Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Neurobiology

Models of place and grid cell firing and theta rhythmicity

Neil Burgess[1,2] and John O'Keefe[3,4]

Neuronal firing in the hippocampal formation (HF) of freely moving rodents shows striking examples of spatialorganization in the form of place, directional, boundary vector and grid cells. The firing of place and grid cells shows an intriguing form of temporal organization known as 'theta phase precession'. We review the mechanisms underlying theta phase precession of place cell firing, ranging from membrane potential oscillations to recurrent connectivity, and the relevant intra-cellular and extra-cellular data. We then consider the use of these models to explain the spatial structure of grid cell firing, and review the relevant intra-cellular and extra-cellular data. Finally, we consider the likely interaction between place cells, grid cells and boundary vector cells in estimating self-location as a compromise between path-integration and environmental information.

Addresses
[1] UCL Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR, UK
[2] UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
[3] Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK
[4] Sainsbury Wellcome Centre for Neural Circuits and Behaviour, University College London, Gower Street, London WC1E 6BT, UK

Corresponding author: Burgess, Neil (n.burgess@ucl.ac.uk)

Current Opinion in Neurobiology 2011, **21**:1–11

This review comes from a themed issue on
Networks, Circuits and Computation
Edited by Peter Dayan, Dan Feldman, Marla Feller

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2011.07.002

Historically the functional extra-cellular electrophysiology of the hippocampus of freely moving rodents has been dominated by two findings. The local field potential (LFP) shows a large-amplitude 4–10 Hz theta rhythm [1], and the majority of principal cells have firing restricted to specific environmental locations ('place cells' [2]). These two phenomena combine in the observation that place cell firing shows 'theta phase precession', whereby spikes are fired at successively earlier phases of the theta rhythm of the LFP as the animal moves through the firing field or 'place field' [3••], see Figure 1. The firing phase correlates better with the distance traveled through the place field than with other variables, such as the time spent in the place field: providing a phase code for the animal's location in addition to the firing rate code [4,5•]. Phase precession occurs because place cell firing is modulated at a frequency slightly higher than LFP theta frequency, and this frequency difference increases with running speed [3••,6•], see [7,8] for supporting evidence.

Several further significant findings have emerged including the discovery of additional spatial cell types in the wider Hippocampal Formation. First, head-direction cells that fire according to the orientation of the head relative to the environment have been found in several locations along Papez's circuit [9] including medial entorhinal cortex (mEC) [10•]. Second, grid cells have been discovered in mEC: cells that fire in a series of environmental locations, which form a triangular grid across the environment [11••]. Grid cells are most numerous in layer II of mEC, where their firing also shows theta-phase precession [12•], but are also found in deeper layers of mEC [10•] and in pre-subiculum and para-subiculum [13•]. Third, boundary vector cells (BVCs), a spatial cell type theoretically predicted to provide one component of place cell firing fields [14,15,16•] have been found in the subiculum [17•] and mEC [13•,18•]. The firing of BVCs is determined by the location of the rat relative to environmental boundaries. Finally, technological advances have allowed intra-cellular recording [19••] from place cells in head-fixed mice navigating a virtual environment, and in freely moving animals [20•]. These intra-cellular data show a theta-band membrane potential oscillation (MPO) that increases in frequency above that of the LFP when the animal enters the place field, with spikes being fired at the peaks of the MPO, see Figure 1f.

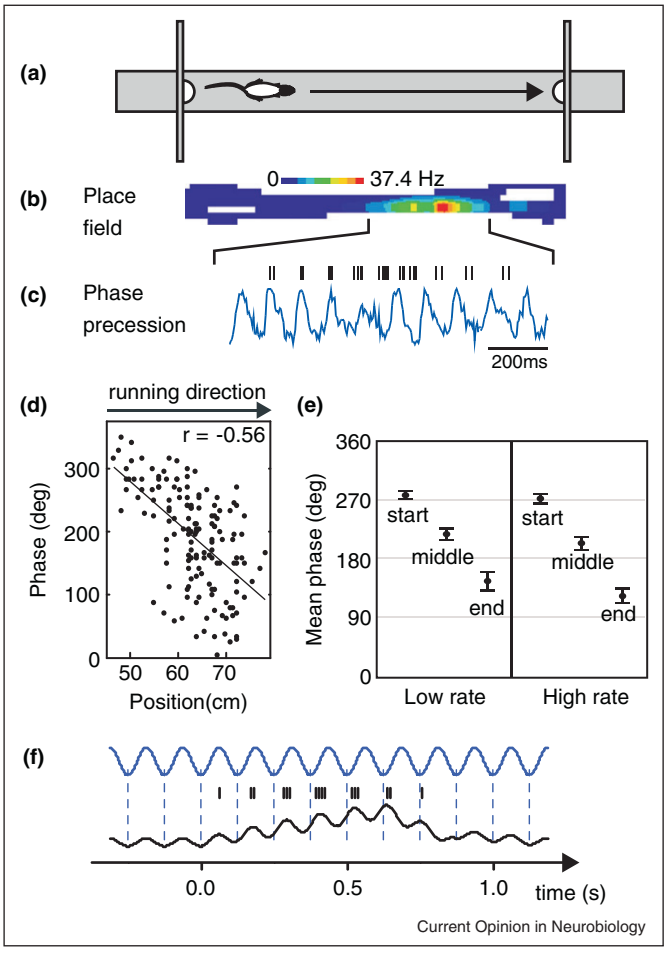
The detailed extra-cellular and intra-cellular data concerning the spatio-temporal patterns of neuronal activity in the hippocampal formation of behaving rodents provides a model system for understanding the neural bases of behavior. Here we review the main computational models of place cell firing and theta phase precession, and how these models are being applied to explain grid cell firing. Finally we consider how place cells might calculate self-location by combining two types of input [2,21–23]: information concerning path integration, mediated by grid cells resulting from theta-band neuronal oscillations [24••,25•,26•,27] and environmental information, mediated by boundary-vector cells [13•,16•,17•].

Models of theta-phase precession of place cell firing

Computational work on theta-phase precession has fallen into two broad camps, those focusing on mechanisms within an individual place cell and those focusing on mechanisms arising from the interaction between large

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

Figure 1



Theta-phase precession of place cell firing. **(a)** As a rat runs on a track, a place cell in the hippocampus fires as the animal passes through a specific region (the 'place field,' **b**). This firing rate code for location is also a temporal code **(c)**: spikes (ticks) are fired at successively earlier phases of the theta rhythm of the local field potential (blue trace), referred to as 'theta-phase precession.' The theta phase of firing correlates with the distance traveled through the place field **(d)** better than with other variables, such as time spent in the place field or the place cell's instantaneous firing rate. Firing phase precesses from late to early phases of theta as the animal runs through the start, middle and end of the place field, irrespective of whether spikes are fired at a low or high rate on that run (**e**; mean and s.e.m. over $n = 34$ cells). Adapted from [5•]. **(f)** Schematic representation of the data of Harvey *et al.* (2009) showing local field potential theta (blue) intracellular membrane potential (MPO, black) and spikes (ticks) from a place cell as a mouse runs from left to right through the place field in a virtual arena. Note that the intracellular MPO increases in amplitude and in frequency relative to the LFP theta when the mouse is in the place field, and that the spikes are aligned to the intracellular MPO. The firing rate peaks in the center of the place field, while the membrane potential shows a more asymmetric ramp-like depolarization.

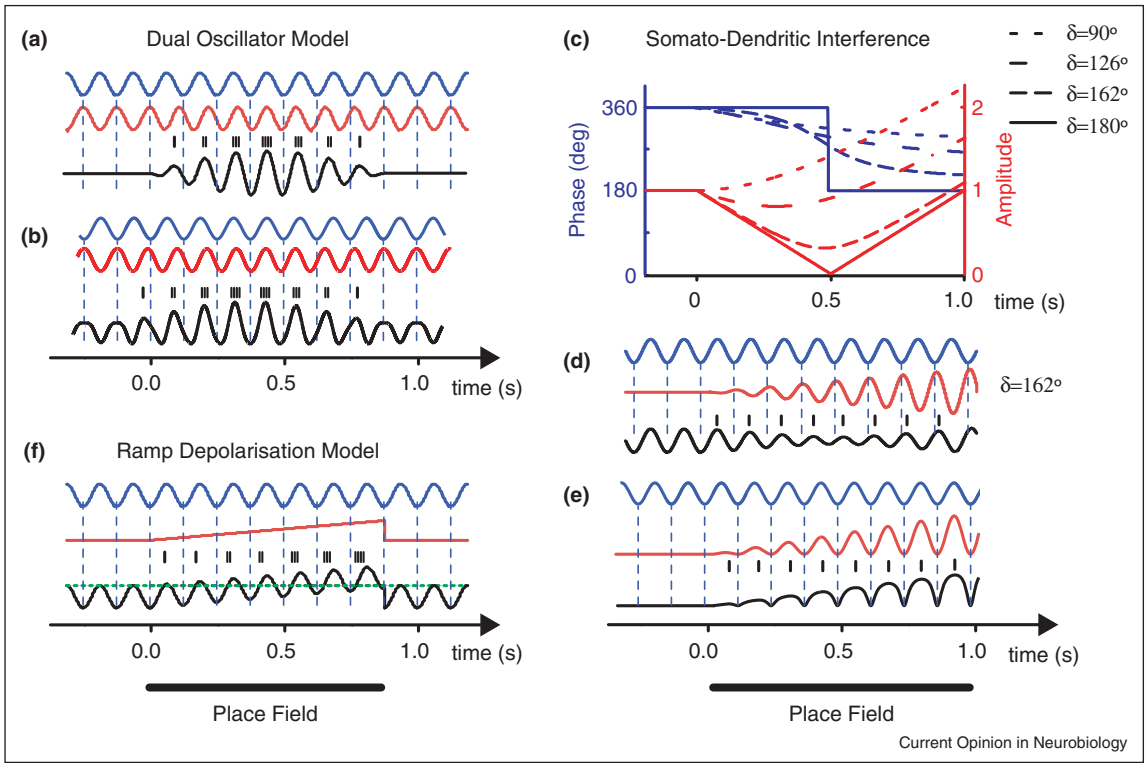
networks of neurons. Models from these two viewpoints are reviewed below, and need not be mutually exclusive. Time will tell which types of mechanism prove most productive in explaining the experimental findings and whether both types of mechanism are necessary for a comprehensive explanation.

Oscillatory mechanisms and intra-cellular data

The Dual Oscillator model ([3••,6•], Figure 2a) posits that the basic mechanism producing precession is an interaction of two oscillations of different frequency: a baseline somatic oscillation at the LFP theta frequency, and an active dendritic oscillation whose frequency increases above baseline when the animal is in the place field, see [28••]. The sum of these oscillations produces a MPO wavelet in the place cell with a frequency above LFP theta and an amplitude peaking in the middle of the place field. Spikes are fired at the peaks of the MPO, and so show phase precession because the MPO has a higher frequency than LFP theta, Figure 2a. The increase in frequency of the active oscillation is assumed to be proportional to running speed, so that the phase advance of spikes reflects distance traveled through the place field, rather than time spent in the field. The two oscillations need not combine additively: the somatic input could be a shunt inhibition leading to a multiplicative model, Figure 2b (see also Figure 1 in [25•]). Note that the net activity of a population of place cells will be modulated at

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

Figure 2



Oscillatory models of phase precession. **(a)** Dual Oscillator model. The somatic MPO (black) is the sum of two oscillatory inputs having different frequencies in the place field: a somatic input proportional to LFP theta ($\sin(2\pi f_b t)$, blue), and a dendritic input ($\sin(2\pi f_a t)$, red) whose frequency (f_a) increases above LFP theta frequency (f_b) in the place field (proportionally to running speed, see Figure 3c). The somatic MPO frequency exceeds LFP theta frequency and its amplitude peaks in the middle of the field. Spikes occur at the peaks of the somatic MPO (ticks; f_b = 8 Hz, f_a = 9 Hz in place field). **(b)** Dual Oscillator model with shunt inhibition. The somatic input can be a shunt (i.e. modulatory) input. Here somatic input ($[3 + \sin(2\pi f_b t)]/2$, blue) multiplies dendritic input ($\sin(2\pi f_a t)$, red) to give the somatic MPO (black). **(c–e)** Somato-Dendritic Interference. The somatic MPO (black) is the sum of two theta-frequency inputs: a somatic input ($\sin(2\pi ft)$, blue), and a dendritic input ($D\sin(2\pi ft + \delta)$, red) with amplitude D, which increases through the place field, and phase advance δ. The MPO can show significant phase precession, but has a *decreasing* amplitude in the place field: $\text{MPO} = R\sin(2\pi ft + \varphi)$, where $R^2 = 1 + D^2 + 2D\cos(\delta)$ and $\varphi = \arctan\{\sin(\delta)/[\cos(\delta) + 1/D]\}$. **(c)** MPO theta-phase (φ) and amplitude (R) for different values of dendritic phase advance (δ). The dendritic amplitude D increases like $2t$ as the animal runs through the place field from t = 0 to 1.0 s, f = 8 Hz. **(d)** Example somatic input (blue), dendritic input (red) and MPO (black) for $\delta = 162^\circ$. **(e)** Somato-Dendritic Interference with divisive inhibition: dendritic input $D[1 + \sin(2\pi ft)]$ is divided by somatic input $[1.5 + \sin(2\pi ft)]$, producing a MPO with low plateaus early in the place field and higher sharper peaks later in the place field. The increasing dendritic amplitude D delays the peak of the flat low early MPOs more than the sharper higher late MPOs, producing phase precession. **(f)** Depolarizing Ramp model. Somatic input is proportional to LFP theta (blue), dendritic input is a ramp-like depolarization in the place field (red). The resulting somatic MPO (black) crosses a firing threshold (green) successively earlier on each cycle of LFP theta, producing successively earlier phases (and greater numbers) of spikes.

the (slower) LFP theta frequency even though all individual cells are showing phase precession, that is, oscillating above this frequency when in their place field [29,30].

The Somato Dendritic Interference model (SDI; [31••] Supplementary Figure 6), see also [28••,32•,33•], posits oscillatory somatic and dendritic inputs to the place cell, both with the same frequency (LFP theta frequency) and a phase difference of 180°. In this model, a ramp-like depolarization of the dendrite in the place field causes the dendritic oscillation to increase in amplitude. In the initial version of the SDI model [32•], the sum of the two inputs produces a MPO that switches abruptly from the phase of the somatic input to the phase of the dendritic input as the dendritic amplitude increases. A smooth transition in phase can be achieved if the dendritic oscillation leads the somatic one by less than 180° (e.g. via delayed conduction of the dendritic input to the soma). However there are significant problems with the SDI model. Significant amounts of phase precession require a choice of parameters that produce a significant *decrease* in the MPO amplitude within the place field (see Figure 2c,d), and this is incompatible with the *in vivo* data, see [19••] and Figure 1f. For this reason, a divisive somatic input has been proposed (i.e. shunt rather than subtractive inhibition [31••]), so that the MPO amplitude will not decrease when the dendritic amplitude increases. Dividing two sinusoids of the same frequency generally changes the amplitude of the resulting MPO rather than its phase. Nonetheless, if parameters are chosen such that

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

the MPO has broad plateaus separated by sharp troughs, the curvature of the MPO plateaus increases with amplitude. In this case, the increasing dendritic amplitude introduces a slope to the plateaus that significantly delays the occurrence of the peaks of the flattest and lowest early MPOs but has successively less effect on the higher and increasingly curved later MPOs, see Figure 2e. This causes an apparent phase precession over the first few MPOs in the place field, but requires spikes to be fired precisely at the peaks of the very flat and low-amplitude MPOs early in the place field. Accordingly, in Losonczy *et al.*'s *in vitro* simulation, most of the MPO phase precession occurs during the first few MPO cycles whose amplitudes are too low to reliably initiate spikes ([31••] Figure 2b, Figure 4e).

The Depolarizing Ramp model [34••] posits a somatic input proportional to LFP theta and a dendritic depolarization that increases in a ramp-like fashion across the place field. This results in a very simple mechanism for phase precession, by which the increasing depolarization allows the somatic MPO to exceed a firing threshold successively earlier within each cycle of LFP theta. See Figure 2f. This mechanism could explain why some of the Losonczy *et al. in vitro* data show spikes being fired at successively earlier phases of the MPO, see Losonczy *et al.*'s [31••] Figure 2a.

The intra-cellular data of Harvey *et al.* [19••] partially distinguish between the dual oscillator and depolarizing ramp models, see Figure 1f. It shows that phase precession results from a MPO that increases in frequency and amplitude within the place field, with spikes fired at the peaks of the MPO, a result consistent with the dual oscillator mechanism. However, these data also show an asymmetrical ramp-like depolarization in the place field, which is not predicted by the dual oscillator model. By contrast, the depolarizing ramp model does predict a ramp-like depolarization that causes phase precession as spikes are fired at successively earlier phases of the MPO (which is locked to LFP theta). The crucial point of Harvey *et al.*'s data is that the ramp-like depolarization does not influence spike timing relative to the MPO, that is, it is not the mechanism causing phase precession. Instead of moving relative to the MPO the spikes stay fixed with respect to it while the MPO itself precesses relative to the LFP theta. This strongly supports dual oscillator as opposed to ramp-depolarization models, and raises the question of why spike-timing reflects MPO peaks rather than an absolute firing threshold in somatic depolarization. One possibility is that the dendrites are acting as voltage controlled oscillators [3••,28••] and the ramp-like depolarization reflects the voltage change that is driving the frequency of the dendritic oscillator. If the dendritic oscillation produced spikelets, the timing of action potentials generation would be primarily determined by the timing of these spikelets rather the slower ramp-like variation in depolarization level, see [20•] for supporting evidence and ([25•] Figure 1) for related simulations.

Recurrent connections and extra-cellular data

The main alternative to the above intracellular models is the Spreading Activation model [35•,36•]. In this model, firing at the end of the place field is driven by feed-forward sensory inputs to the place cell at early phases of LFP theta, but activity also spreads from place cells with place fields earlier along the route to place cells with place fields further along the route. Thus, firing nearer to the start of the place field reflects input from place cells with place fields nearer to the start of the route, and occurs at *later* phases due to the transmission delay in the arrival of these inputs via a chain of cells with place fields earlier on the route. Changes in firing phase as the rat runs through the place field occur because the feed-forward inputs to the population of place cells change. In [35•] place cell firing occurs at the peak of the synaptic input arriving within each theta cycle, consistent with the observation of spikes at the MPO peaks [37]. In [36•] local oscillatory processes in the gamma and theta bands also constrain firing times.

The connections required by the spreading activation model could be formed by synaptic plasticity if the animal runs repeatedly along the route, and are consistent with a reported backward spread of place cell firing with experience [34••]. However, it is less clear how the model explains the phase precession observed in open environments in which arbitrary novel routes can be taken [38,39,40], or the observation that blocking NMDA receptors prevents the backward spread of firing but does not affect phase precession [41].

Two aspects of the extra-cellular data on theta phase precession provide strong constraints on mechanism. First, the firing rate and firing phase dissociate: firing phase continues to precess with distance traveled through the place field irrespective of whether firing rate is rising (entering the place field) or falling (leaving the place field), and whether many or few spikes are fired on that particular run, see Figure 1e and [5•]. Second, phase precession is characterized by *increasing* phase variability from the start to the end of the place field, see Figure 1d,e and [5•], the opposite of that predicted by the spreading activation model.

The Depolarizing Ramp and SDI models struggle to show independence between firing phase and firing rate, since both are closely linked via the level of dendritic depolarization. To deal with this, Losonczy *et al.* propose an additional *ad hoc* mechanism for the SDI model: an activity-dependent change in the time course of feedback inhibition, so that late phase firing is inhibited in the second half of the place field. This mechanism can allow

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

early firing phases to be maintained while dendritic drive decreases, but would not produce *continued* phase precession in the second half of the field. It also introduces a dependence on the neuronal activity during each run. The spreading activation model produces phase precession as a result of the physical movement of the animal past environmental cues, and is thus less consistent with observations of intrinsically generated phase precession in a running wheel [42•], but note that physical motion does occur in running wheels [43], and see discussion in [44].

The divisive SDI model and the Spreading Activation model predict *decreasing* phase-variability through the place field. In the SDI model, firing at the start of the field results from spikes being fired at the peaks of low, flat MPOs from which spike-timing would be unreliable compared to the later more sharply peaked MPOs. The spreading activation model also predicts increased phase variance at the start of the place field (where *late* phase firing is driven by input from other place cells), due to dispersion in synaptic transmission from one place cell to the next, whereas firing at the end of the field reflects direct environmental input. In the Dual Oscillator model any error in the rate of increase of MPO frequency with running speed would result in increasing phase variability through the place field when multiple runs at different speeds are combined, a prediction more consistent with experimental findings.

Models of grid cell firing

Oscillatory mechanisms

Grid cells show a regularly repeating spatial firing pattern more reminiscent of an interference pattern than the unimodal firing pattern of most place cells (Figure 3a), suggesting that the Dual Oscillator model might be extended to the grid cells in layer II of mEC [23,27]. These cells were subsequently shown to exhibit theta-phase precession, see [12•] and Figure 3b.

In the Dual Oscillator model the frequency of the dendritic oscillation increases with running speed so that its phase encodes distance traveled [3••,6•], thus place cells could be considered 'speed-controlled oscillators' [8], see Figure 3c. To generate 2D spatial firing patterns, we proposed the existence of 'velocity-controlled oscillators' (VCOs), that increase in frequency according to running speed in a specific preferred direction (i.e. the dot product of velocity with preferred direction), see [24••,25•,26•,27] and Figure 3c,d. These VCOs might be driven by synaptic input from the directionally modulated cells common in the deeper layers of mEC [10•] and elsewhere along Papez's circuit [9,45]. Their firing phase encodes displacement along their preferred direction (Figure 3d). If multiple VCOs with different preferred directions converge onto a grid cell, the grid-like spatial firing pattern can result, see Figure 3d.

Although two VCOs would be sufficient to perform path integration, and support grid cell firing (if their preferred directions differ by 60° or 120°), using three or more VCOs to drive grid cell firing confers robustness to error accumulation, and would allow simple unsupervised learning algorithms to select VCOs with preferred directions differing by multiples of 60° [24••,46]. Recent analysis suggests that different VCOs should be instantiated in different cells rather than different dendrites, to avoid synchronization [47•], see [25•,26•] for further discussion.

The multiple oscillator model makes specific predictions relating the frequency of theta-band modulation of firing rate to grid scale and running speed [25•], which have been broadly verified [48•]. Predictions regarding the relationship between MPOs in mEC layer II stellate cells and their depolarization level [49] and probable grid scale (inferred from their dorso-ventral location) [50•] have also been broadly verified. Recent evidence suggests that the predicted VCOs exist as 'theta cells' (interneurons found throughout the septo-hippocampal circuit) whose interburst frequency shows a cosine modulation by running direction and a linear increase with running speed (Welday *et al. Soc Neurosci Abstr*, 2010, 203.20).

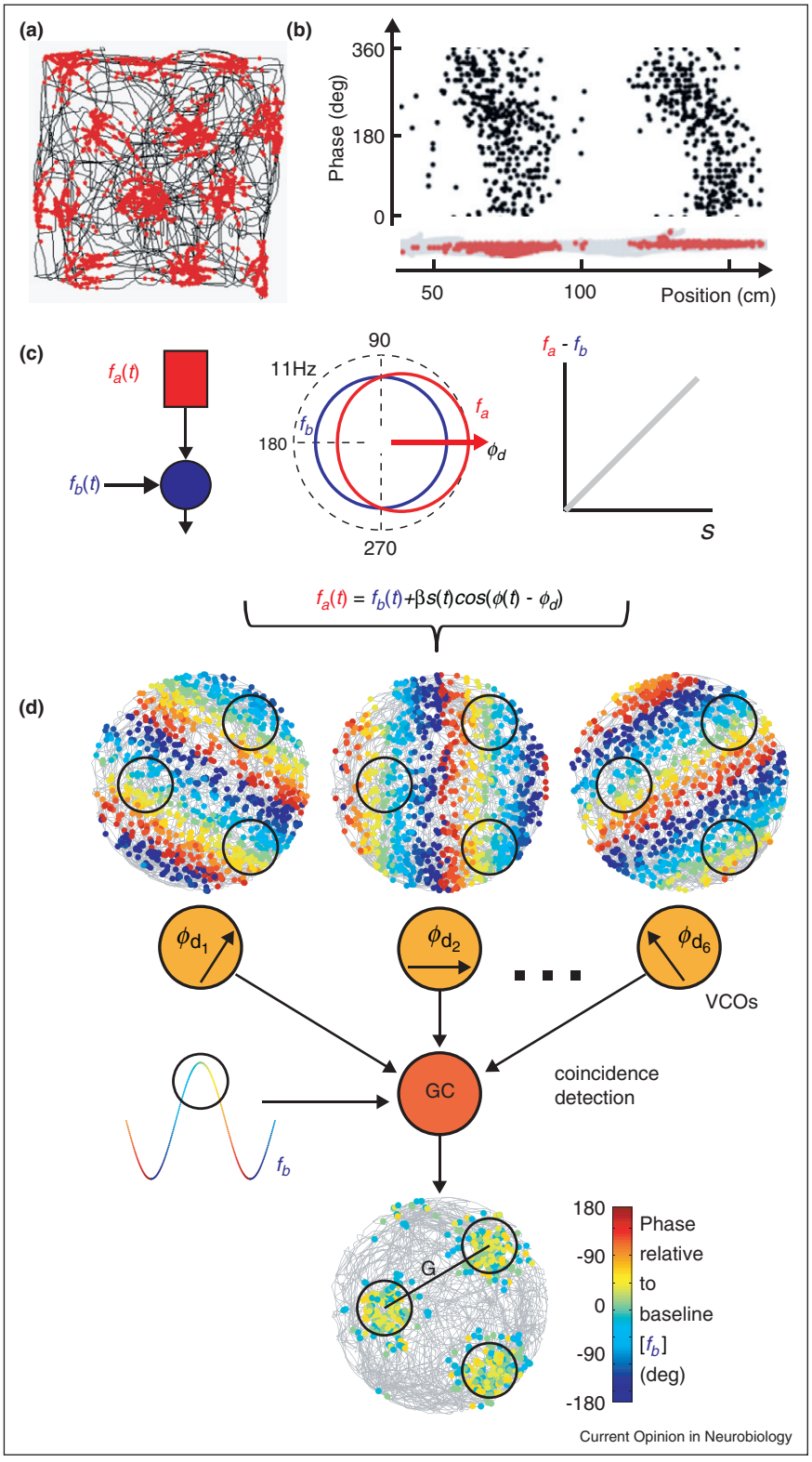
The multiple oscillator model implies that LFP theta reflects two components: a baseline frequency and an increase in frequency with running speed that is driven by the increase in individual VCO frequencies with running speed [25•]. These two components should parallel the distinction between arousal-related and movement-related theta mechanisms (see, e.g. [51]), and manipulations that affect the latter component should also affect grid scale. Consistent with this suggestion, exposure to environmental novelty, which reduces theta frequency [52], causes an increase in grid scale (Barry *et al.*, *Soc Neurosci Abstr*, 2009, 101.24). The observation of non-theta-modulated grid cell firing in the deeper layers of mEC [10•] and in bats (Yartsev *et al.*, *Soc Neurosci Abstr*, 2010, 203.15), was not predicted by the multiple oscillator model. According to the model, these cells would have to inherit their grid-like firing patterns from theta modulated cells firing elsewhere in the brain or during earlier exploration of the environment.

Recurrent connections

The multiple oscillator model focuses on single grid cells rather than network-level interactions. However, there must be coupling between grid cells, or their inputs. MPOs in slices are too irregular to work as posited by the multiple oscillator model. By contrast, *in vivo* LFP shows a regular coherent theta rhythm – indicating widespread coordination of MPOs, and interactions between mEC cells can be seen in slices [53•]. Interactions, or common inputs, are also indicated by the common orientation of grids [11••,54•], and the way that local populations of grid cells have grids of

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

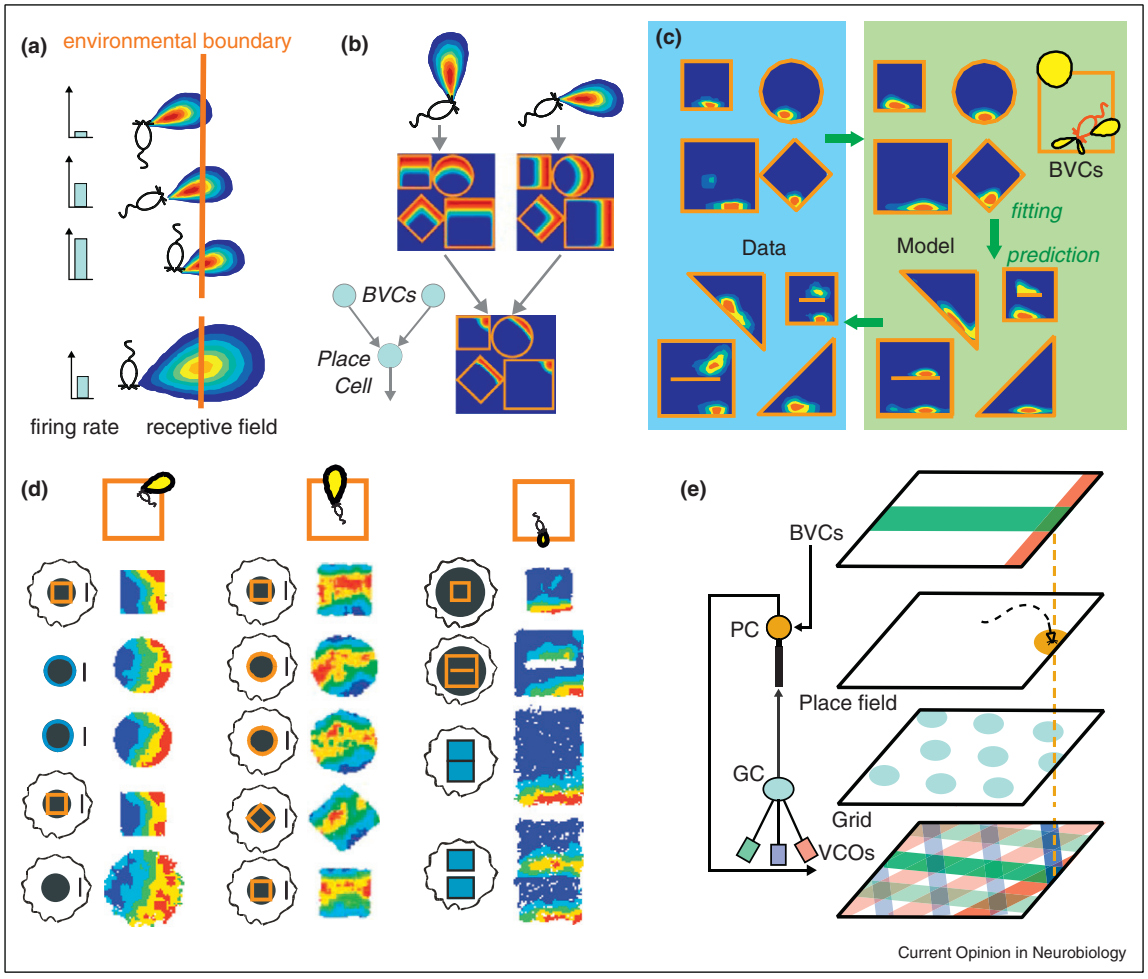
Figure 3



Multiple oscillator model of grid cell firing. **(a)** Example of the spatial distribution of spikes from a grid cell (red dots) as a rat forages in a 1m^2 box (path shown in black). Adapted from [11••]. **(b)** Example of theta-phase precession in a grid cell from medial entorhinal cortex (layer II) as a rat runs left-to-right through two of its firing fields on a linear track. Black dots (above) show theta-phase of spikes, red dots (below) show spatial position on the track. Adapted from [12•]. **(c)** A 'velocity-controlled oscillator' (VCO) extends the dual oscillator model (see Figure 2a) to two dimensions: the active oscillation

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

Figure 4



Environmental inputs to place cells, and interactions with grid cells. **(a–c)** 'Boundary vector cells' (BVCs) as the environmental inputs to place cells. **(a)** An example BVC tuned to respond to a boundary nearby to the East (above), and one tuned to respond at a longer distance (below). **(b)** A place cell's firing can be modeled as the thresholded sum of its BVC inputs. Firing rate maps are shown for four environments (small square, circle, square rotated relative to distal cues, large square) for two different BVCs (above). The firing rate maps for the place cell are shown below. **(c)** A place cell's firing patterns in several different shaped environments (top left) can be used to infer the BVCs driving its firing (top right). The inferred model can then predict how the place cell will fire in new environmental configurations (bottom right), usually producing a reasonable qualitative fit when the place cell's firing is recorded in these new configurations (bottom left). Adapted from [16•]. **(d)** Three example boundary vector cells recorded in the subiculum. Each column shows the receptive field (above), and firing rate map in a series of environments (below). Adapted from [17•]. **(e)** Schematic proposed interaction between place cells (PC), BVCs and grid cells (GC). BVCs anchor place fields to the environment and place cells anchor grid cell firing fields to the environment (via phase-resetting of velocity controlled oscillators (VCOs) in the multiple oscillator model). In return, grid cells provide a path integrative input to place cells. Adapted from [24••].

similar spatial scale [11••] and that this scale increases dorso-ventrally in discrete steps [54•]. In terms of the multiple oscillator model, coupled velocity-controlled oscillators can support sufficiently regular oscillations [55], and the model extends to coherent populations of grid cells if the velocity-controlled oscillators are arranged as ring attractors [45].

The main network-level model of grid cell firing, the Continuous Attractor model [56•,57,58], extends

(Figure 3 Continued Legend) has a frequency (f_a) that varies relative to the baseline frequency (f_b) like: $f_a(t) = f_b(t) + \beta s(t)\cos(\phi(t)-\phi_d)$, where $s(t)$ is running speed, $\phi(t)$ is running direction and ϕ_d is that VCO's preferred running direction. The dependence of the active frequency on running direction and speed is shown in middle and right panels respectively (the preferred direction is left-to-right). These dependencies cause the phase of the active oscillation relative to baseline to reflect displacement along the preferred direction (see mid top panel of **d**). In the dual oscillator model: $f_a(t) = f_b(t) + \beta s(t)$. **(d)** Multiple VCOs with different preferred directions combine with each other, and the somatic baseline input, to produce grid firing. Grid scale depends on the constant β as: $G = 2/\sqrt{3}\beta$. Adapted from [25•,48•], see also [26•].

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

preceding models of the firing of head-direction cells [22,59••,60] and place cells [59••,61,62]. Grid-like firing patterns across the population of cells result from symmetrical recurrent connectivity in which cells with similar response patterns experience mutual excitation while cells with dissimilar firing patterns experience mutual inhibition. Asymmetric interactions matching the animal's speed and direction of movement causes these firing patterns to shift so that each cell exhibits a grid-like firing pattern as a function of the animal's location. This asymmetric connectivity might be mediated by interconnections between grid cells with direction-dependent firing [10•]. This can allow phase precession to occur as the rat runs through grid cell firing fields in all direction [63••]. The use of spike after-depolarization to set an intrinsic rhythm of reactivation, see [36•], removes the need for sensory input to initiate the sequence of firing within each theta cycle, and changes in the time-course of after-depolarization could explain dorso-ventral changes in grid scale [63••].

The symmetric recurrent connectivity of Continuous Attractor models complements the Multiple Oscillator model: potentially providing additional spatial and temporal stability, either to grid cells directly [56•,57,58], or to velocity-controlled oscillators [45]. Evidence for this aspect of attractor models includes the common orientation of different grids [11••,54•] and the step-wise increase in grid scale [54•]. The proposed asymmetric interactions for shifting firing patterns according to the animal's movement provide a clear alternative to the multiple oscillator model.

Interactions between the different types of spatial cell

The long-term stability of the firing patterns of place and grid cells relative to the environment indicates that firing locations are determined by environmental information as well as the mechanisms for path integration discussed above. Recording from the same place [14] or grid [54•] cell during geometric manipulation of a familiar environment indicates a special influence of environmental boundaries on firing locations, see also [64]. Computational modeling of place fields [15,16•] predicted the existence of input cells tuned to respond to the presence of an environmental boundary at a specific distance in a specific allocentric direction ('boundary vector cells'), see Figure 4a,c. Cells with these properties have since been found in subiculum [17•] and mEC [13•,18•], see Figure 4d.

Place cells are thought to combine both path integrative and environmental inputs [2]. The former input is probably provided by the theta system and grid cells, while the latter input is provided by boundary vector cells and local cues such as distinctive smells or textures. The hippocampus and entorhinal cortex are mutually interconnected [65], so that return projections from place cells could provide environmental stability for the grids. See [23,24••] and Figure 4f. Such an organization would be consistent with the disruption of grid cell firing by hippocampal inactivation [12•]; the disruption of the grid cells, but not boundary vector cells, place cells or head direction cells, by disruption of the theta system [18•,66•]; and the observation of stable place cell firing before stable grid cell firing in early development studies [53•,67•]. This view predicts that the oscillatory component of place cell firing in [19••] and Figure 1d reflects path integrative processes involving grid cells, while the ramp-like depolarization reflects input from boundary-vector cells or local cues and gates firing: determining the firing field and potentially affecting the numbers of spikes fired per run but not their theta-phase.

Conclusions

A range of models relate theta-phase precession in hippocampal place cell firing to membrane potential oscillations and recurrent connectivity. Some of these models also provide the basis of models of path integration and grid cell firing. However, environmental inputs are also a crucial part of self location, for which boundary-vector cells may play a key role. This field has seen a recent explosion of both experimental results and computational models. Critically, computational modeling has begun to drive forward experimental advances by making testable predictions, potentially bringing this area of cognitive neuroscience into line with more established sciences.

Acknowledgements

This work was supported by the Medical Research Council and the Wellcome Trust, UK, and the SpaceBrain grant of the European Union.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Vanderwolf CH: **Hippocampal electrical activity and voluntary movement in the rat**. *Electroencephalogr Clin Neurophysiol* 1969, **26**:407-418.

2. O'Keefe J: **Place units in the hippocampus of the freely moving rat**. *Exp Neurol* 1976, **51**:78-109.

3. •• O'Keefe J, Recce ML: **Phase relationship between hippocampal place units and the EEG theta rhythm**. *Hippocampus* 1993, **3**:317-330.
The phase of place cell firing relative to the theta rhythm in freely moving rats relfects the location of the animal Suggests that this results from the summation of two theta-band oscillations with slightly different frequencies (the dual oscillator model).

4. Jensen O, Lisman JE: **Position reconstruction from an ensemble of hippocampal place cells: contribution of theta phase coding**. *J Neurophysiol* 2000, **83**:2602-2609.

5. • Huxter J, Burgess N, O'Keefe J: **Independent rate and temporal coding in hippocampal pyramidal cells**. *Nature* 2003, **425**:828-832.
The rate of firing and the theta-phase of firing of place cells can vary independently, potentially encoding different types of information simultaneously using rate and phase codes.

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

6. Lengyel M, Szatmary Z, Erdi P: **Dynamically detuned oscillations**
• **account for the coupled rate and temporal code of place cell firing**. *Hippocampus* 2003, **13**:700-714.
Computational analysis of the dual oscillator model, demonstrating that firing phase correlates with distance travelled if the dendritic oscillation increases in frequency (relative to the somatic oscillation) proportional to running speed.

7. Maurer AP, Van Rhoads SR, Sutherland GR, Lipa P, McNaughton BL: **Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus**. *Hippocampus* 2005, **15**:841-852.

8. Geisler C, Robbe D, Zugaro M, Sirota A, Buzsaki G: **Hippocampal place cell assemblies are speed-controlled oscillators**. *Proc Natl Acad Sci USA* 2007, **104**:8149-8154.

9. Taube JS: **Head direction cells and the neuropsychological basis for a sense of direction**. *Prog Neurobiol* 1998, **55**:225-256.

10. Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP,
• Moser MB, Moser EI: **Conjunctive representation of position, direction, and velocity in entorhinal cortex**. *Science* 2006, **312**:758-762.
The deeper layers of medial Entorhinal cortex contain grid cells whose firing is modulated by head-direction ('conjunctive cells'), as well as head-direction cells.

11. Hafting T, Fyhn M, Molden S, Moser MB, Moser EI:
•• **Microstructure of a spatial map in the entorhinal cortex**. *Nature* 2005, **436**:801-806.
The discovery of grid cells in layer II of medial entorhinal cortex, also showing that the spatial scale of the grid-like firing patterns increase as the recording location is moved dorso-ventrally, and that neighboring (same-scale) grids are offset relative to each other but have a common orientation.

12. Hafting T, Fyhn M, Bonnevie T, Moser MB, Moser EI:
• **Hippocampus-independent phase precession in entorhinal grid cells**. *Nature* 2008, **453**:1248-1252.
Grid cells in layer II of medial Entorhinal cortex show theta-phase precession, similar to that seen in place cell firing, and this persists for several minutes after innactivation of the hippocampus proper.

13. Solstad T, Boccara CN, Kropff E, Moser MB, Moser EI:
• **Representation of geometric borders in the entorhinal cortex**. *Science* 2008, **322**:1865-1868.
The discovery of cells in medial entorhinal cortex that fire whenever the animal is near to a boundary in a specific allocentric direction ('border cells'), that is, a subset of the 'boundary vector cells' predicted in [14,15,16•] but with only short-range responses.

14. O'Keefe J, Burgess N: **Geometric determinants of the place fields of hippocampal neurons**. *Nature* 1996, **381**:425-428.

15. Burgess N, Jackson A, Hartley T, O'Keefe J: **Predictions derived from modelling the hippocampal role in navigation**. *Biol Cybern* 2000, **83**:301-312.

16. Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J: **Modeling**
• **place fields in terms of the cortical inputs to the hippocampus**. *Hippocampus* 2000, **10**:369-379.
Defines the properties of the neocortical inputs required to determine the spatial firing fields of place cells: cells tuned to fire whenever an environmental boundary occurs at a specific distance along a specific allocentric direction ('boundary vector cells').

17. Lever C, Burton S, Jeewajee A, O'Keefe J, Burgess N: **Boundary**
• **vector cells in the subiculum of the hippocampal formation**. *J Neurosci* 2009, **29**:9771-9777.
Discovery of the 'boundary vector cells' predicted by Refs. [14,15,16•], in the subiculum.

18. Koenig J, Linder AN, Leutgeb JK, Leutgeb S: **The spatial**
• **periodicity of grid cells is not sustained during reduced theta oscillations**. *Science* 2011, **332**:592-595.
Disruption of the theta rhythm by innactivation of the medial septum disrupts the spatial firing pattern of grid cells in medial entorhinal cortex, but not of hippocampal place cells, or other spatial cells in medial entorhinal cortex (including boundary vector cells).

19. Harvey CD, Collman F, Dombeck DA, Tank DW: **Intracellular**
•• **dynamics of hippocampal place cells during virtual navigation**. *Nature* 2009, **461**:941-946.
Simultaneous intra-cellular and extra-cellular recording from hippocampal place cells as a mouse navigates in virtual reality. The findings show that theta-phase precession of place cell firing reflects a membrane potential oscillation whose amplitude and frequency increase in the firing field, consistent with the prediction in [3••].

20. Epsztein J, Lee AK, Chorev E, Brecht M: **Impact of spikelets on**
• **hippocampal CA1 pyramidal cell activity during spatial exploration**. *Science* 2010, **327**:474-477.
Intra-cellular recording from hippocampal place cells in freely moving rats, showing that most action potentials are triggered by spikelets, probably reflecting dendritic spikes.

21. McNaughton BL, Barnes CA, Gerrard JL, Gothard K, Jung MW, Knierim JJ, Kudrimoti H, Qin Y, Skaggs WE, Suster M, Weaver KL: **Deciphering the hippocampal polyglot: the hippocampus as a path integration system**. *J Exp Biol* 1996, **199**:173-185.

22. Redish AD: *Beyond the Cognitive Map: From Place Cells to Episodic Memory*. Cambridge MA: MIT Press; 1999.

23. O'Keefe J, Burgess N: **Dual phase and rate coding in hippocampal place cells: theoretical significance and relationship to entorhinal grid cells**. *Hippocampus* 2005, **15**:853-866.

24. Burgess N, Barry C, O'Keefe J: **An oscillatory interference**
•• **model of grid cell firing**. *Hippocampus* 2007, **17**:801-812.
Describes how grid cell firing could reflect the interference of multiple oscillatory inputs whose frequencies vary linearly with running speed and as a cosine function of running direction ('velocity controlled oscillators'). These oscillations could occur either in dendritic subunits or in separate cells. Phase reset from place cells maintains oscillatory phase coherence. This model was first presented in [27].

25. Burgess N: **Grid cells and theta as oscillatory interference:**
• **theory and predictions**. *Hippocampus* 2008, **18**:1157-1174.
Quantitative predictions, from the oscillatory interference model of grid cell firing, for the frequencies of local field potential theta, theta-band firing rhythmicity, grid scale and running speed in freely moving animals.

26. Hasselmo ME: **Grid cell mechanisms and function:**
• **Contributions of entorhinal persistent spiking and phase resetting**. *Hippocampus* 2008, **18**:1213-1229.
Implementation of the oscillatory interference model of grid cell firing in which different velocity-controlled oscillators occur in different cells rather than in different dendritic subunits, consistent with the finding of persistent spiking cells *in vitro*.

27. Burgess N, Barry C, Jeffery KJ, O'Keefe J: **A grid and place cell model of path integration utilizing phase precession versus theta**. *Computational Cognitive Neuroscience Conference Poster*; *Washington, DC: 2005* http://posters.f1000.com/PosterList?posterID=225.

28. Kamondi A, Acsady L, Wang XJ, Buzsaki G: **Theta oscillations in**
•• **somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials**. *Hippocampus* 1998, **8**:244-261.
Study of somatic and dendritic membrane potentials in CA1 pyramidal cells in anaethetised rats. Dendritic depolarisation produces dendritic spikes and large amplitude dendritic membrane potential oscillations in the theta range. Proposes a somato-dendritic interference model, in which increasing dendritic oscillation amplitude overcomes hyperpolarising somatic input at successively earlier phases, but also suggests the presence of intrinsic dendritic oscillations.

29. Burgess N, O'Keefe J, Recce M: **Using hippocampal 'place cells' for navigation, exploiting phase coding**. In *Neural Information Processing Systems*, vol 5. Edited by Hanson SE, Cowan JD, Giles CL. Morgan Kaufmann; 1993:929-936.

30. Geisler C, Diba K, Pastalkova E, Mizuseki K, Royer S, Buzsaki G: **Temporal delays among place cells determine the frequency of population theta oscillations in the hippocampus**. *Proc Natl Acad Sci USA* 2010, **107**:7957-7962.

31. Losonczy A, Zemelman BV, Vaziri A, Magee JC: **Network**
•• **mechanisms of theta related neuronal activity in hippocampal CA1 pyramidal neurons**. *Nat Neurosci* 2010, **13**:967-972.
In vitro simulation of the somato-dendritic interference model by mimicking the proposed somatic and dendritic inputs to place cells using glutamate uncaging to see if they generate a membrane potential oscillation consistent with theta-phase precession.

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

32. Magee JC: **Dendritic mechanisms of phase precession in hippocampal CA1 pyramidal neurons**. *J Neurophysiol* 2001, **86**:528-532.
Tests the somato-dendritic interference model via patch-clamping *in vitro*, to see if out-of-phase oscillatory somatic and dendritic inputs of the same frequency generate a membrane potential oscillation consistent with theta-phase precession.

33. Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G: **Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells**. *Nature* 2002, **417**:738-741.
Extra-cellular data from freely moving rats consistent with the somato-dendritic model in that place cell firing phase shows a correlation with instantaneous firing rate.

34. Mehta MR, Lee AK, Wilson MA: **Role of experience and oscillations in transforming a rate code into a temporal code**. *Nature* 2002, **417**:741-746.
Increasing experience within a trial increases both the robustness of place cell phase precession and the asymmetry of the firing fields. Proposes the depolarizing ramp model, in which increasing depolarization through the firing field drives earlier firing within each theta cycle.

35. Tsodyks MV, Skaggs WE, Sejnowski TJ, McNaughton BL: **Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model**. *Hippocampus* 1996, **6**:271-280.
Proposes the spreading activation model of place cell theta-phase precession, in which sensory-driven early-phase firing propagates via recurrent connections in CA3 to drive (later-phase) firing of place cells with firing fields further along the track.

36. Jensen O, Lisman JE: **Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells**. *Learn Mem* 1996, **3**:279-287.
Applies a model that stores sequential events within successive gamma cycles in each theta cycle to explain theta phase precession of place cell firing. The upcoming sequence of place cells activated along a familiar path are successively retrieved via recurrent connections in CA3 in a manner analogous to Ref. [35•], but further organised by local dynamics in the gamma and theta bands.

37. Romani S, Sejnowski TJ, Tsodyks M: **Intracellular dynamics of virtual place cells**. *Neural Comput* 2010, **23**:651-655.

38. Burgess N, Recce M, O'Keefe J: **A model of hippocampal function**. *Neural Netw* 1994, **7**:1065-1081.

39. Skaggs WE, McNaughton BL, Wilson MA, Barnes CA: **Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences**. *Hippocampus* 1996, **6**:149-172.

40. Huxter JR, Senior TJ, Allen K, Csicsvari J: **Theta phase-specific codes for two-dimensional position, trajectory and heading in the hippocampus**. *Nat Neurosci* 2008, **11**:587-594.

41. Ekstrom AD, Meltzer J, McNaughton BL, Barnes CA: **NMDA receptor antagonism blocks experience-dependent expansion of hippocampal ''place fields''**. *Neuron* 2001, **31**:631-638.

42. Pastalkova E, Itskov V, Amarasingham A, Buzsaki G: **Internally generated cell assembly sequences in the rat hippocampus**. *Science* 2008, **321**:1322-1327.
Theta-band temporal organisation of place cell firing as rats run in a running wheel resembles theta phase precession in foraging rats, suggesting that it is determined by intrinsic dynamics rather than physical movement relative to environmental sensory input.

43. Shin J: **The interrelationship between movement and cognition: theta rhythm and the P300 event-related potential**. *Hippocampus* 2010 doi: 10.1002/hipo 20792.

44. Lisman J, Redish AD: **Prediction, sequences and the hippocampus**. *Philos Trans R Soc Lond B Biol Sci* 2009, **364**:1193-1201.

45. Blair HT, Kishan G, Zhang K: **Phase coding and central pattern generation by ring attractors: a model of theta cells, grid cells, and place cells**. *Hippocampus* 2008, **18**:1239-1255.

46. Mhatre H, Gorchetchnikov A, Grossberg S: **Grid cell hexagonal patterns formed by fast self-organized learning within entorhinal cortex**. *Hippocampus* 2010 doi: 10.1002/hipo 20901.

47. Remme MW, Lengyel M, Gutkin BS: **Democracy-independence trade-off in oscillating dendrites and its implications for grid cells**. *Neuron* 2010, **66**:429-437.
Computational analysis showing that independent membrane potential oscillations in different dendritic subunits would rapidly synchronize. Implies that oscillatory grid cell models require oscillators with different frequencies to be in different cells.

48. Jeewajee A, Barry C, O'Keefe J, Burgess N: **Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats**. *Hippocampus* 2008, **18**:1175-1185.
Verification of the quantitative prediction of Ref. [25•] relating the (theta-band) frequency of modulation of grid cell firing to grid scale, running speed and local-field potential theta frequency.

49. Giocomo LM, Hasselmo ME: **Computation by oscillations: Implications of experimental data for theoretical models of grid cells**. *Hippocampus* 2008, **18**:1186-1199.

50. Giocomo LM, Zilli EA, Fransen E, Hasselmo ME: **Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing**. *Science* 2007, **23**:1719-1722.
The first experimental paper to relate the (inferred) spatial scale of grid cell firing to the frequency of theta-band membrane potential oscillations *in vitro*.

51. O'Keefe J: **Hippocampal neurophysiology in the behaving animal**. In *The Hippocampus Book*. Edited by Andersen P, Morris RGM, Amaral DG, Bliss TVP, O'Keefe J. Oxford: Oxford Neuroscience; 2006:475-548.

52. Jeewajee A, Lever C, Burton S, O'Keefe J, Burgess N: **Environmental novelty is signaled by reduction of the hippocampal theta frequency**. *Hippocampus* 2008, **18**:340-348.

53. Langston RF, Ainge JA, Couey JJ, Canto CB, Bjerknes TL, Witter MP, Moser EI, Moser MB: **Development of the spatial representation system in the rat**. *Science* 2010, **328**:1576-1580.
Developmental study showing the emergence of directional, place and grid-like representations as rat pups first start to explore their environment. Shows adult-like directional firing at the earliest ages, and that development of stable grid-like representations co-occurs with development of synchrony in medial entorhinal stellate cell membrane potentials characteristic of interneuronal coupling.

54. Barry C, Hayman R, Burgess N, Jeffery KJ: **Experience-dependent rescaling of entorhinal grids**. *Nat Neurosci* 2007, **10**:682-684.
Manipulating environmental geometry affects grid cell firing patterns similarly to place cell firing [14]. The effect reduces with experience of the environments, suggesting experience-dependent connections between place or boundary-vector cells and grid cells. Grid scale varies across cells in a step-wise fashion, and even grids of different spatial scale have common orientations, consistent with attractor models.

55. Zilli EA, Hasselmo ME: **Coupled noisy spiking neurons as velocity-controlled oscillators in a model of grid cell spatial firing**. *J Neurosci* 2010, **30**:13850-13860.

56. Fuhs MC, Touretzky DS: **A spin glass model of path integration in rat medial entorhinal cortex**. *J Neurosci* 2006, **26**:4266-4276.
The first continuous attractor model of grid cell firing.

57. McNaughton BL, Battaglia FP, Jensen O, Moser EI, Moser MB: **Path integration and the neural basis of the 'cognitive map'**. *Nat Rev Neurosci* 2006, **7**:663-678.

58. Burak Y, Fiete IR: **Accurate path integration in continuous attractor network models of grid cells**. *PLoS Comput Biol* 2009, **5**:e1000291.

59. Zhang K: **Representation of spatial orientation by the intrinsic dynamics of the head-direction cell ensemble: a theory**. *J Neurosci* 1996, **16**:2112-2126.
The theoretical basis for the application of continuous attractor models to head-direction cells and place cells.

60. Skaggs WE, Knierim JJ, Kudrimoti HS, McNaughton BL: **A model of the neural basis of the rat's sense of direction**. *Adv Neural Inf Process Syst* 1995, **7**:173-180.

61. Samsonovich A, McNaughton BL: **Path integration and cognitive mapping in a continuous attractor neural network model**. *J Neurosci* 1997, **17**:5900-5920.

62. Conklin J, Eliasmith C: **A controlled attractor network model of path integration in the rat**. *J Comput Neurosci* 2005, **18**:183-203.

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002

63. •• Navratilova Z, Giocomo LM, Fellous JM, Hasselmo ME, McNaughton BL: **Phase precession and variable spatial scaling in a periodic attractor map model of medial entorhinal grid cells with realistic after-spike dynamics**. *Hippocampus* 2011, doi:10.1002/hipo.20939, in press.
Combines the spreading activation model of place cell phase precession [34••,35•] and continuous attractor model of grid cell firing [55,56•,57] to model the spatial and temporal structure of grid cell firing via a combination of recurrent interactions and intrinsic dynamics.

64. Muller RU, Kubie JL: **The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells**. *J Neurosci* 1987, **7**:1951-1968.

65. van Strien NM, Cappaert NL, Witter MP: **The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network**. *Nat Rev Neurosci* 2009, **10**:272-282.

66. • Brandon MP, Bogaard AR, Libby CP, Connerney MA, Gupta K, Hasselmo ME: **Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning**. *Science* 2011, **332**:599.
Disruption of the theta rhythm by innactivation of the medial septum disrupts the spatial firing pattern of grid cells in medial entorhinal cortex, but not the directional firing of directionally modulated cells there.

67. • Wills TJ, Cacucci F, Burgess N, O'Keefe J: **Development of the hippocampal cognitive map in preweanling rats**. *Science* 2010, **328**:1573-1576.
Developmental study showing the emergence of directional, place and grid-like representations as rat pups first start to explore their environment. Shows adult-like directional firing and theta rythmicity at the earliest ages, and that spatially stable place cell firing precedes spatially stable grid cell firing by several days.

Please cite this article in press as: Burgess N, O'Keefe J. Models of place and grid cell firing and theta rhythmicity, Curr Opin Neurobiol (2011), doi:10.1016/j.conb.2011.07.002