



# Spatial rate/phase correlations in theta cells can stabilize randomly drifting path integrators

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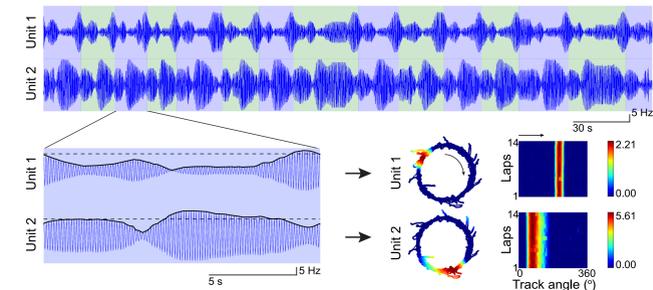
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## Summary

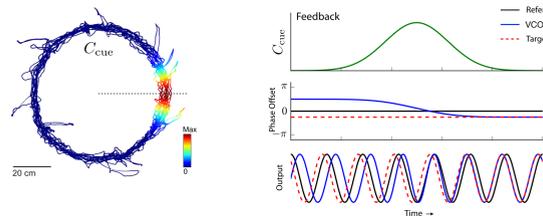
The spatial firing of place cells and grid cells is thought to reflect the association of environmental features, such as external sensory cues and local boundaries, with the path integration of idiosyncratic cues, such as movement direction and speed. Models of path integration as temporal phase interference among neural oscillators, supported by evidence of theta cells with directionally tuned burst frequency (Welday et al., 2011), must address the critical problem that interference patterns randomly drift in space in the presence of intrinsic phase noise (Monaco et al., 2011; Blair et al., 2014). Here, we present a synchronization theory in which a hypothetical population of theta-rhythmic (6–10 Hz) “location-controlled” oscillators (or LCOs) mediates the ability of environmental features to stabilize path integration in a downstream layer of velocity-controlled oscillators (VCOs). We suppose that representations of objects/landmarks or boundaries are weakly theta-modulated and combine to form spatially modulated inputs to the LCOs that are fixed to the environment. This environmental drive combines with ongoing theta oscillations to create a robust correlation between higher firing rates and earlier theta phases of bursting. We show that this rate/phase correlation in LCOs is sufficient to selectively entrain VCOs to prevent drifting with noise. This entrainment requires associative learning during early theta phases at LCO-to-VCO synapses to construct spatially antiphase inputs that drive the environmental feedback to VCOs. We provide a mathematical derivation, an abstract rate–phase model, and an implementation of this sensory feedback mechanism in a spiking network model of phasic bursting neurons. Notably, we present preliminary recording data from subcortical regions in rats, including lateral septum, showing theta cells that qualitatively match the spatial rate/phase correlations of our hypothesized LCOs. These results support a hybrid “place-to-grid” framework where temporal and attractor mechanisms may be complementary without depending on the fine tuning of phase or connectivity

## Multiple oscillator model of hippocampal-like spatial maps

- Path integration in the phase of velocity-controlled oscillators (VCOs) can produce synchronization patterns in space such as grid or place cells



- However, these spatial patterns are highly susceptible to biological levels of period variance (phase noise) in the oscillators
- Theta phase-code feedback driven by environmental features may be one mechanism for correcting errors as oscillator phases randomly drift



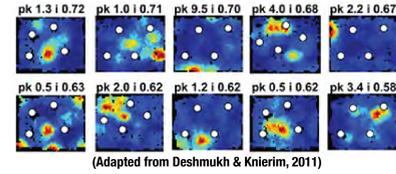
(Adapted from Monaco et al 2011)

- We studied a generic implementation of a sensory-based phase-code feedback in the previous study (Monaco et al 2011), but here we present a mechanistic hypothesis that posits a novel functional cell type that we call the “location-controlled” theta oscillator or LCO.

## Environmental vector inputs

### LVCs

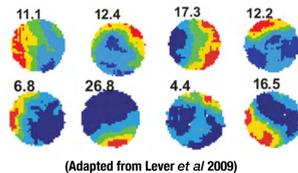
- Information about landmarks and their location in the environment is encoded by object-related activity in lateral entorhinal cortex (LEC) or landmark-vector cells (LVCs) in hippocampus (Deshmukh & Knierim 2011, 2013; Deshmukh et al 2012)
- LEC activity is only weakly theta modulated (Deshmukh et al 2010)



(Adapted from Deshmukh & Knierim, 2011)

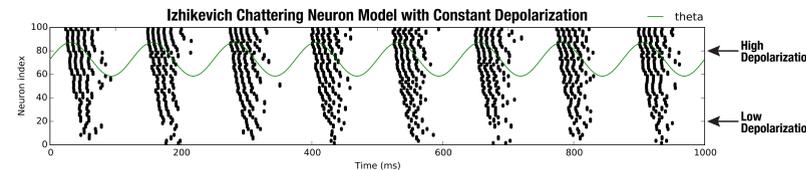
### BVCs

- Hartley et al (2000) proposed a model of boundary-vector cells as inputs to hippocampal place cells to explain place field dependence on environmental geometry
- BVC-like cells were subsequently discovered in subiculum (Lever et al 2009), along with border cells in MEC and other areas (Savelli et al 2008; Solstad et al 2008)



(Adapted from Lever et al 2009)

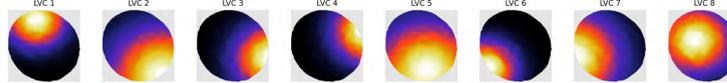
## Robust rate-to-phase conversion



- Converting a rate code to a temporal code can be achieved robustly in bursting neurons by combining depolarization with an ongoing theta oscillation (as shown experimentally in CA1 place cells by Mehta, Lee, & Wilson, 2002)
- This mechanism produces firing at earlier theta phases for higher firing rates

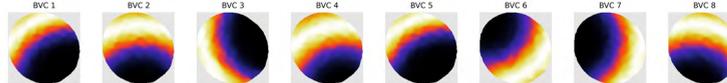
## Simplified rate/phase model

### LVCs



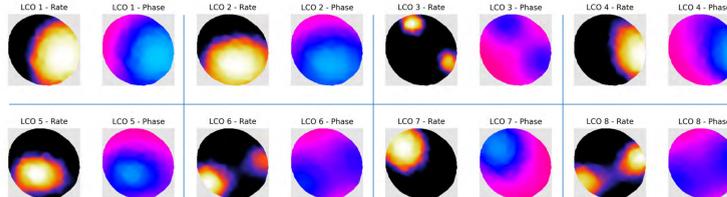
- LVCs carry a firing-rate code and are not theta-modulated in this model, though biological landmark-vector cells or other carriers may be weakly theta-modulated
- The LVC output may theoretically represent an average over a set of place cells

### BVCs



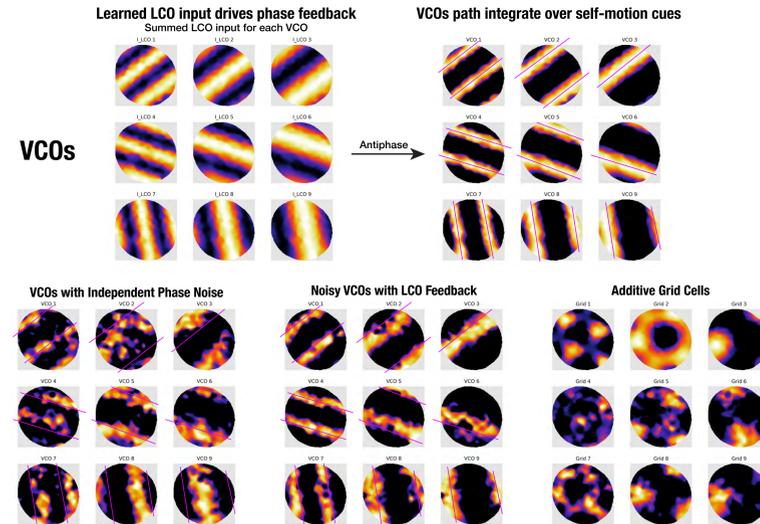
- Boundary-vector representations are computed as a skewed Gaussian profile that peaks at a preferred radial distance from the arena boundary in the preferred direction

### LCOs



- Theta oscillations and landmark/boundary information (from BVC/LVCs) are integrated within putative “location-controlled oscillators” using a firing-rate nonlinearity that creates a correlation between high firing rates (red, left plots) and early theta phases (copper, right plots)

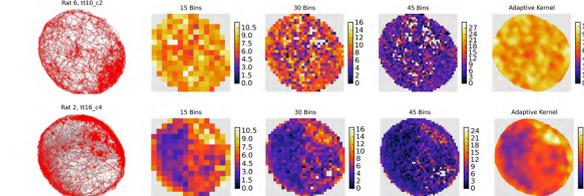
## Antiphase LCO inputs entrain drifting VCOs



## Are there spatially informative theta cells with stable rate/phase correlations?

- The Blair lab has been collecting data from long-duration recording sessions (~3 hrs) of freely exploring rats in an 80cm cylindrical arena
- Tetrodes were located in subcortical and hippocampal areas with theta-rhythmic fast spiking interneurons to examine whether arena-scale spatial correlations in firing phase were temporally stable in a way that may provide environmental resetting information to the path integrator
- Despite long recordings, wall following, longer stops and pauses, and other factors produce highly non-uniform sampling of the arena; the following is a preliminary attempt to make smooth estimates of firing rate and phase across the arena

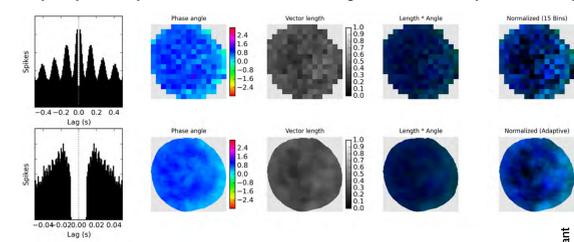
### Adaptive Gaussian kernel smoothing for ratemaps: Comparison to standard binning



- (Top) Typical theta cell with weak spatial modulation

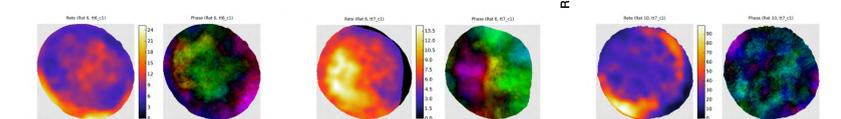
- (Bottom) Example of a theta cell with arena-scale smooth spatial modulation of firing rate with location

### Adaptive phase maps with mean resultant vector length as a measure of phase variability

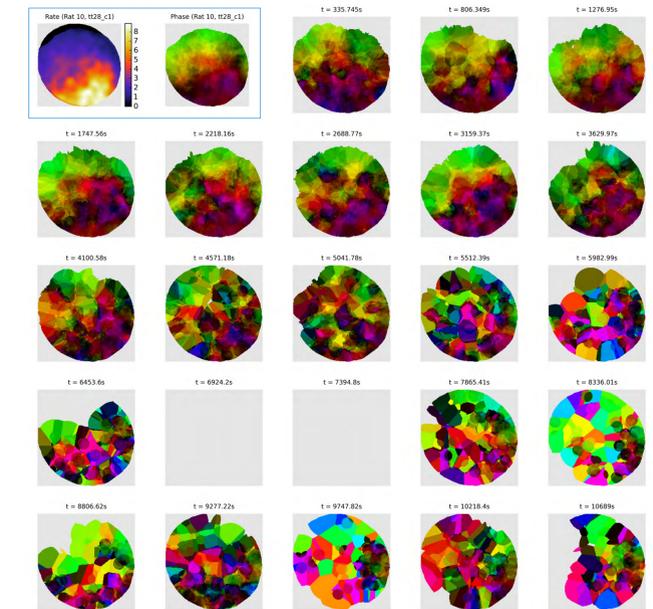


- Strong theta cell with subtle gradient in phase from later phase in the arena west to slightly earlier (lighter blue) phase in the arena east. The adaptive kernel is able to reveal more detail in this gradient

### Rate/phase estimates for a set of example theta cells

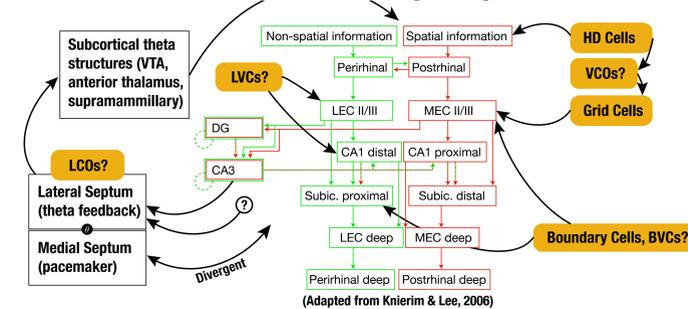


## Stability of phase across space



- An example theta cell from lateral septum with strong rate/phase correlation across space (two left plots on top row). Estimated phase distributions for a series of time windows across the recording session demonstrate that the overall structure of the phase modulation can remain stable, despite increasingly fewer moments of fast locomotion toward the end of the session from which to sample.

## Candidate networks for feedback



## Conclusion

We previously demonstrated a model of synchronization among multiple oscillators that performed path integration along randomized preferred directions (Monaco et al 2011). Using that model, we showed that generalized phase-code feedback could correct errors caused by intrinsic variability in the underlying oscillations, but did not characterize any specific mechanism for the feedback pathway. Here, we tested the hypothesis that theta-modulated subcortical areas such as lateral septum could support theta cells with spatial correlations of high firing rate and early theta phase, based on mechanisms established by Mehta et al (2002). Putative LCOs fire strongest at early theta phases at a particular location in the environment determined by landmarks and boundaries. By learning an input basis set of antiphase LCOs, we showed that a layer of VCOs produce spatial patterns that remain fixed relative to the environment, and that grid cells constructed from these VCOs withstand drifting due to intrinsic phase noise. Thus landmark-based rate/phase correlations in extrahippocampal areas may provide the sensory feedback required by temporal models of neural representations of space.

**Acknowledgements** This work is supported by CRCNS grant NIH R01MH079511 to K. Zhang, H. T. Blair, and J. J. Knierim.

**References** Barry et al (2006). Rev Neurosci, 17(1-2):71–97; Deshmukh et al (2012). Hippocampus, 22(10):2045–58; Deshmukh & Knierim (2011). Front Behav Neurosci, 5:69; Deshmukh & Knierim (2013). Hippocampus, 23(4):253–267; Deshmukh et al (2010). J Neurophysiol, 104(2):994–1006; Hartley et al (2000). Hippocampus, 10:369–379; Izhikevich (2003). IEEE Trans Neural Netw, 14(6):1569–72; Knierim et al (2006). Hippocampus, 16(9):755–64; Lever et al (2009). J Neurosci, 29(31):9771–7; Luo et al (2011). Science, 333(6040):353–7; Mehta et al (2002). Nature, 417(6890):741–6; Monaco et al (2011). Front Comput Neurosci, 5:39; Savelli et al (2008). Hippocampus, 18(12):1270–1282; Solstad et al (2008). Science, 322(5909):1865–8; Takamura et al (2006). Hippocampus, 16(8):635–44