UCL NEUROSCIENCE

Neural mechanisms of spatial cognition

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Outline

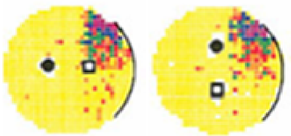
- ***Environmental inputs, boundary vector cells & (single) place cells***
- *Implications for human memory*
- *Path integration & "theta phase precession"*
- *Oscillatory Interference model of (single) grid cell firing*
    - *The 'baseline' oscillation and LFP theta*
- *Systems-level issues*
    - *Novelty & environmental inputs - path integration interactions*
    - *Hybrid OI-attractor model of (populations of) GCs*
- *Implications for human memory*
    - *A systems-level model of spatial memory & imagery*

Place cell firing represents current location using environmental inputs and path integration. *O'Keefe, 1976; Chen et al., 2013*

1. Environmental sensory information

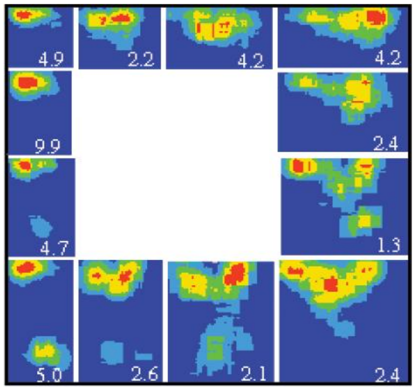
Environmental boundaries particularly influence place cells:
See also (Muller & Kubie, 1987)

Unlike discrete landmarks



Cressant et al., J Neurosci 1997

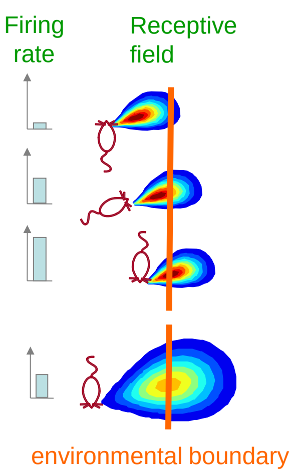
122cm

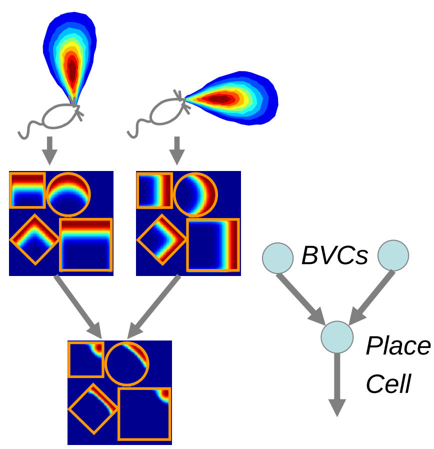


61cm *O'Keefe & Burgess, 1996*

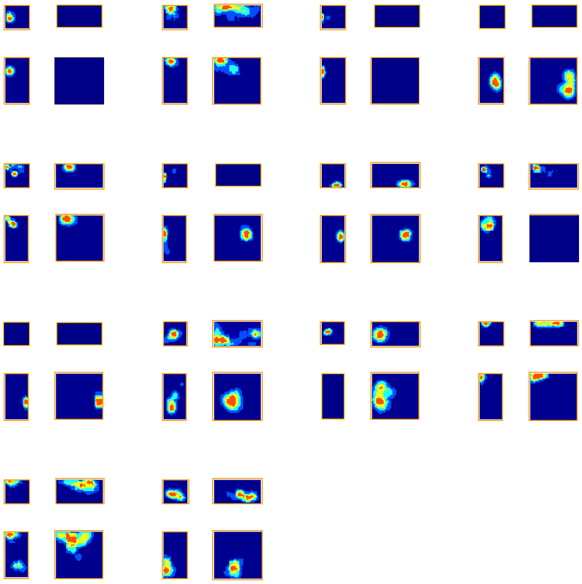
Place cell firing as a thresholded sum of "Boundary Vector Cell" inputs

Boundary Vector Cells (BVCs)



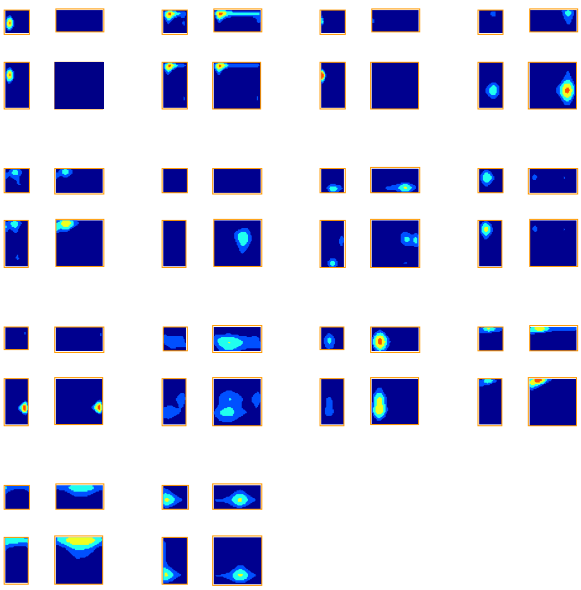


Hartley et al., Hippocampus (2000); Burgess et al Biol Cyb (2000); O'Keefe & Burgess, 1996



Data

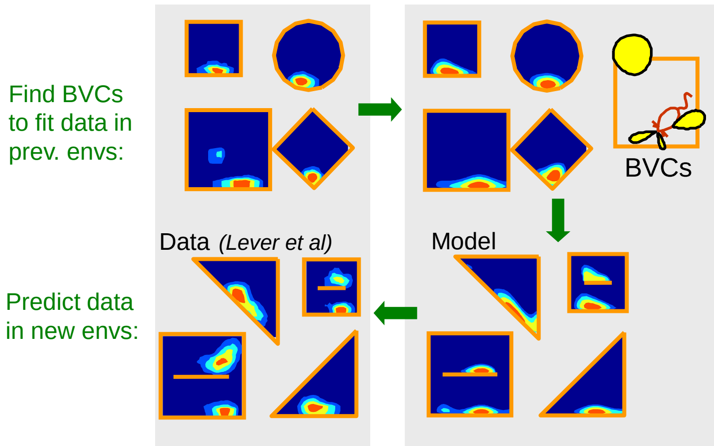
O'Keefe & Burgess (1996)



Model

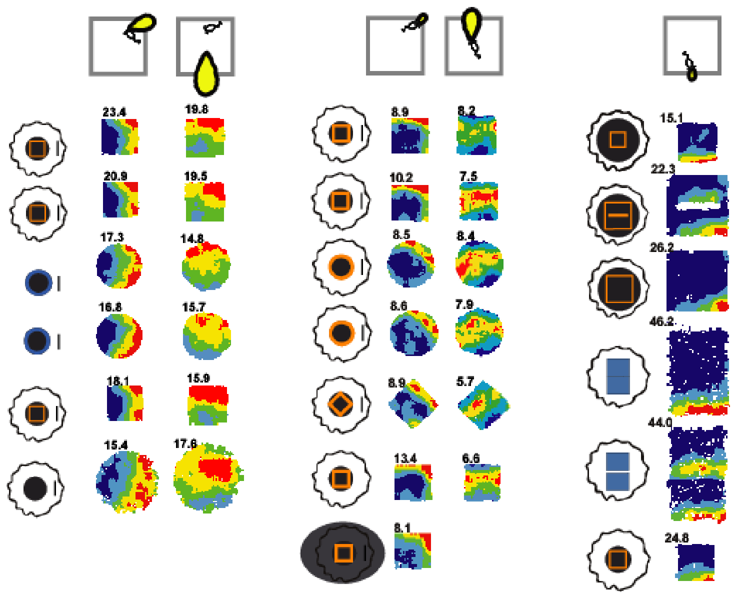
Hartley et al., Hippocampus (2000)

Place cell firing in new environmental layouts can be predicted using BVCs.



Hartley et al., Hippocampus (2000)

BVCs subsequently found in subiculum & entorhinal cortex



Barry, Lever et al Rev Neurosci 2006;
Lever, Burton, Jeewajee, O'Keefe, Burgess, J Neurosci 2009; Solstad et al Science, 2008

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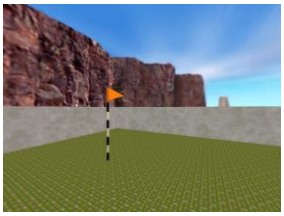
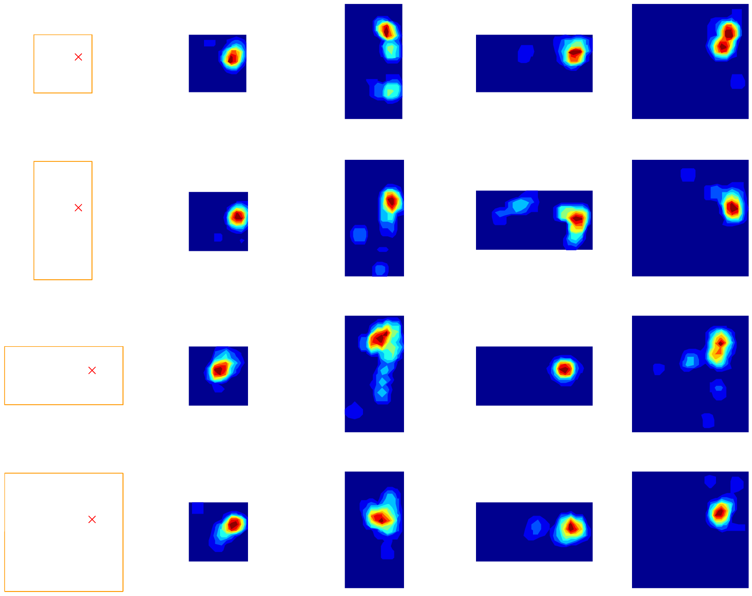
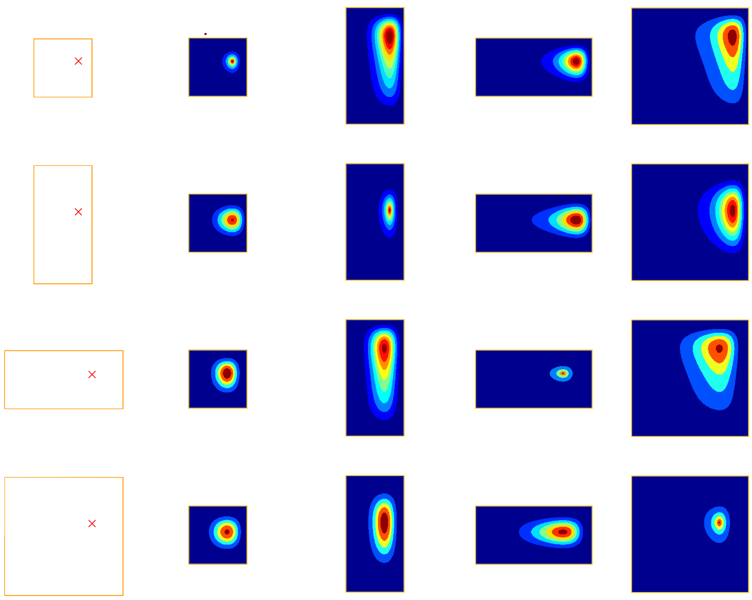
BVC model predicts human search distributions after manipulations of environmental shape



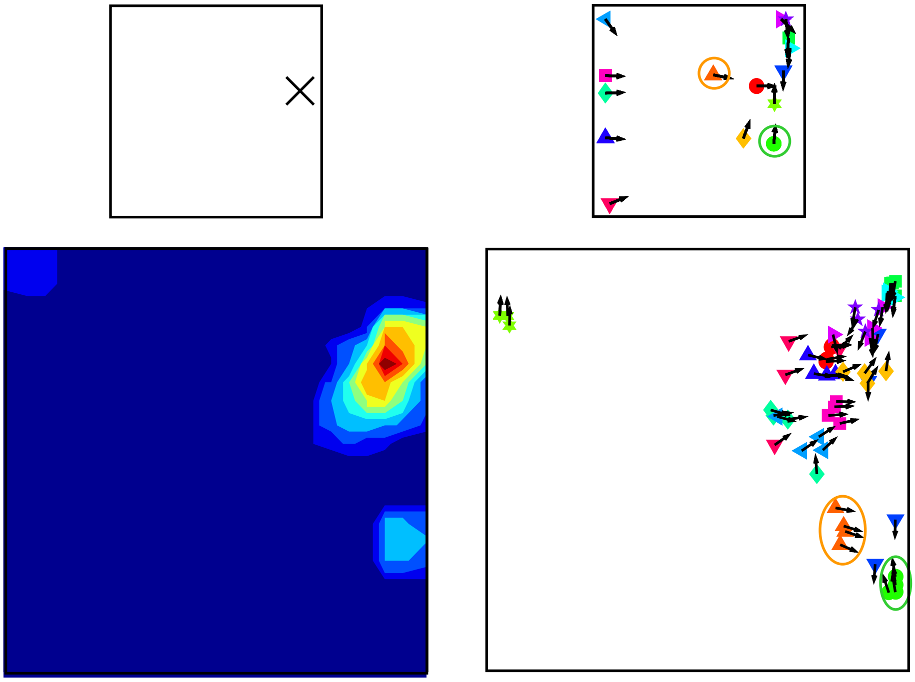
Hartley, Trinkler, Burgess, Cognition (2004)



Data



Model



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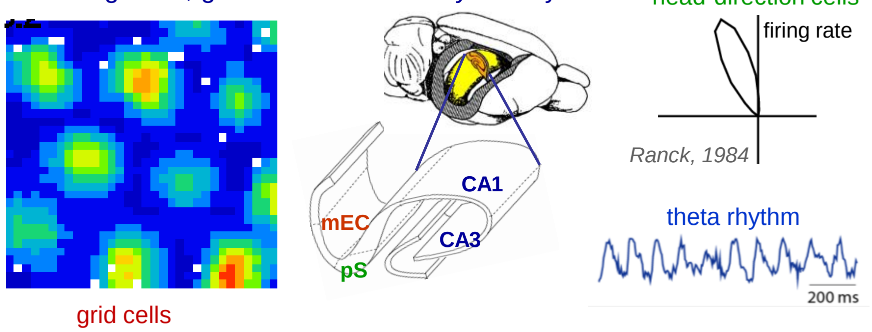
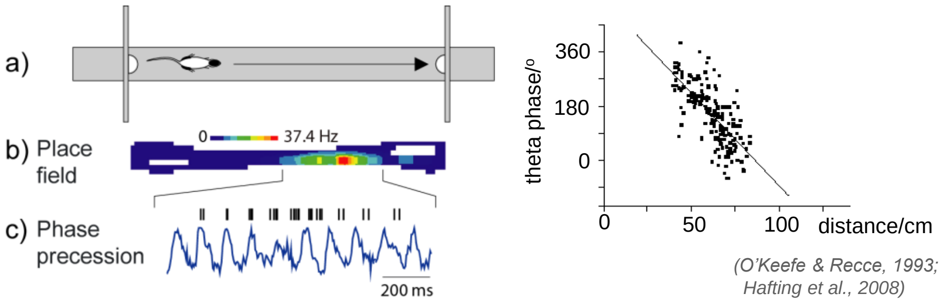
Path integration, grid cells and theta rhythmicity.



Theta-phase of place & grid cell firing encodes distance travelled

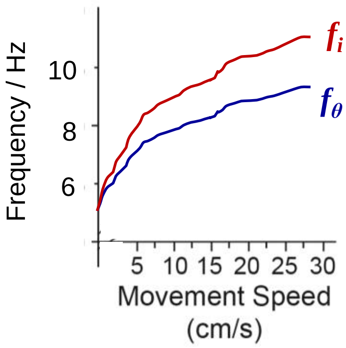


(O'Keefe & Recce, 1993; Hafting et al., 2008)

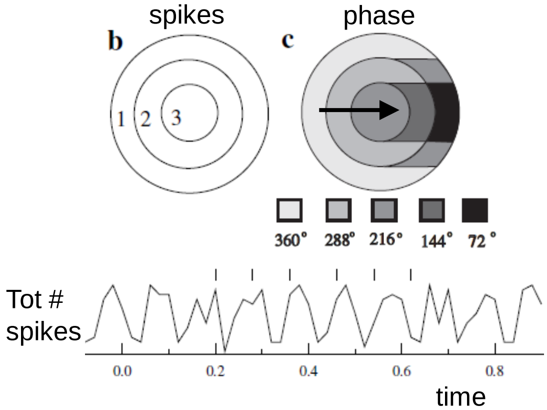
Theta-phase of place & grid cell firing encodes distance travelled
But running speed and theta frequency vary..

⇒ Intrinsic firing freq exceeds LFP theta freq by amount prop. to speed.

$f_i - f_\theta \sim speed$



LFP theta ~ net activity of
of phase-precessing place cells
Burgess et al., NIPS 93; Giesler et al., 2010

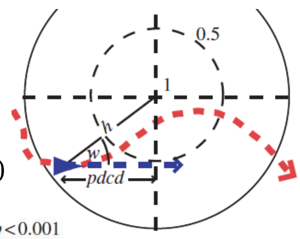


LFP theta & intrinsic firing frequencies are NOT INDEPENDENT!!

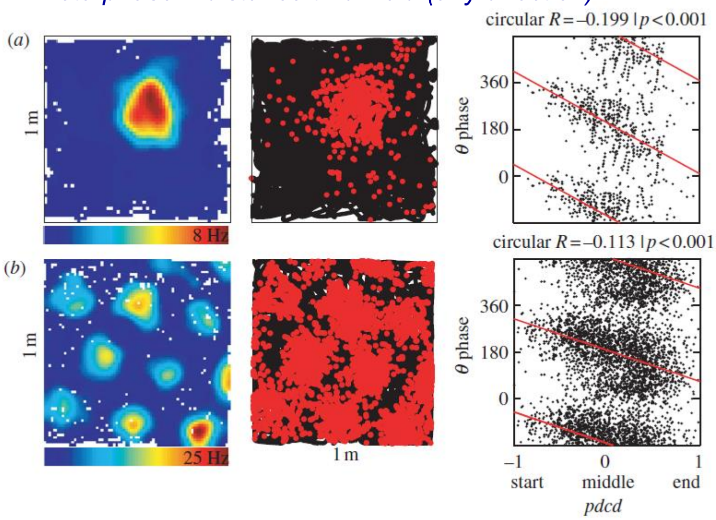
Theta phase precession in 2D

Map firing fields onto unit circle and find distance to field peak on current direction

$pdcd = h\cos(w)$

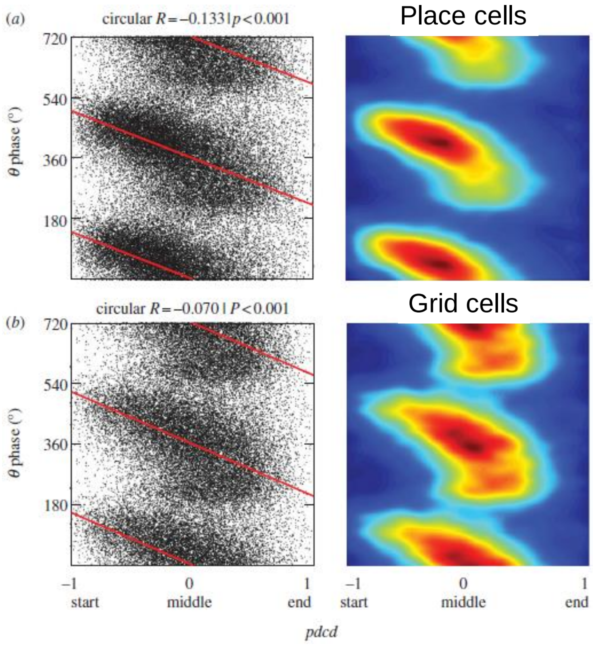


Theta phase ~ distance thru' field (any direction)



Jeewajee et al., 2014;
Climer et al., 2013;
Huxter et al., 2008;
Skaggs et al 1996;
Burgess et al., 1994

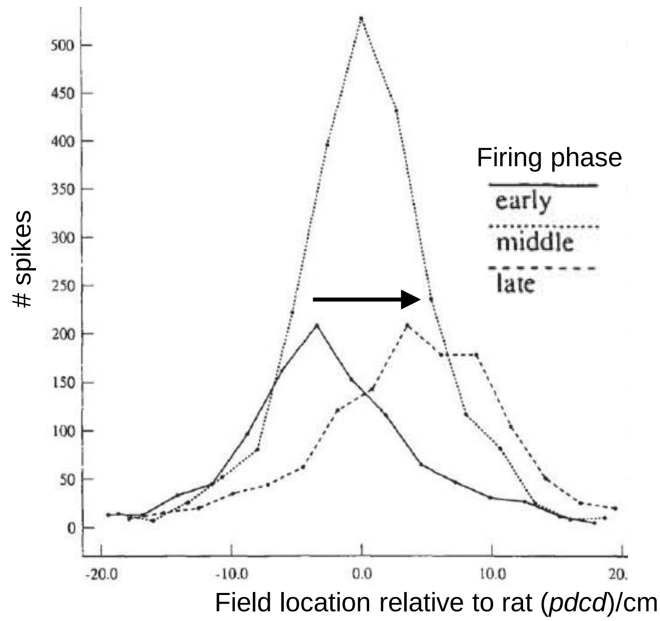
Theta phase precession in 2D, pooled data



Jeewajee et al., 2014;

Place cell population "forward sweeps" and theta phase precession: Two sides of the same coin, during motion?

But not re/prelay during non-theta?



Burgess et al, 1994;
Skaggs et al., 1996;
Johnson & Redish 2007
Gupta et al., 2012

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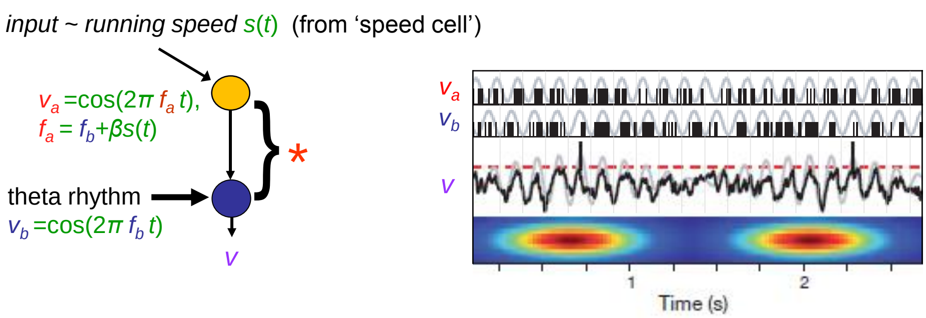
The Dual Oscillator model of theta-phase precession in place cell firing.

Speed-controlled oscillators give theta-phase coding of distance



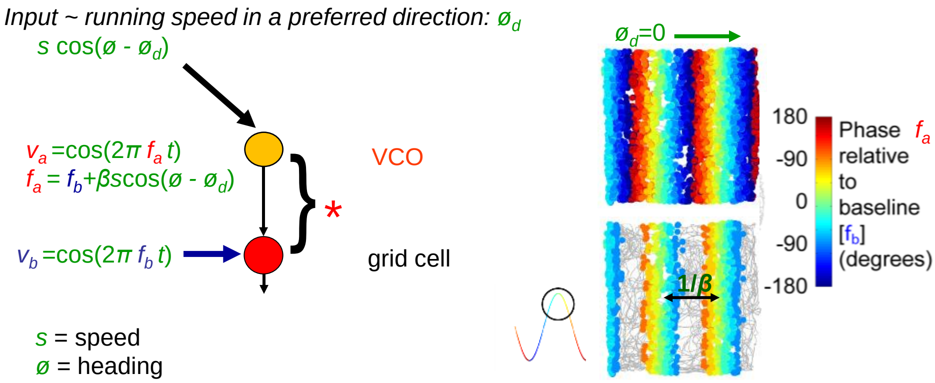
* phase difference is time integral of frequency difference which ~ running speed
i.e. theta-phase of v_a integrates running speed to give distance travelled

But distance travelled ≠ path integration
& place cells don’t have repeating firing fields

O’Keefe & Recce, 1993; Lengyel et al., 2003; Geisler et al., 2007; Burgess et al 2007.

Model of path integration and grid cell firing.

Velocity-controlled oscillators (VCOs) represent displacement along ‘preferred’ directions



* phase difference is time integral of frequency difference,
i.e., VCO theta-phase ~ displacement in preferred direction $ø_d$
β sets spatial scale

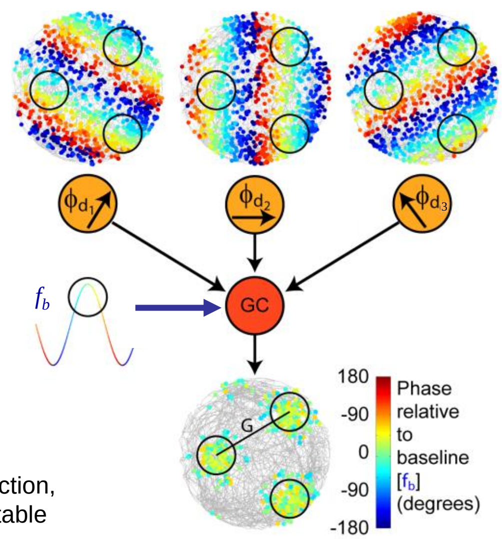
Burgess et al.,2005

Burgess, Barry, O’Keefe, Hippocampus, 2007; Burgess, Hippocampus, 2008

Model of path integration by grid cells and theta rhythmicity.

Velocity-Controlled Oscillators (VCOs)
Firing *phase* codes displacement
along preferred directions ($ø_d$):
$f_a = f_b + \beta\, s(t) \cos\{ø(t) - ø_d\}$

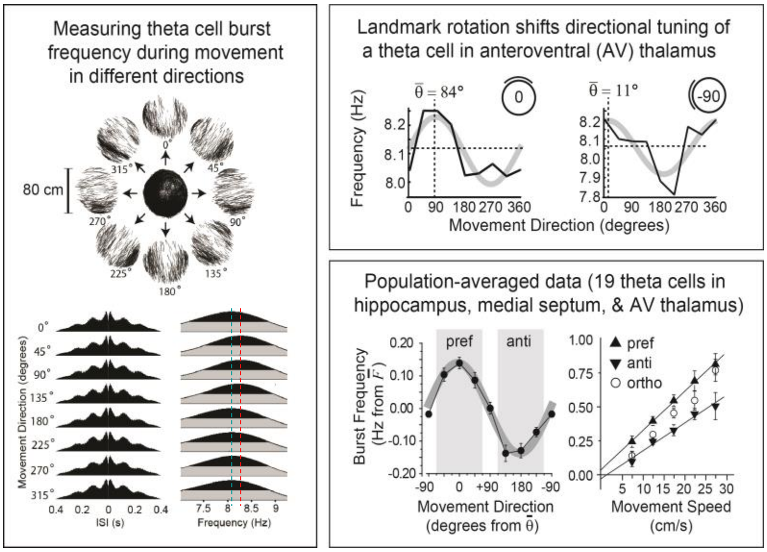
VCOs drive grid cell firing:



3 VCOs => Automatic phase-error correction,
and triangular grids are most stable

Burgess, Hippocampus, 2008. See also Hasselmo, Hippocampus, 2008.

Cosine directional tuning of “theta cell” intrinsic frequency



Welday et al., J Neurosci., 2011

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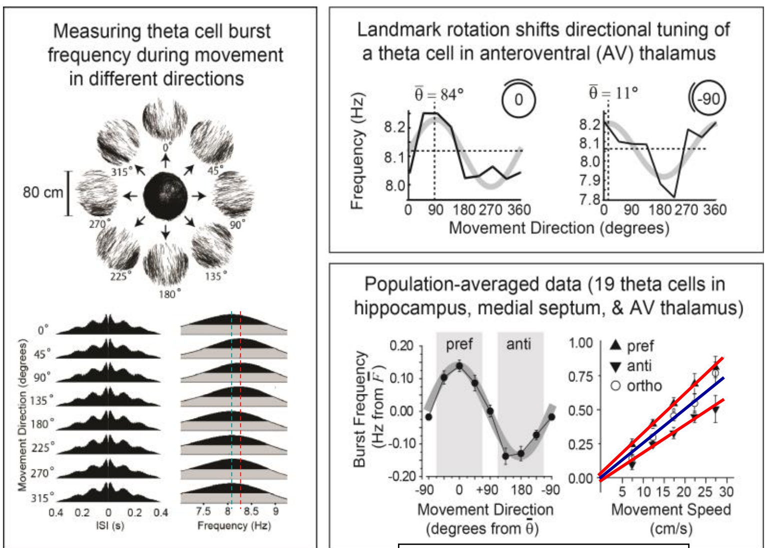
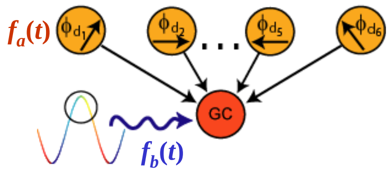


$$f_a \approx f_b + \beta s(t)\cos\{\varnothing(t)-\varnothing_d\}$$
$$f_b \approx f_0 + \gamma s(t)$$

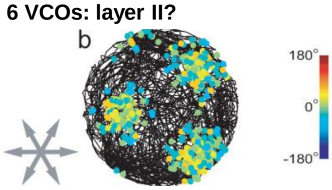
Welday et al., J Neurosci., 2011

Configurations of VCOs & grid cell

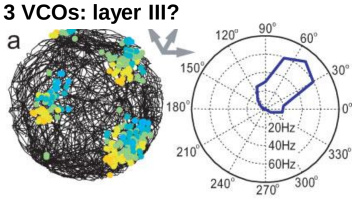
Burgess, Hippocampus, 2008



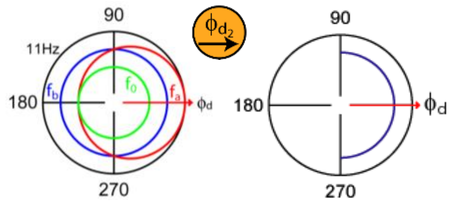
6 VCOs: layer II?



3 VCOs: layer III?



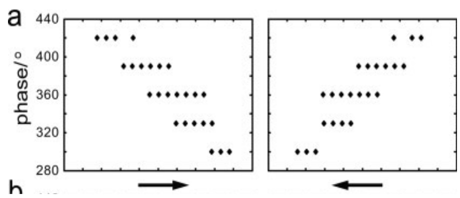
directionally modulated VCO inputs



freqs vs $\varnothing(t)$ x **filter vs $\varnothing(t)$**

$f_a(t) = f_b(t) + \beta\, s(t) \cos\{\varnothing(t) - \varnothing_d\}$

$f_b(t) = < f_a(t) >_{\varnothing_d}$



Phase precession

Measurable predictions for Grid Cells: intrinsic firing freq. f_i

depend on implementation of basic eqn: $f_a(t) = f_b(t) + \beta s(t) \cos(\varnothing(t) - \varnothing_d)$

Directionally modulated VCO inputs & $f_i = (f_a + f_b)/2$ implies:

$$f_i(t) = f_b(t) + \frac{\beta s(t)}{\pi} = f_b(t) + \frac{2 s(t)}{\sqrt{3}\pi G}$$

since scale $G = 2/\sqrt{3}\beta$

But we don't know $f_b(t)$.

If $f_b(t) = f_0 + \gamma\, s(t)$, $f_a(t) = f_0 + s(t)(\gamma + \beta \cos\{\varnothing(t) - \varnothing_d\})$

$$< f_i(t) >_{\phi(t)} = f_0 + \left(\gamma + \frac{2}{\sqrt{3}\pi G}\right) s(t)$$

NB if $\gamma \geq \beta$ then $f_a \geq f_0$

If LFP theta freq $f_\theta(t) \approx f_b(t)$ we could estimate γ and $f_0 = f_\theta(s=0)$ from LFP

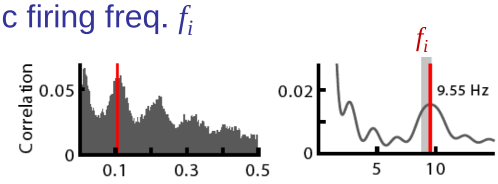
$s(t)$ = running speed
G = grid scale
$\varnothing(t)$ = running direction
$\varnothing_d$ = preferred direction

Burgess, Hippocampus, 2008

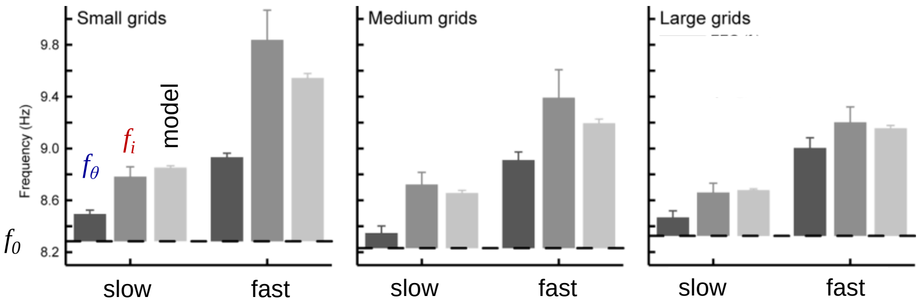
Predictions for grid cell intrinsic firing freq. f_i

$$f_i = f_0 + \left(\gamma + \frac{2}{\sqrt{3\pi G}}\right) s(t)$$

where $f_b = f_0 + \gamma s(t)$



Jeewajee, Barry, O'Keefe, Burgess, 2008



<median> 12.4 28.2 cm/s

NB need to estimate f_0 and γ per trial and carefully control for speed

(cf Stensola et al., 2013)

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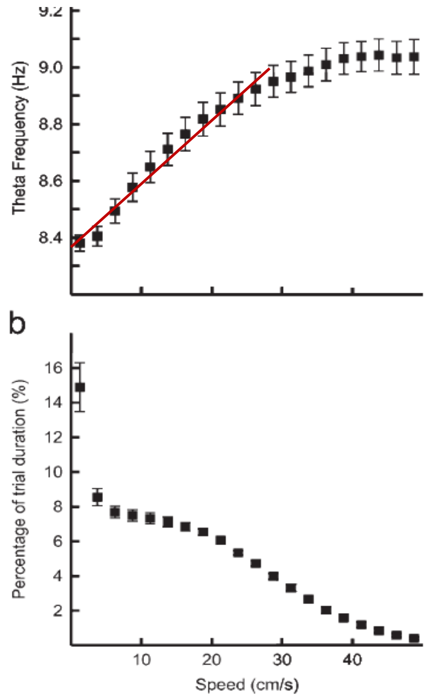
How to model LFP theta freq (f_θ)?

Try: $f_b(t) = f_0 + \gamma\, s(t)$;

$f_\theta \approx \langle f_b \rangle = f_0 + \langle\gamma\rangle\, s(t)$

- roughly true in *Jeewajee et al 2008* data.



Burgess, 2008

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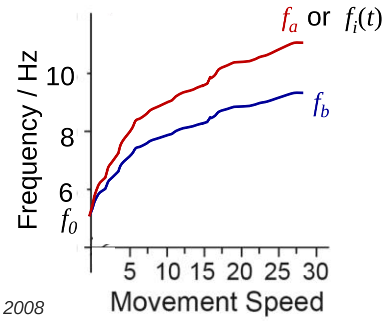
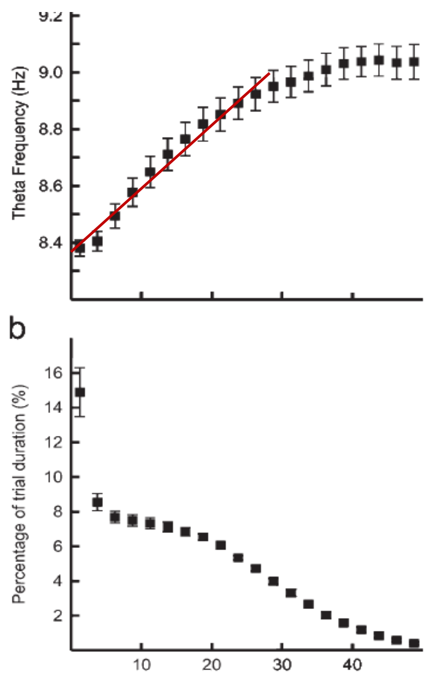
Need not be true in general, model only requires:

$f_a(t) = f_b(t) + \beta s(t)\cos(\phi(t) - \phi_d)$

=> $f_i(t) = f_b(t) + \dfrac{2s(t)}{\sqrt{3\pi G}}$



Burgess, 2008



Jeewajee et al., 2008

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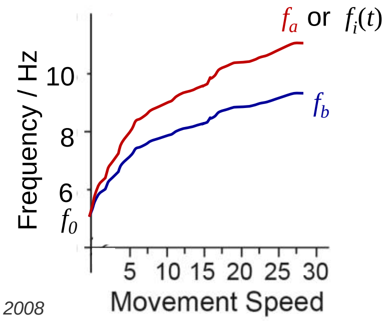


Burgess, 2008

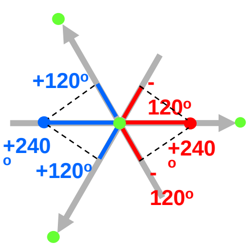
A FINAL COMMENT

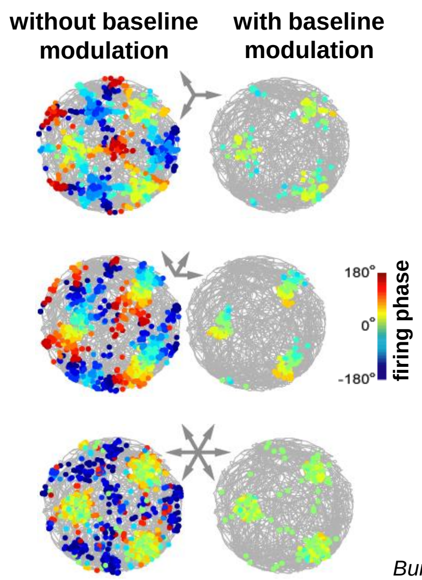
$f_b(t) = \langle f_a(t) \rangle_{\varnothing_d}$

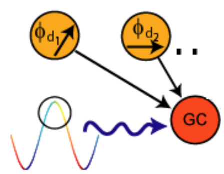
ARE NOT INDEPENDENT!

Baseline input can be useful to remove out-of-field coincidences.

Can consider baseline as just another VCO, with no direction dependence.
It selects times at which other VCOs are sampled



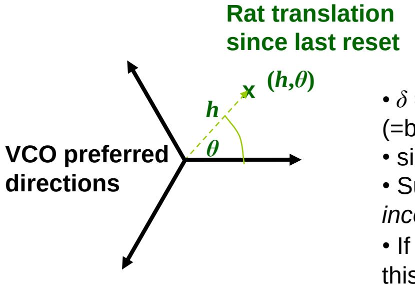




Burgess, Hippocampus, 2008

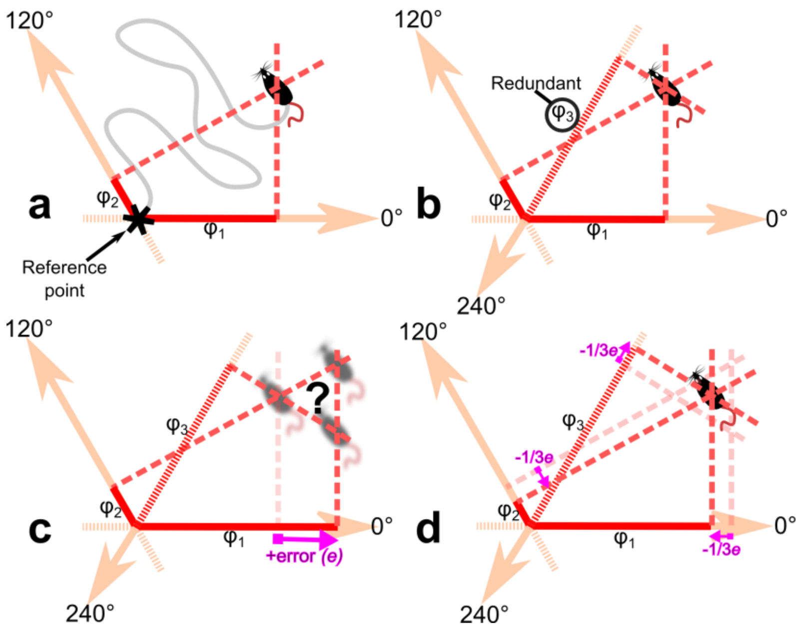
Baseline can perform phase noise cancellation among 3 velocity controlled oscillators

- VCO phase tracks displacement along its preferred direction.
- Using 3 or more VCOs allows for consistency checking (*Burgess, 2008*)
- Common noise in movement signal is removed (only relative VCO phases matter, NB baseline freq is mean of local VCO freqs)



- δ = sum of VCO phases should always be 0 (=baseline peak phase);
- size of δ indicates error/ inconsistency.
- Subtracting $\delta/3$ from all VCO phases *removes inconsistency* and *reduces error*.
- If baseline $f_b(t)$ is mean of local VCOs $< f_a(t) >_{\varnothing d}$ this occurs automatically (consider the phases relative to baseline) ..

Chris Burgess, Neil Burgess, in prep.

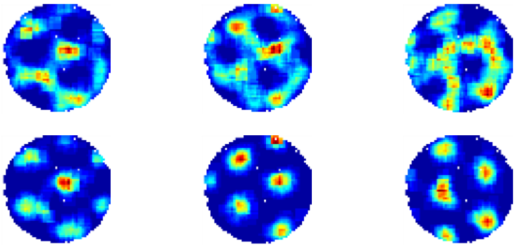


Chris Burgess, Neil Burgess, in prep.

Baseline $f_b(t)$ as mean of local VCOs $< f_a(t) >_{\o d}$ effectively performs this subtraction

$f_b(t)$ independent of VCOs ($f_a(t)$)

$f_b(t) = < f_a(t) >_{\o d}$

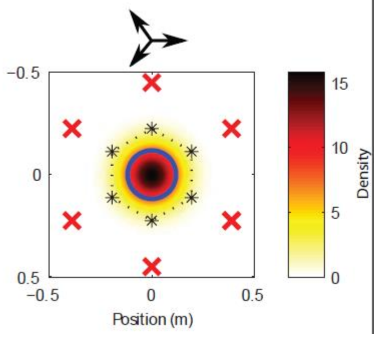


– is providing $< f_a(t) >_{\o d}$ a role for local interneuronal coupling?

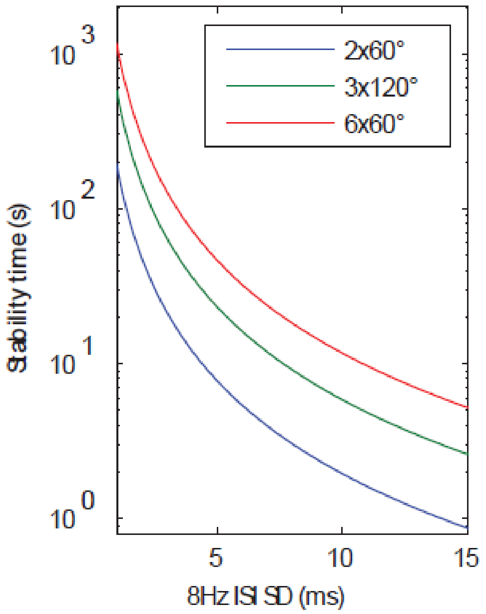
5min trial, 3 VCOs, additive noise in VCO phase: sd=0.006 /ms ~ 1.34ms per cycle

Chris Burgess, Neil Burgess, in prep.

Stability time?



+ if N phase shifted VCOs with a given preferred direction form a ring attractor *(Blair et al 2008)* then stability time ~ $\sqrt{N}$



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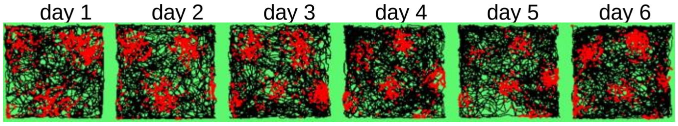
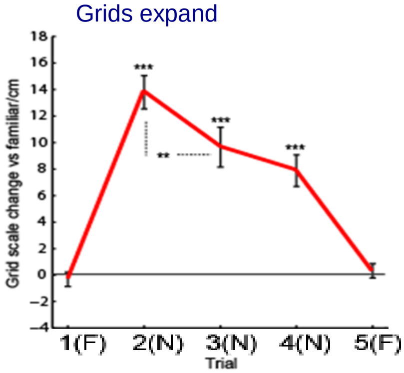
Novelty & grid scale

day 1 day 2 day 3 day 4 day 5 day 6

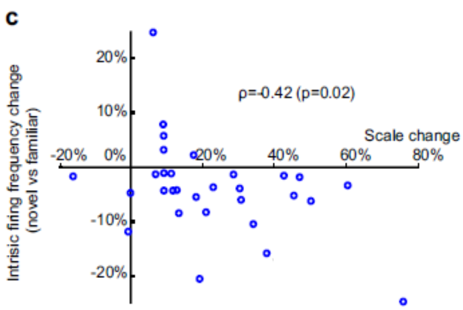


novel familiar

Grids expand

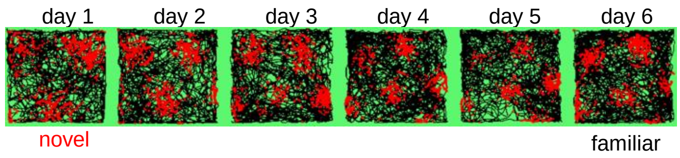


Expansion ~ reduction in f_i

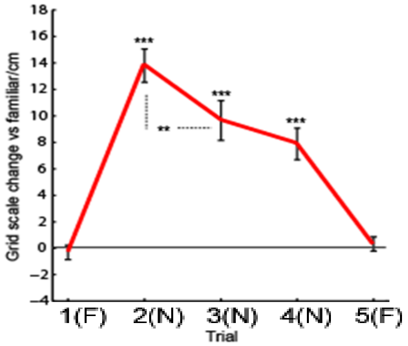


Barry, Ginzberg, O’Keefe, Burgess, PNAS, 2012

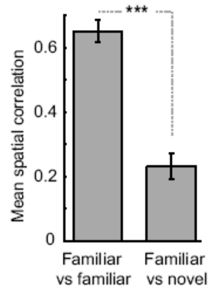
Novelty & grid scale

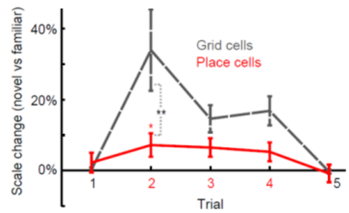


Grids expand



Place cells remap





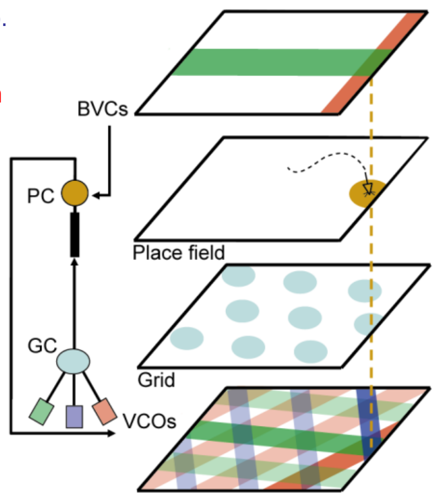
Barry, Ginzberg, O'Keefe, Burgess, PNAS, 2012

Interactions between place cells and grid cells.

Self-location is a compromise between environmental and path integrative info.

Environmental information

Path integration



Burgess et al, 2007

NB Grids expand, BVCs do not: mismatch could cause PC remapping *Burgess, 2008*
NB PCs do not *require* GC input, e.g. development *Wills et al., 2010; Langston et al 2010*
NB PCs combine PI and visual inputs in VR *Chen, et al 2013; Ravassard et al 2013*

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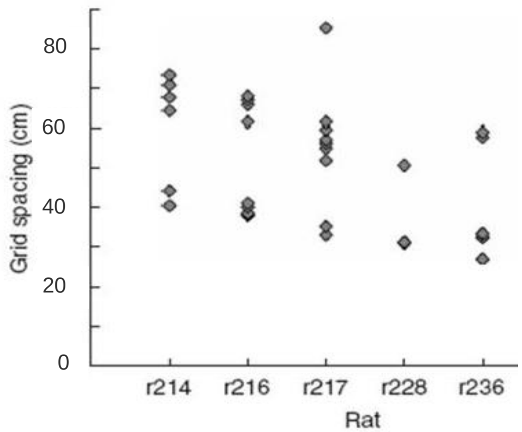
OI models a single cell, but grid cells are interconnected..

Grid cell "modules" *(Barry et al.,2007; Stensola et al., 2013);*



Barry, Hayman, Burgess, Jeffery, 2007;
see also Stensola et al., 2013

OI models a single cell, but grid cells are interconnected..

Grid cell “modules” *(Barry et al.,2007; Stensola et al., 2013);*
should increase stability, see *Burgess 2007; 2008; &* continuous attractor models
(Fuhs & Touretzky, 2006; McNaughton et al., 2006; Burak & Fiete, 2008)

Grid cell’s spatial responses remain constant relative to each other, even when changing relative to the world (after novelty expansion)
(*Yoon, Barry, Hayman, Burgess, Fiete, 2013)*

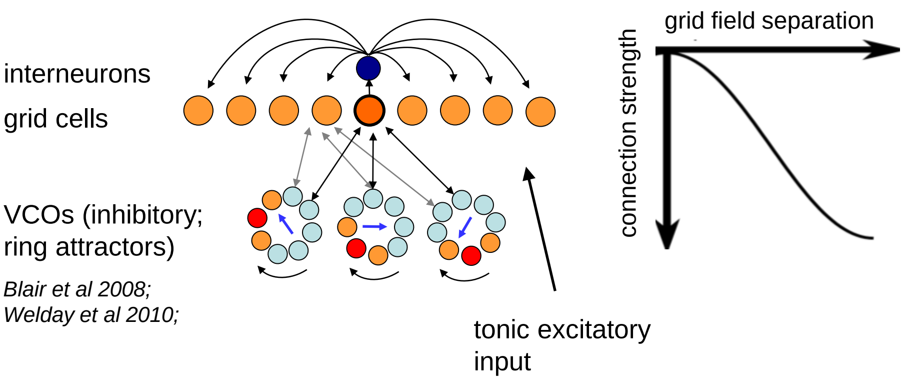
..via interneurons *Couey et al 2013*

A Hybrid OI – CA model

Bush & Burgess, in press.

Also Hasselmo; Blair..

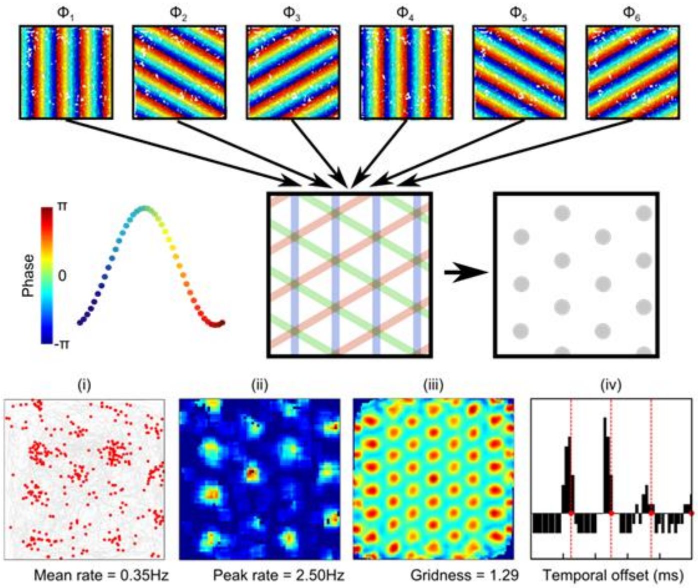
OI performs path integration.
Recurrent connectivity provides additional relative spatial stability.



2D: 36x16 GCs, 12x16 INs, 4x6x30 VCOs
1D: 48x10 GCs, 12x10 INs, 10x6x30 VCOs

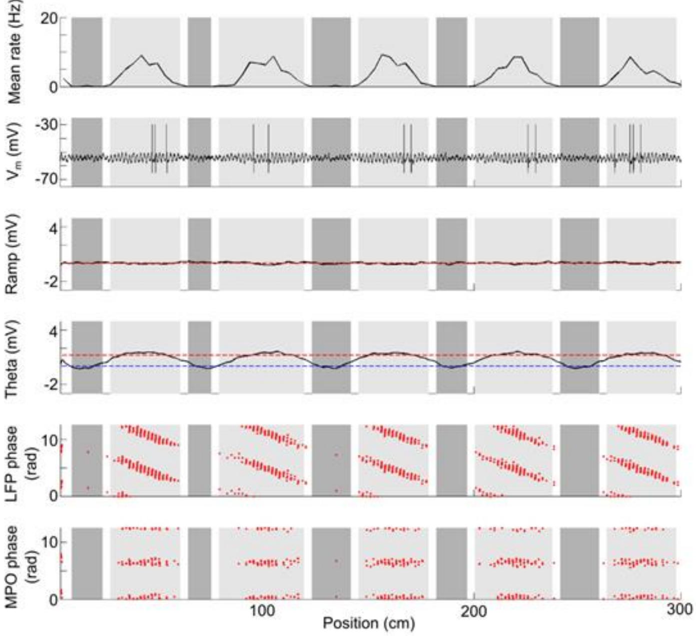
OI model alone

Bush & Burgess, in press.

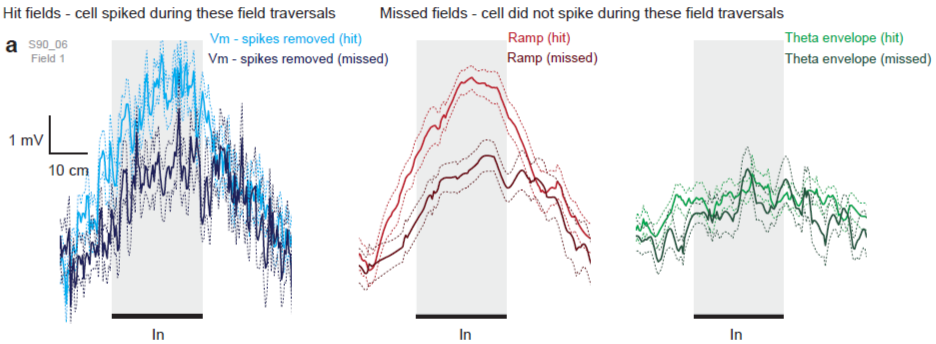


OI model alone

Bush & Burgess, in press.



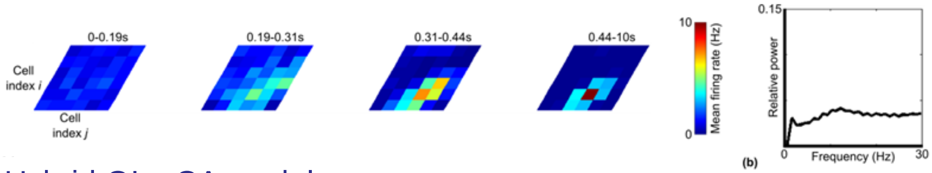
Intra-cellular recording in VR linear track
=> depolariztion ~ firing, more than theta envelope



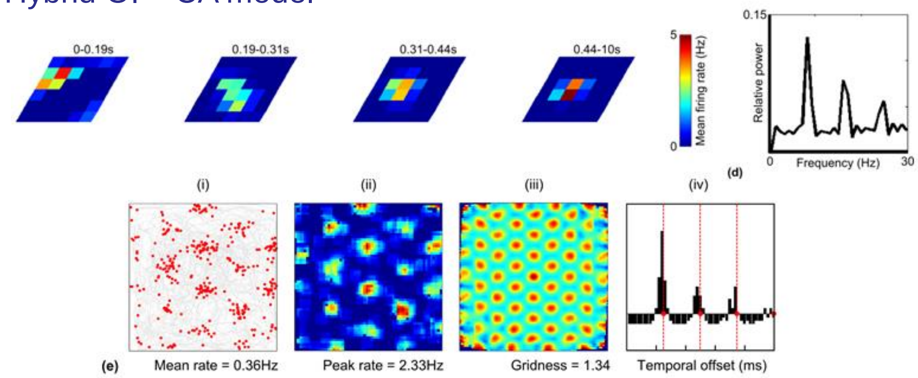
Domnisoru et al 2013;
Schmidt-Heiber & Hausser 2013

CA model alone

Bush & Burgess, in press.

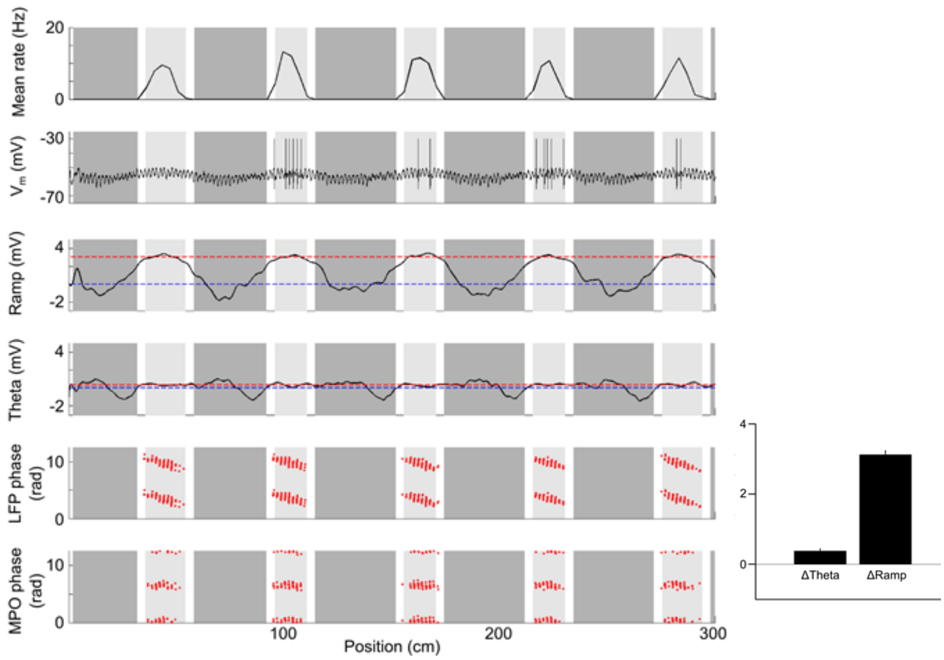


Hybrid OI – CA model



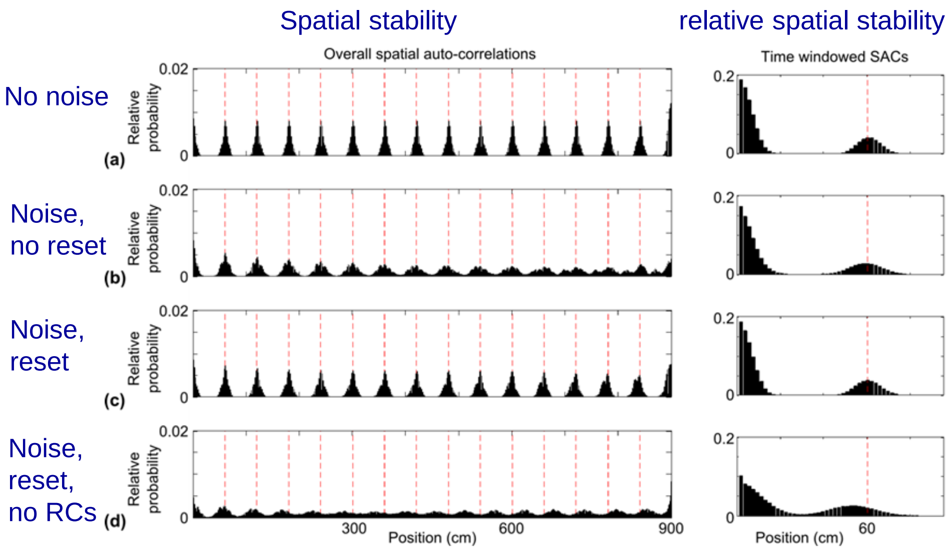
Hybrid OI – CA model

Bush & Burgess, in press.



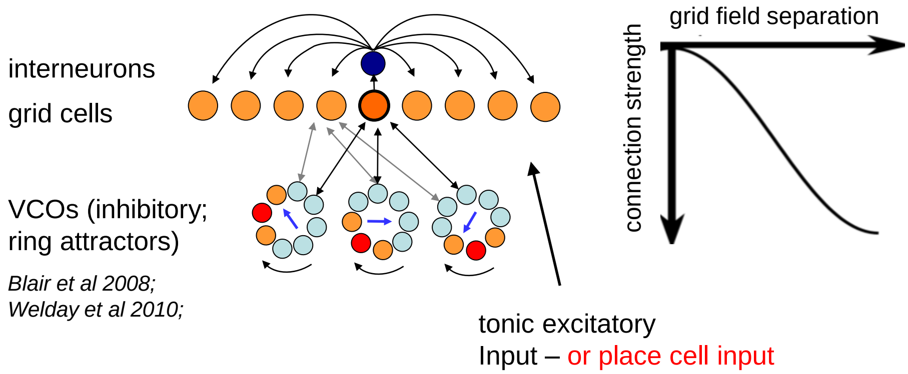
Phase noise and VCO phase resetting

Bush & Burgess, in press.



Phase noise and VCO phase resetting

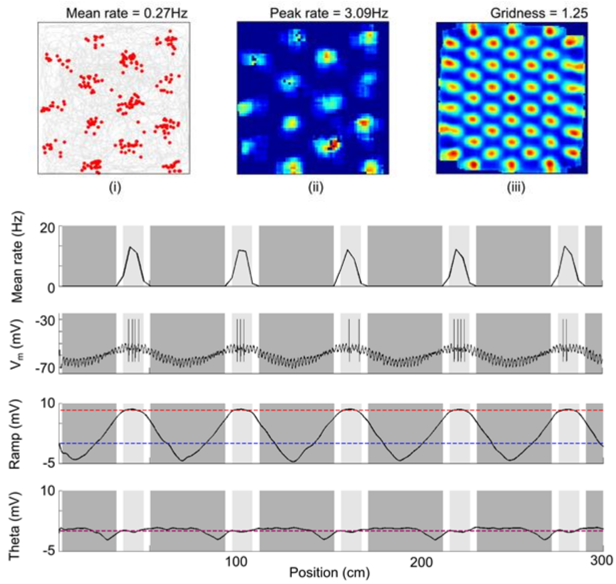
Learn reverse association from GCs to VCO rings, so that stability in GCs (from recurrent connections or place cell inputs) can reset VCOs.



Bush & Burgess, in press.

2D: 36x16 GCs, 12x16 INs, 4x6x30 VCOs
1D: 48x10 GCs, 12x10 INs, 10x6x30 VCOs

Place cell input in familiar environment, with phase resetting
(random initial VCO phases)



Bush & Burgess, in press.

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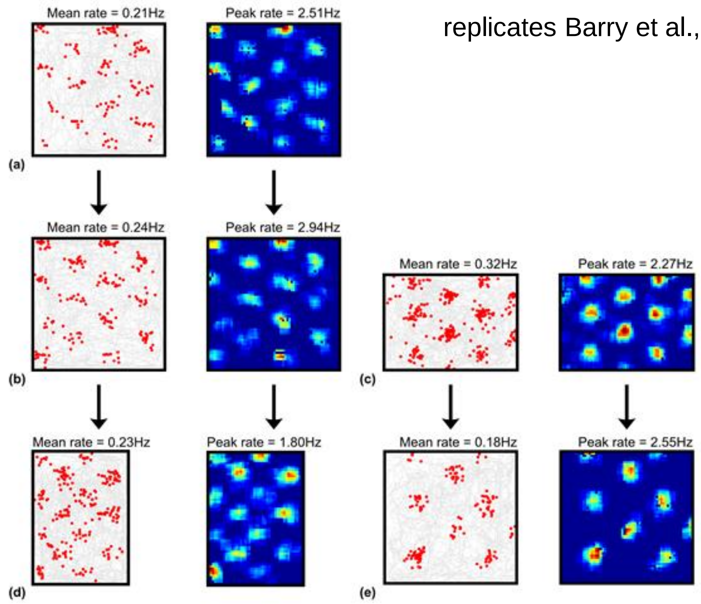

replicates Barry et al., 2007 expt.

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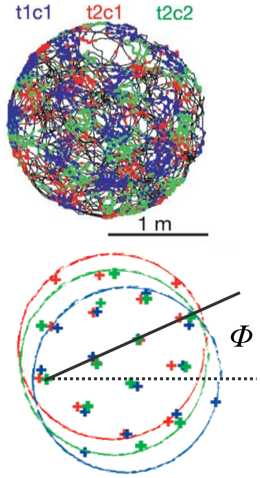
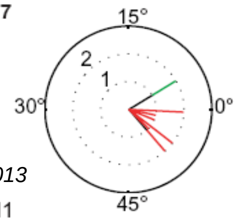
Can we detect grid cells in the humans?

The grids of nearby cells
share orientation & scale



Hafting et al., 2005

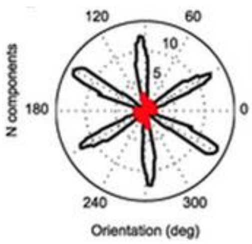
And grid orientation is clustered across modules



(in all 5 rats)

Barry et al., 2007;
see also Stensola et al., 2013

n=11
wavelengths=3
spread=13.4°
P<0.0001

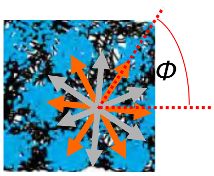


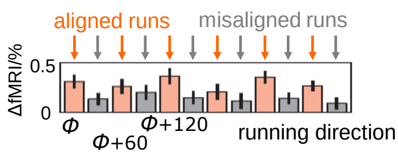
Also true for Fourier components vs env.

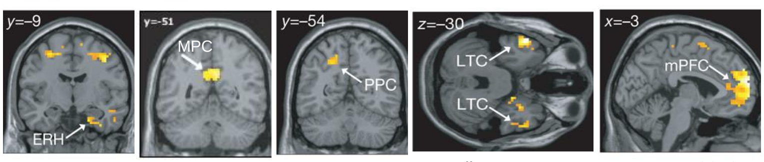
(Krupic, Burgess, O'Keefe, 2012)

Can we detect grid cells in the humans?

Large populations of *aligned* grids => changes in fMRI signal with virtual running direction







Doeller, Barry, Burgess, Nature, 2010

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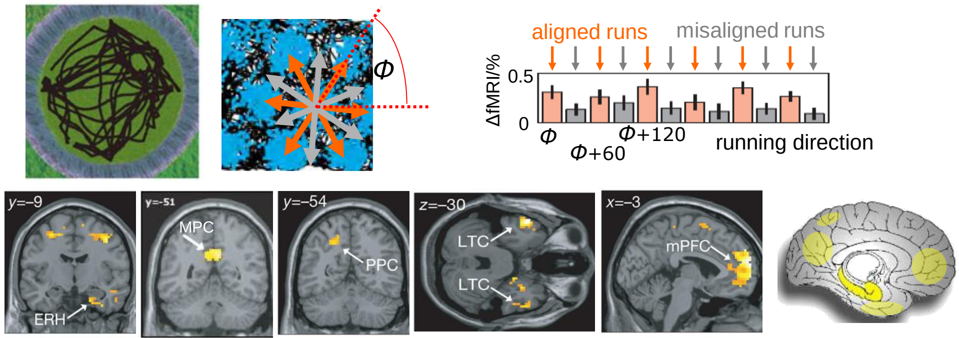


Doeller, Barry, Burgess, Nature, 2010

Autobiographical memory system

Grid cells allow path integration, and movement of viewpoint in imagery?
Add grid cells to BBB model..

Conclusions

Self-location is calculated in the hippocampal formation as a compromise between environmental (Boundary Vector Cells) and movement-related (Theta, Grid Cells) information.

Computational understanding of neuronal representations in rodents allows mechanistic models of human spatial memory and imagery.

Septo-Hippocampal circuit required for head-direction and self-motion (theta/VCOs) - imposing and moving a *single viewpoint* in memory and imagery, and novelty/encoding (ACh?)

Thanks to: (UCL)

Caswell Barry
Daniel Bush
Ali Jeewajee
Robin Hayman
Chris Burgess

John King
John O'Keefe
Kate Jeffery
Daniel Manson

Colin Lever (Durham)
Tom Hartley (York)
Christian Doeller (Nijmegen)
Sue Becker, Patrick Byrne (McMaster)

wellcome trust
MRC Medical Research Council

Additional comments/ questions

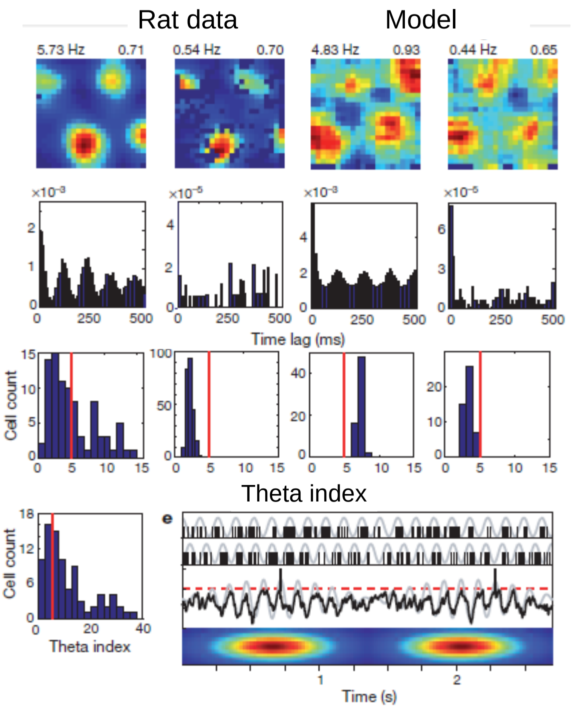
Grids & theta in Bats

Very low firing rate bat grid cells (mean *peak* rate ~0.5Hz) show little theta modulation – similar to grid cells from the OI model or from rats, if firing rate matched.

Do bats not need PI (echo-location so good; crawling is v slow, flying is hard to integrate)?

Is vestigial grid cell firing supported by sensory input in a familiar environment (is there theta in novelty)?

Yartsev et al., Nature 2011
Barry et al Nature 2012

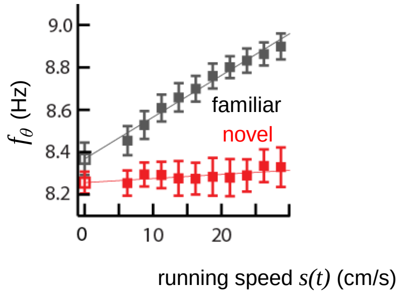


Spatial properties are independent of the baseline frequency f_0

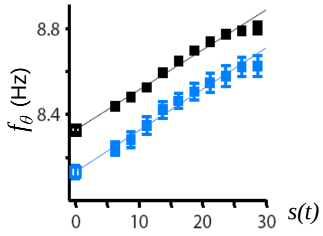
Implies two components of theta frequency?

LFP theta frequency: $f_\theta \sim f_0 + \langle\gamma\rangle s(t)$

Type I ~ dependence on running speed
Movement-related,
Effect of novelty (& spatial scale)



Type II ~ intercept f_0
Arousal, alert immobility,
Effect of anxiolytic drugs



CDP (bendzodiaz.),
Buspirone (5HT),
CB1 agonist

Wells et al., J Neurosci, 2013

Spatial properties are independent of the baseline frequency f_0

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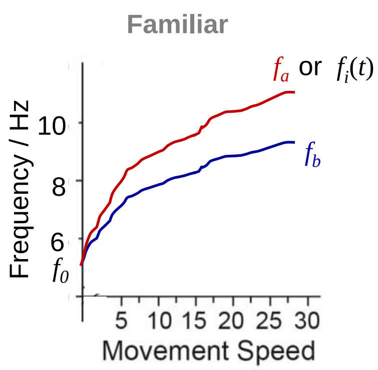
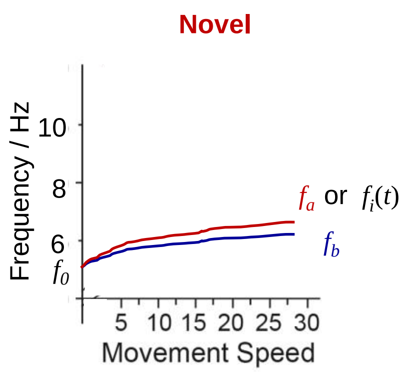
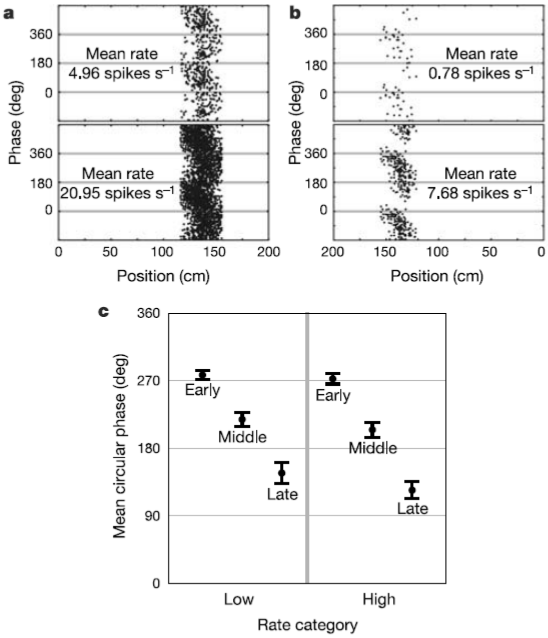




Theta phase precession is independent of run-by-run variations in firing rate



Huxter, Burgess, O'Keefe, Nature (2003)