Grid cells and the entorhinal map of space

Edvard I. Moser
Kavli Institute for Systems Neuroscience,
Centre for Neural Computation,
NTNU, Trondheim
Tolman writing to Hebb (1958):

“I certainly was an anti-physiologist at that time and am glad to be considered as one then. Today, however, I believe that this (physiologizing) is where the great new break-throughs are coming.”

Courtesy of Steve Glickman
1959 -:

Significant progress in deciphering cortical computation was made at the 'low end' of the cortex, near the sensory receptors

D. H. Hubel and T. N. Wiesel (courtesy M. Reyes/T.N. Wiesel)

1971 -: The high end...

J. O’Keefe

Felleman and van Essen, 1991
Trondheim 1996-

Where and how was the place signal generated?

Ailin Moser

V.H. Brun

M.P. Witter

Andersen et al 1971
CA1 cells continued to express place fields after lesion of the intrinsic hippocampal pathway, suggesting that the source of the place signal is external

Brun et al. (2002). *Science* 296:2243-2246

Best candidate: the *entorhinal cortex*
We then recorded from **dorsal medial entorhinal cortex**, which provides the strongest cortical input to the dorsal hippocampus where the place cells were found.

Entorhinal cortex of a rat brain (seen from behind):

![Entorhinal cortex diagram]

Fyhn et al. (2004). *Science* 305:1258-1264

Entorhinal cells had **multiple** fields and the fields exhibited a **regular** pattern. But what was the pattern?
Entorhinal cells had spatial fields with a periodic hexagonal structure.

The fields formed a grid that covered the entire space available to the animal.

We called them grid cells.


Grid cells have at least three dimensions of variation

1. Phase

2. Scale

3. Orientation

Phase, scale and orientation may vary between grid cells. How are these variations organized in anatomical space?
Grid phase (x, y-locations) is distributed:
All phases are represented within a small cell clusters

(cell from Stensola et al 2012)
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... similar to the *salt-and-pepper* organization of many other cortical representations (orientation selectivity in rodents, odours, place cells)
Grid scale (spacing) follows a dorso-ventral topographical organization

Fyhn et al. (2004). *Science* 305:1258-1264
But within animals, the steps in grid spacing are discrete, suggesting that grid cells are organized in modules.

The average **scale ratio** of successive modules is constant, i.e., grid scale increases as in a geometric progression. Although the set point is different for different animals, modules scale up, on average, by a factor of ~1.42 (\sqrt{2}).

A geometric progression may be the optimal way to represent the environment at high resolution with a minimum number of cells (Mathis et al., 2012; Wei et al. 2013).

Within modules, the grid map is rigid and universal: Scale, orientation and phase relationships are preserved.
Grid maps: Scale, orientation and phase relationships are preserved across environments.

Entorhinal cortex

Crosscorrelation of assembly of rate maps: pattern is preserved – just shifted

... in sharp contrast to the place-cell map of the hippocampus, which can remap completely (Muller/Kubie 1987)

Hippocampus (CA3):
Grid-like cells have since been reported in bats, monkeys and humans, suggesting they originated early in mammalian evolution.

Krubitzer and Kahn, 2003; Buckner and Krienen, 2013; Fyhn et al., 2008; Killian et al., 2012; Yartsev et al., 2011; Jacobs et al., 2013.
1. Mechanism for geometric alignment

To be useful for navigation, grid cells cannot only respond to self-motion cues. They must also anchor to external reference frames. How?
Grid orientation is remarkably similar across animals. The same few orientation solutions are expressed in different animals....

What are then the factors that determine orientation?

Tor & Hanne Stensola
Grid orientation is determined by the cardinal axes of the local environment

Stensola et al. (2015).  
*Nature*, in press
Grid orientation is determined by the cardinal axes of the local environment

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Grid orientation is determined by the cardinal axes of the local environment.

But the alignment is not perfect. After normalization to the nearest wall, grid orientations peak not at 0° but at ±7.5°.

Orientations shy away from both 0° and ±15°!
What is special about 7.5°?

7.5° minimizes symmetries with the axes of the environment

Helpful to disambiguate geometrically similar segments of the environment?
What is the mechanism behind the 7.5° offset?

The rotation differed between the 3 grid axes...

Differential rotation of the grid axes implies **elliptification** of the grid pattern:

Rotational offset and elliptic deformation were correlated:

Elliptification and axis rotation may thus be common end products of shearing forces from the borders of the environment.


\[ f(x, y) = \begin{bmatrix} x + \gamma_1 y \\ y + \gamma_2 x \end{bmatrix} \]

elliptification
classical rotation
Minimizing ellipticity along one wall axis (by **analytically reversing** the shearing) completely removed the bimodality in the offset distribution, for all axes...

... implying that grid patterns are anchored - and distorted - in an axis-dependent manner by shear forces from specific boundaries of the environment.

Shear forces along the walls cause elliptification and axis-dependent grid rotation

AXIS ORTHOGONAL TO SHEAR FORCES:

The data point to shearing as the mechanism for grid distortion and rotation and imply that local boundaries exert distance-dependent effects on the grid.

Animation by T. Stensola
2. Fine-scala functional anatomy

To understand how grid patterns are generated, and how grid cells interact with other cell types, we need to determine **how the network is wired together**.

But tetrode recordings are not sufficient for this purpose.
Determining the fine-scale functional topography of the entorhinal space network:

**Optical imaging** with a fluorescent calcium indicator would improve the spatial resolution beyond that of tetrodes...

But access to the medial entorhinal cortex is a challenge...

Possible solution: Accessing the entorhinal surface through a prism

Tsao et al., unpublished; See Heys et al, Neuron, Dec 2014, for a similar approach
Imaging grid cells of GCaMP6-injected mice in a linear virtual environment

Tsao et al., unpublished
Hundreds of entorhinal cells can be imaged at cell or sub-cell spatial resolution in GcAMP6-expressing cells during virtual navigation.

Tsao et al., unpublished
Grid cells can be identified as cells with periodic firing fields.

Non-gridcell

Tsao et al., unpublished
Grid cells are distributed but form functionally homogeneous clusters

Grid cells cluster more than expected by chance:
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[Diagram of grid cells with a circle highlighting a cluster]
Grid cells are distributed but form functionally homogeneous clusters.

Grid cells cluster more than expected by chance:

Adjacent grid cells have grid phases that are more similar than expected by chance:

Grid clusters belong preferentially to the same grid module:

Tsao et al., unpublished...
3. Mechanism of hexagonal symmetry: How is the grid pattern generated?
Most (all) network models for grid cells involve continuous attractors...

...where

- localized firing may be generated by mutual excitation between cells with similar grid phase
- and such activity is translated across the sheet in accordance with the animal's movement in the environment (e.g. as expressed in speed cells)

BRAIN SURFACE:
Grid cells arranged according to grid phase (xy positions). Cells with similar fields mutually excite each other. (with an inhibitory surround).

THIS EXPLAINS LOCALIZED FIRING BUT WHERE DOES THE HEXAGONAL PATTERN COME FROM?
Origin of hexagonal structure

Competition between self-exciting blobs with inhibitory surrounds may cause the network to self-organize into a hexagonal pattern, in which distances between blobs are maximized.

Similar self-organization may occur with purely inhibitory surrounds (inverted Lincoln hat):
Self-organization of grid network in a continuous attractor model

Then, when the activity bumps are translated across the network in accordance with the animal’s movement, using speed and direction signals, it will yield grid fields in individual cells.
> HALF A CENTURY HAS PASSED AND TOLMAN´S MAP HAS BEEN ´PHYSIOLOGIZED´

“Today, however, I believe that this (physiologizing) is where the great new breakthroughs are coming..”

E.C. Tolman (1958)

SUMMARY

• Grid cells define hexagonal arrays that tessellate local space.
• Grid modules are organized in anatomical space.
• Grid cells cluster discontinuous modules.
• The intrinsic functional organization of a grid module is preserved across environments.
• Fine-scale grid-cell architecture can be investigated with 2-photon calcium imaging.
• Grid cells may be generated by attractor networks.
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Abrikosov, 1957