the exact same orientation across cells. Even if mechanisms were put in place to allow each neuron to begin with identical sets of dendritic inputs, the model lacks a mechanism to maintain the relative orientation preferences of different cells. Over time, with no mechanism to bind together the orientation preferences of cells, the relative orientation preferences must drift. The model therefore predicts, contrary to experiment, that under realistic conditions of noise and plasticity, the orientations of even nearby cells will be different, and that all orientations should be represented with equal probabilities.

A related contrasting prediction of the two model classes, this one untested by experiment, is the stability of the spatial phase relationship between pairs of neurons with the same period. In the continuous attractor models, the relative spatial phase of cells is set and stabilized by attractor dynamics which drives pattern formation. Thus, the spatial phase relationship between pairs of cells is predicted to be stable over long timescales, whether the rat is moving around or is stationary, despite the inevitable stochasticity in inputs to and responses of single neurons (Burak and Fiete, 2008). By contrast, in the temporal interference models (in which the interference takes place separately in each cell within dMEC), no mechanism exists to stabilize the relative spatial phase relationships between neurons; small amounts of stochasticity will drive a random walk in the spatial phase relationship between any pair of neurons.

New models based on temporal interference, which are presented elsewhere in this issue (Hasselmo, 2008; Blair et al., 2008; Burgess, 2008), remedy some of the major ailments of the MPO temporal interference model. Blair et al. (2008) propose that subcortical inputs to dMEC consist of ring attractor networks. Each cell in a ring network has the same temporal oscillation frequency, but a different phase; firing frequency is modulated by velocity input along a certain direction. Thus, all grid cells that receive input from different cells in one ring network (in addition to receiving a common reference oscillatory input) will have the same spatial period and different phases, and will share the same orientation. By generating velocity-modulated oscillatory cells of all phases through attractor networks, and using these as inputs to the grid cell network, Blair et al. (2008) solve the problem of equi-orientation of equi-period cells in the independent cell temporal interference models. However, the model still relies on temporally phase-coherent activity (with coherent phase over several 100s of cycles) in the neural oscillators to produce grids over a time-scale of even a minute without the help of external resetting inputs, when there is little evidence of such temporally coherent oscillations in the brain.

In turn, Hasselmo (2008) proposes that instead of the theta rhythm, persistent spiking cells (Hasselmo and Brandon, 2008) of the entorhinal cortex provide the regular periodic input to the grid cells. The requirement of phase coherence across 300 or more theta cycles then translates into a requirement for phase coherence over a similar number of spikes during persistent firing (i.e., cells should fire faithfully at the same phase referenced to a pure sine wave of the same frequency). Although the recorded theta oscillation appears not to be sufficiently phase coherent, it is possible that persistent spiking activity is, which can be checked in the experimental data. In this model, the question of why cells that share a period also share exactly the same orientation, persists.

Continuous attractor models contain, as an important feature, cells that receive direct velocity- modulated head-direction input (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burak and Fiete, 2008). As a result, the responses of these cells are both grid-like and direction selective, like the conjunctive grid- and head-direction cells found in layer III and deeper layers of dMEC (Sargolini et al., 2006). By contrast, the MPO temporal interference model (Burgess et al., 2007) does not require the existence of such cells to produce grid responses.

A localized defect present in the response of any cell in continuous attractor models is predicted to exist in the exact same form in the response of every cell in the network, because the defect must lie in the underlying population pattern from which all single neuron responses are built (Burak and Fiete, 2008). In the temporal interference models, there is no necessary reason to expect a potential local defect in the response of one cell to be shared across cells.

Finally, the two classes of model differ markedly in their respective predictions for size, structure and connectivity in

TABLE 1.

Comparison Between Continuous Attractor Models (CTA) and Temporal Interference Models (TI) for Predictions of Grid Cell Properties

Properties	TI-MPO	TI-CAR	TI-PF	CTA	dMEC
Orientations of cells with the same period	Different	Identical	Different?	Identical	Identical
Phase relationships between neurons	Random walk	Random walk	Random walk	Stable	?
Necessity of conjunctive grid/head direction cells	No	No	No	Yes	?
Necessity of membrane potential oscillations	Yes	No	No	No	?
Lateral (recurrent) connectivity	No	No	No	Yes	Yes

Three different versions of the temporal interference model (Burgess et al., 2007) are considered: the original membrane potential oscillation-based version (TI-MPO) proposed by O'Keefe and Burgess (2005), and Burgess et al. (2007), the model based on continuous attractor rings (TI-CAR) proposed by Blair et al. (2008) in this issue, and the model based on persistent firing cells (TI-PF) proposed by Hasselmo and Brandon (2008), also reviewed in this issue (Hasselmo, 2008). The last column (dMEC) lists what is known about the properties of real grid cells. Both conjunctive grid/head direction cells and MPOs are found in dMEC, but it is unclear whether they are necessary for the formation of grid responses. The predictions are discussed in detail in the text.

dMEC. Continuous attractor network models suggest that it is critical for dMEC to consist of 1000s of neurons. By contrast, the individual cell computations of all temporal interference models suggest that the number of neurons in dMEC can be quite small, numbering in the 10s or 100s, and in their present incarnations offer few critical reasons for why dMEC is as large as it is.

As mentioned earlier, the continuous attractor models predict strong recurrent connectivity within dMEC, specifically, the presence of strong local inhibitory interactions mediated by interneurons between pairs of projection neurons with different phases. The temporal interference models predict that cells within dMEC do not have to be connected to each other, because they are based on computations within single cells. In the continuous attractor models, dorsal dMEC cells are predicted to receive head direction and velocity with greater gain (more or stronger synapses) than ventral dMEC cells, to explain the difference in the periodicity of their responses. By contrast, the different periods in the temporal interference models are based on differing underlying frequencies of the theta oscillation along dMEC. In the temporal interference model, the spatial period might vary nearly continuously (up to the discreteness of single neuron spacing) along the dMEC axis in the temporal interference models, again in contrast to the prediction by continuous attractor models of functionally discrete networks of neurons and a discrete set of grid periods. The differences between the model classes, and each of their comparisons with experimental results, are summarized in Table 1.

LEARNING AND THE DEVELOPMENT OF GRID CELL NETWORKS

The problem of how connectivity might form in path integrating grid cell networks, whether based on continuous attractor dynamics or the interference of temporal oscillations, has received relatively little attention, with the exception of one attempt to explain mechanistically how the atopographic phase arrangement of grid cells may arise with help from a training network with grid activity that is topographically organized (McNaughton et al., 2006). Kropff and Treves (2008) also address some of the assumptions needed for the development of the connectivity required by their model.

McNaughton et al. (2006) propose a three-step mechanism: First, they posit the existence of a training network with aperiodic boundaries and local Mexican-hat connectivity which forms a topographic grid pattern. Second, they assume that the training network, although lacking a velocity shift mechanism, will spontaneously undergo pure translations with the help of stochastic inputs or inherent stochasticity. Third, they propose that the training network, with the help of spatially random feed-forward connections to a blank-slate target dMEC network could, through activity-dependent associative plasticity, write its own pairwise recurrent weights into dMEC, but with neurons now arranged atopographically. The assumed translations of the training network would activate at short latencies neurons with similar phases. Temporally associative learning rules would wire together target neurons with similar phases, even if they are far apart in the target network. Neurons responding at different phases will tend to be activated at longer latencies and will cease to excite each other, if the temporal rule contains a negative lobe at intermediate temporal separations. Although attractive, the proposal was untested by simulations.

Steps 1 and 3 are plausible, but the proposal is undermined by a problem in the assumption of step 2. Based on simulation results on the dynamics of aperiodic networks (Burak and Fiete, 2006; Burak and Fiete, 2008), we know that an aperiodic network is prone to rotation, even when equipped with a structured velocity shift mechanism that is designed to produce pattern translations and driven by pure translational velocity inputs and in the absence of noise. When the network contains no velocity shift mechanism, or if the dynamics are stochastic, or both, the issue is far more serious: rotations become as likely as translations. Relative phase relationships between grid cells

in the training network are only meaningful for pure translations, in the absence of rotation. When the training network rotates while continuing to train the dMEC network, existing phase relationships and any potential to drive periodic responses in the target dMEC network will be destroyed.

From a broader perspective, assuming atopographic connectivity in the grid cell network does not actually add much complexity to the intriguing theoretical question of how connectivity in the grid cell network is established. An assumption of topography may simplify the explanation for the first of the two central elements of continuous attractor models (the formation of a translation-invariant pattern), because each neuron need only make local Mexican-hat connections with its neighbors. However, the second element (a velocity coupling mechanism) involves the development of an elaborate relationship between the outgoing synapses from a neuron, and the velocity response of itself and its targets. The establishment of such complex, response-dependent connectivity is likely to rely on activity-based plasticity mechanisms. If activity-based mechanisms are invoked to explain the formation of a velocity coupling mechanism, it may be possible to use similar activity-dependent mechanisms instead of physical proximity to explain the formation of the necessary connectivity to support periodic single-neuron responses. An essential problem is to determine how the pattern orientation is stabilized over the slow time-scales on which plasticity mechanisms may act to further stabilize the network, either by generating periodic connectivity or establishing some anisotropy that favors a specific network orientation.

It is possible that both aspects of connectivity in the network—the component responsible for periodic pattern formation without topography, and the velocity shift mechanism—may arise through plasticity mechanisms acting on supervised input from visually driven place cells in the hippocampus, in a manner similar to that proposed by Hahnloser (2003) for the emergence of head-direction cells. Specifically, assume initially a literal place assignment for each grid cell, driven by visually informed place cell input as the rat explores a small area, as juvenile rats are wont to explore only small regions around their nest (Pierre and Renner, 1998). As the rat moves around in the presence of sensory cues, the place cell population activity reflects the rat's current position in the space. Then, associative learning rules with positive and negative lobes (for contiguous vs. more temporally separated spikes, respectively) in excitatory and inhibitory (Haas et al., 2006) cell populations acting on the recurrent synapses within the dMEC network might drive both pattern formation and velocity shifts.

A notable absence in continuous attractor models of grid cell activity is that, unlike the temporal interference models, they do not assign a role to the prominent theta and gamma oscillations present in entorhinal cortex and throughout the hippocampal formation. It remains unknown whether such oscillations are necessary for the grid patterning of neurons in dMEC. Within the attractor network framework, oscillations may be important for the problem of learning, in the formation of the network. By analogy to the role theta oscillations are thought to play in bringing behavioral time-scale hippocampal place cell sequences down to the precise millisecond domain (via phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996)), thus allowing suitable microscopic plastic mechanisms to associate such behavioral events (O'Keefe and Recce, 1993; Skaggs et al., 1996; Louie and Wilson, 2001; Mehta et al., 2002; Dragoi and Buzsaki, 2006), oscillations and phase precession in the entorhinal cortex (Frank et al., 2001; Hafting et al., 2008) may play a role in the development of dMEC circuitry based on associative plasticity.

THE ROLE OF INTERACTIONS BETWEEN DMEC AND THE HIPPOCAMPUS

The general framework emerging from these investigations is consistent with numerous suggestions that preceded the discovery of grid cells (Sharp, 1999; Eichenbaum et al., 1999; Hartley et al., 2000; Redish, 2001; Gothard et al., 2001): that the idiothetic path integrator is likely to reside in the entorhinal cortex, while hippocampus takes as one of its inputs the idiothetically integrated position estimate, and combines it with input from various sensory modalities to perform further spatial (and nonspatial) associations and computations. Thus, grid cell input is neither necessary nor sufficient for spatial patterning in place cells in the presence of spatially informative sensory inputs (but it does play an important role in sharpening or improving the accuracy of spatial representations in the hippocampus (Brun et al., 2008b)), and it is necessary for driving place fields when external sensory cues are absent.

We describe next how feedback interactions between the hippocampus and entorhinal cortex (Eichenbaum and Lipton, 2008) may play a vital role in generating a more coherent and accurate representation of position in space than either could alone, both in the presence and absence of external sensory cues. The feedback may be so intimate that it may not make sense, strictly speaking, to exclusively assign the labels of path integrator and nonpath integrator to hippocampus and entorhinal cortex, respectively.

For many reasons, idiothetic path integration is inaccurate. Even if self-motion signals were absolutely accurate representations of the rat's movements, which they are not, and therefore contribute to errors in position representation, the integrator is itself likely to add noise, biases (Etienne et al., 1998; Etienne and Jeffery, 2004), or other errors associated with representational limitations. We imagine the role of the hippocampus in spatial navigation to be multi-faceted: (1) To store memories of routes and landmarks in associative maps. (2) To interpret corrective external sensory inputs from landmarks and accordingly reset the grid phase through feedback connections to dMEC, Figure 5. (3) Even in the absence of sensory cues, the hippocampus could continue to serve an essential error-correcting role, to reduce errors introduced by the path integrator: The grid capacity for position representation is far larger than necessary for representing the range of a rat. The excess set of phase vectors, which in principle would represent remote, never-visited and never-to-be-visited locations, might be accessed in

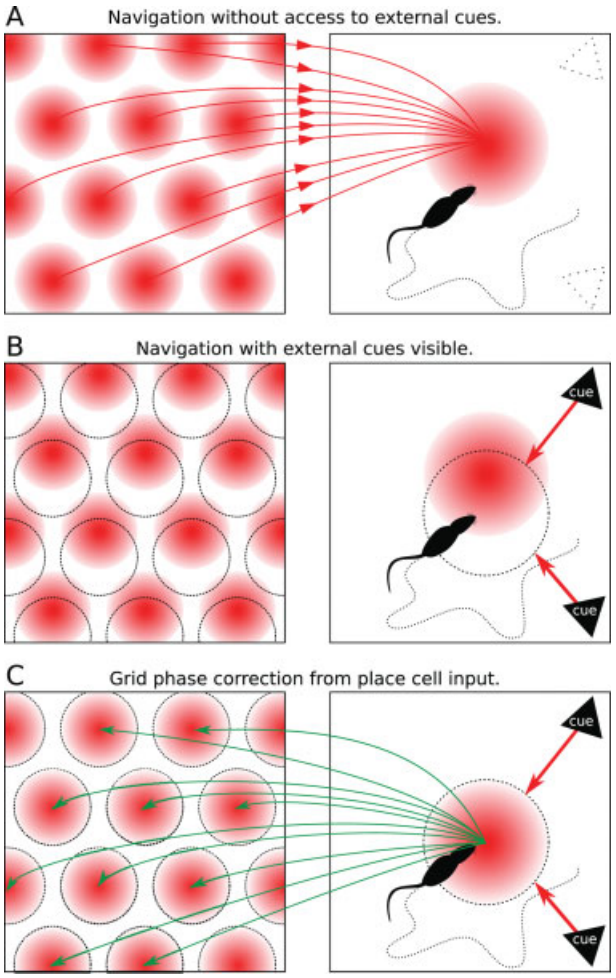

FIGURE 5. Place cell phase correction of the grid pattern using external reference points. (A) In the absence of external sensory input, the position of the activity pattern over the grid cells (left column) is updated using proprioceptive input (McNaughton et al., 2006). Feed-forward connections from dMEC to the hippocampus lets the animal keep track of its position and activates place cells (right column) in the hippocampus (Solstad et al., 2006; Hayman and Jeffery, 2008). Place cells that indicate where the rat thinks it is fire, but these do not necessarily correspond to the correct position of the animal. (B) Because of errors in the velocity input to the grid cells, the grid pattern might become misaligned with time. When external cues become available, they act as reference points that induce place cell activity in the hippocampus. The sensory input overrides the idiothetic input from the grid cells, and the correct place cells are activated. (C) Feedback connections from the hippocampus to the grid cells correct the phase of the grid pattern from the external reference points. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

dMEC through independent inaccurate path integration in different grids, or through undesirable grid rotations. However, place cells are only assigned to actual, previously visited locations and the "correct" corresponding grid states. When sensory inputs are absent, the place cell whose input phase vector maximally matches the instantaneous erroneous grid phase vector will become active due to grid cell input, and will in turn activate its own correct grid phase vector, thereby resetting the grid cell phases to a value representing a "correct" position within the plausible range. In this mutual bootstrapping approach, grid cells and place cells could together achieve dramatically more accurate idiothetic path integration performance than would otherwise be possible.

From the perspective of downstream readout areas like the hippocampus, understanding the grid cell code as a modulo code suggests which computations may be performed easily, and which might be difficult to accomplish. Specifically, the distributed, high-capacity representation in dMEC produces a large set of unique and distinct 'labels', based on the grid cell phase across lattices, for a large number of locations over large spaces. The dMEC position representations are also 'whitened' in a second sense (see also the section 'Position coding by grid cells'): the labels for two locations are equally different, whether the distance between two locations is very large or relatively small (beyond a separation corresponding to the size of the smallest grid period) (Fiete et al., 2008). Thus, the grid cell code is a natural and ideal precursor for generating a well-separated (Leutgeb et al., 2007) label-based readout of distinct locations, such as the place cell code.

On the other hand, metric computations about real space, such as those involved in computing the distance or angle from the present location to a remote place (at a distance greater than the scale of individual grids), are very difficult based on grid phases, even though in principle that information resides in the dMEC code (Fiete et al., 2008). An interesting question therefore is whether such metric information about real space is ever extracted, and if it is, where and how such computations are performed.

OPEN QUESTIONS

New experimental and theoretical results have been arriving at a rapid pace since the original discovery of grid cells only three years ago (Hafting et al., 2005). However, so far experimental research has failed to decisively eliminate any of the theoretical models. As new technologies emerge at the horizon, we hope that experiment and theory can become more tightly coupled to further our understanding of grid cells. Neural imaging (Helmchen et al., 2001; Dombeck et al., 2007) and photostimulation (Arenkiel et al., 2007; Han and Boyden, 2007; Hausser and Smith, 2007; Huber et al., 2008), if targeted to functional groups of neurons, could directly probe the continuous attractor hypothesis by recording many individual neurons simultaneously and then perturbing them in meaningful ways or measuring their cross-correlations over long periods of time. Similarly, recent advances with intracellular recordings in behaving animals (Fee, 2000; Lee et al., 2006) could be applied to test the feasibility and predictions of the temporal interference model. As head-mounted microdrives become smaller, the future promises wireless devices that can record extracellular activity in behaving rats in much greater arenas (Meister et al., 2007) to test the extent of ranges over which rats uniquely rep-

resent position. Another possibility is recordings in a virtual reality setting, where the available space for exploration is infinite (Holscher et al., 2005; Dombeck et al., 2007).

It is exciting to dream of new tools, but available tools can already yield important data. Basic behavioral studies to quantify path integration performance in the absence of sensory input would reveal how well the intrinsic neural path integrator performs, and would set critical minimum standards for how well the intrinsic path integrator models must perform. Standard electrophysiological studies in juvenile animals will reveal whether grid cell responses develop pre- or post-natally, and if they develop postnatally, such studies will elucidate the dynamics of learning and plasticity in dMEC. Lesion studies that can reversibly inactivate rhythm-producing inputs and regions of the hippocampal formation in adult and juvenile animals may begin to probe whether oscillations are necessary for grid cell dynamics or establishment, respectively (Vertes and Kocsis, 1997; Vertes et al., 2001; Pan and McNaughton, 2004; Bassett et al., 2007; Hafting et al., 2008). Cortex cooling (Lomber et al., 1999) or pharmacological interventions (Liu et al., 2007) which reduce the efficacy of recurrent connections in superficial cortical layers without greatly affecting the efficacy of feed-forward inputs, could help to determine the importance and functional role of recurrent connectivity in the generation of grid responses. Simultaneous single-unit recordings of grid cell phase relationships and stability from multiple grid cells (with the same or different periods) could test the contrasting implications of the different dynamical models. Recordings from animals where external spatially informative cues have been eliminated should give important insights to the function of grid cells as a path integrator. Real-time interactions between dMEC and the hippocampus is so far unexplored territory; simultaneous entorhinal cortical-hippocampal recording and perturbation could provide interesting results about grid phase resetting by hippocampal place cells and place cell formation and remapping by grid cells.

On the theoretical side, the understanding of mechanisms that generate grid cells is at best incomplete. The temporal interference models, which assign a primary role to temporal oscillations in the generation of grid responses, do not take into account the real fact that theta oscillations are not coherent in phase over more than a few periods, or about a second. Temporal interference models also suggest that recurrent connectivity is not necessary for grid cell activity, and they present few compelling functional hypotheses about why dMEC contains more than $\sim$100 neurons.

Continuous attractor models have little need for and no explanation of temporal oscillations for the generation of grid-like activity in dMEC. Is there are role for such oscillations in continuous attractor models? Presently, continuous attractor models suggest that oscillations are not necessary for grid cell activity. It's possible that the main role of such oscillations is in learning or gating the flow of information between areas of the hippocampal formation (Engel et al., 2001; Melloni et al., 2007), rather than in the generation of grid responses, but the latter possibility, which is not excluded by experiment, has received little attention in the context of continuous attractor models. Also in the continuous attractor models, does nontopographic connectivity in dMEC imply that the network is periodic, because neural locations are irrelevant and thus boundaries are poorly defined? Or does it nevertheless make sense to talk about boundary, based on their connectivity to a smaller set of neurons than neurons in the bulk?

In future studies we hope for a less piecemeal and more critical assessment of the biological plausibility of all aspects of each model, and a clear comparison of model requirements and predictions against the collected body of existing data.

Independently of the dynamical model under consideration, important mysteries remain. Both classes of model lack explanations for how the appropriate connectivity among neurons and their inputs emerges over development or through learning. The lack of topology in the grid cell network raises the question of why some cortical brain areas (e.g., visual cortex with its orientation columns and ocular dominance stripes (Bonhoeffer and Grinvald, 1991; Ohki et al., 2006; White and Fitzpatrick, 2007)) are arranged topographically, but others are not (Koulakov and Chklovskii, 2001). The mechanistic origin of boundary responses in dMEC—if boundary cells are an integral part of the dMEC network, rather than feed-forward readouts of hippocampal input or dMEC output—is unclear (Barry et al., 2006; Savelli et al., 2008).

Finally, the time may be ripe for cross-fertilization with the machine learning field of robot navigation without prior knowledge and with autonomously devised maps of the explored space (Brooks, 1985; Durrant-Whyte and Bailey, 2006). This navigation condition is typical for animal explorers. Devising robots to perform such tasks makes explicit certain necessary conditions and computations for navigation in the real world regardless of the platform (robotic or biological), which may otherwise not be appreciated or be taken for granted. In this context, insights on necessary computations could prompt the search for neural loci of similar computations. Conversely, discoveries about how biology solves such problems, for example, through the interaction of path integrative modules in the entorhinal cortex and more sensory- based modules in the hippocampus, may suggest efficient algorithms for combining information from different modalities in the engineering context.

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