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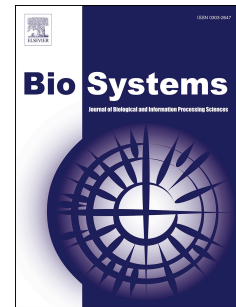
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## 1 BIOSYSTEMS – SHORT COMMUNICATION

### 2 THE GRID-CELL NORMATIVE MODEL: UNIFYING ‘PRINCIPLES’

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#### 9 Abstract

10 Sorscher et al. recently proposed a normative model for the emergence of entorhinal grid cells in the  
11 brain's navigational system. Using computational modeling of place-to-grid cell interactions, the  
12 authors characterized the fundamental nature of grid cells through information processing. However,  
13 the normative model does not consider certain discoveries that complement or contradict the  
14 conditions for such emergence. By briefly reviewing current evidence, we draw some implications on  
15 the interplay between place cell replay sequences and intrinsic grid cell oscillations related to the  
16 hippocampal-entorhinal navigation system that can extend the normative model.

#### 17 Introduction

18 Alzheimer's disease is the most common dementia affecting multiple brain functions, including  
19 memory. Although the exact cause of Alzheimer's disease is unknown, one of the first manifestations  
20 is difficulty to spatially navigate through familiar environments (Ness and Schultz, 2021; Ying et al.,  
21 2022). The entorhinal cortex is one of the first damaged brain areas during this disease, drastically  
22 affecting entorhinal grid cells (**Fig. 1A**) (Jun et al., 2020). Grid cells fires at regular intervals as an animal  
23 navigates an open area, and during Alzheimer's disease the animal's capacity to store and integrate  
24 information about location, distance, and direction is reduced (Fyhn et al., 2008; Moser et al., 2008).

25 One fundamental goal in spatial navigation research is discovering the mechanisms underlying the  
26 complex processes of the interaction between grid cells and other neurons, particularly place cells -  
27 neurons located within the hippocampus, which are triggered in response to an animal entering  
28 specific places in its local environment (O'Keefe and Dostrovsky, 1971). Experimental evidence  
29 reported that CA1 and CA3 hippocampal populations (**Fig. 1A**) encode differently experiences in new  
30 environments (Dong et al., 2021). Understanding the principles governing both cell types is crucial as  
31 it would allow us to reveal the problems behind Alzheimer's at a neural level (Jun et al., 2020).

32 In a recent paper in *Neuron*, Sorscher et al. (Sorscher et al., 2023) have made a step toward unraveling  
33 the mechanistic conditions for the grid cell emergence during path integration (i.e., the capacity of  
34 accurately estimating and integrating distances and directions as an animal moves through its  
35 environment (Moser et al., 2008)). However, Sorscher et al.'s proposal has also been questioned (Frey  
36 et al., 2023) in whether it has a role in other domains further than path integration, which deserves a  
37 deeper evaluation.

### 38 **A theory for the origins of grid cells**

39 Sorcher et al. (2023) trained three different models where grid-like activity emerged: a simple feed-  
40 forward neural network, a Long Short-Term Memory-based (LSTM) and a recurrent neural network  
41 (RNN). Among these, LSTM and RNN were trained to path integrate and form dynamical systems  
42 within the continuous attractor network (CAN) theory (see (Gardner et al., 2022) for biological  
43 evidence). The other model is a simple feed-forward network with one hidden layer that does not path  
44 integrate nor exhibit temporal dynamics, thus the attractor concept cannot be applied to it (cf., (Benas  
45 et al., 2023)). Sorcher et al. argue that this heterogeneity of the models producing grid cells under very  
46 similar conditions makes their results general enough to write an 'unified theory'. However, these  
47 models share common networks and neurons properties, as explained below, which makes  
48 questionable the claim for a unified theory.

49 By eschewing the explanatory power of computational modeling in theoretical neuroscience, Sorscher  
50 et al. accounted for the critical spatial components of the brain's navigation system to identify  
51 principles for a normative framework on path integration. CAN is based on the notion that a grid cell  
52 network has a circular network topology involving excitatory and inhibitory synapsis to control an  
53 'activity packet' (bump) correlating to the animal's movements through linear velocity. Using two  
54 idealized computational models trained to path integrate (Banino et al., 2018; Sorscher et al., 2023)  
55 and biological evidence, Sorscher et al. assumptions were three-fold: (i) place and grid cells are  
56 connected, sharing information about the environment; (ii) grid cells are recurrently connected; (iii)  
57 grid cells receive velocity information allowing the collective activity of the cells to update as the  
58 animal traverses the environment. Inspired on a third linear computational model presented (Dordek  
59 et al., 2016), to which only the (i) assumption applies the authors also proposed two critical constraints  
60 to favor the grid cell's hexagonal pattern in all the analyzed models: (A) to impose place field  
61 definitions with surround inhibition enabling the emergence of grid cells; (B) to define a non-negativity  
62 constraint related to place-to-grid cell synaptic projection on hidden unit activations, which forces grid  
63 cells to fire above a certain threshold or show no firing rate. These constraints correspond to specific  
64 design restrictions to each network model. It must be highlighted that the linear model is not trained  
65 to path integrate, but rather to generate grid cells form place cell inputs (Benas et al., 2023; Kropff  
66 and Treves, 2008). These findings are also open to new avenues for comprehending the dynamics of  
67 the brain's navigation system as recently discussed by Morris & Derdikman (Morris and Derdikman,  
68 2023). Namely, discussion on whether grid-cell modules are generated by CAN, whether velocity can  
69 be accounted as a signal that moves entorhinal activity bumps, and whether place-cell activity  
70 constitutes a summation of entorhinal grid cell modules.

71 One should then ask why the research community waited around two decades to identify these  
72 relevant, but certainly unrealistic requirements, because the conditions seem sufficient for predicting  
73 spatial location and path integration (Moser et al., 2008). Despite the relevance and crucial

74 implications, the underlying assumptions in the Sorscher et al.'s normative model are met only in  
75 particular circumstances or are not even plausible in the biological realm (Frey et al., 2023). One also  
76 wonders whether these conditions are needed for grid cell emergence from place fields or are still  
77 valid when considering other grid features, such as grid-cell coding sequences, as new evidence  
78 suggests (Killian and Buffalo, 2018).

79 The situation around the normative model is at best unclear. It remains uncertain how the necessary  
80 conditions are achieved such that place cell dynamics self-organize given the animal-environment  
81 interaction to produce the grid cells. Does the proposed normative model for grid cell emergence can  
82 be adopted when considering the named low plausible modeled features? It is open to discussion  
83 whether Sorcher et al.'s assumptions might be biased towards path integration and not considering  
84 other scenarios, such as visual grid cell maps (Killian et al., 2012).

#### 85 **Still lacking a unified theory for grid cell emergence**

86 Granting focus to the analyzed models, in Sorcher et al. the grid-like activity emerged from specific  
87 network topologies (see also (Zilli, 2012) for other network models). Note also that the LSTM and RNN  
88 model's outputs were sequences of place cell activations (i.e., place fields resembled the simulated  
89 animal's path). Despite the convenience of using these models, there are three main concerns we  
90 want to highlight. First, it is known that biological grid cells show multiple scale modules as observed  
91 from the dorsal-to-ventral medial entorhinal cortex (Bush et al., 2015). Because the studied models  
92 only generated one grid cell spacing, the issue is that if only one grid module is used, or even if all the  
93 modules share the same scale, two different spatial points could have the same grid cell code from  
94 the animal's perspective, generating uncertainty on self-differentiating these places (Weber and  
95 Sprekeler, 2018). To alleviate this tension, one could consider other handcraft models proposed in  
96 (Lillicrap et al., 2020) and see the constraints that are needed for grid cell emergence with different  
97 spacings. Second, Sorscher et al.'s models were based on backpropagation despite it has no clear

98 physical interpretation (Skaggs and McNaughton, 1996). Finally, the analyzed models also have fixed  
99 definitions of place fields since the beginning of the simulations. This feature contrasts biological  
100 evidence by showing that place cell's fields are observed progressively and sequentially (Ji and Wilson,  
101 2007).

## 102 **Discussions and Implications**

103 The primary lesson from Sorscher et al. and Frey et al. is that the normative model for the emergence  
104 of grid cells must be carefully evaluated before going further on its acceptance as principles in the  
105 'cognitive map' community. In this endeavor, it is crucial to use computational models in different  
106 scenarios to characterize the necessary and sufficient conditions to ensure coherent dynamics  
107 between place and grid cells for path integration. Sorscher et al. reported that any set of stable spatial  
108 responses with a similar spatial correlation structure as place cells can lead to the emergence of grid  
109 cells. However, new arguments (Morris and Derdikman, 2023) have been proposed in that place cells  
110 are generated from spatially selective non-grid cells upstream, which contrasts partially with Sorscher  
111 et al. claims.

112 Although Sorcher et al.'s results are significant from the computational modelling standpoint, they  
113 also showed that individual connections or architectures cannot explain the true nature of grid cells.  
114 To understand the emergence of grid activity in all the analyzed models, the coupled relationship  
115 between place and grid cells should be considered. These changes could explain what type of  
116 information is coded into grid cells and extend the proposed normative model to other tasks different  
117 than path integration.

118 Given that grid cell sequences has been recently reported experimentally (Cogno et al., 2022), we can  
119 consider two more situations: first, the activation sequences of place cells (Ji and Wilson, 2007) could  
120 have a role in generating grid cell sequences due to place-to-grid connectivity (Dordek et al., 2016;  
121 Fyhn et al., 2004); second, there should be some mechanisms for coordinating the inter-module grid

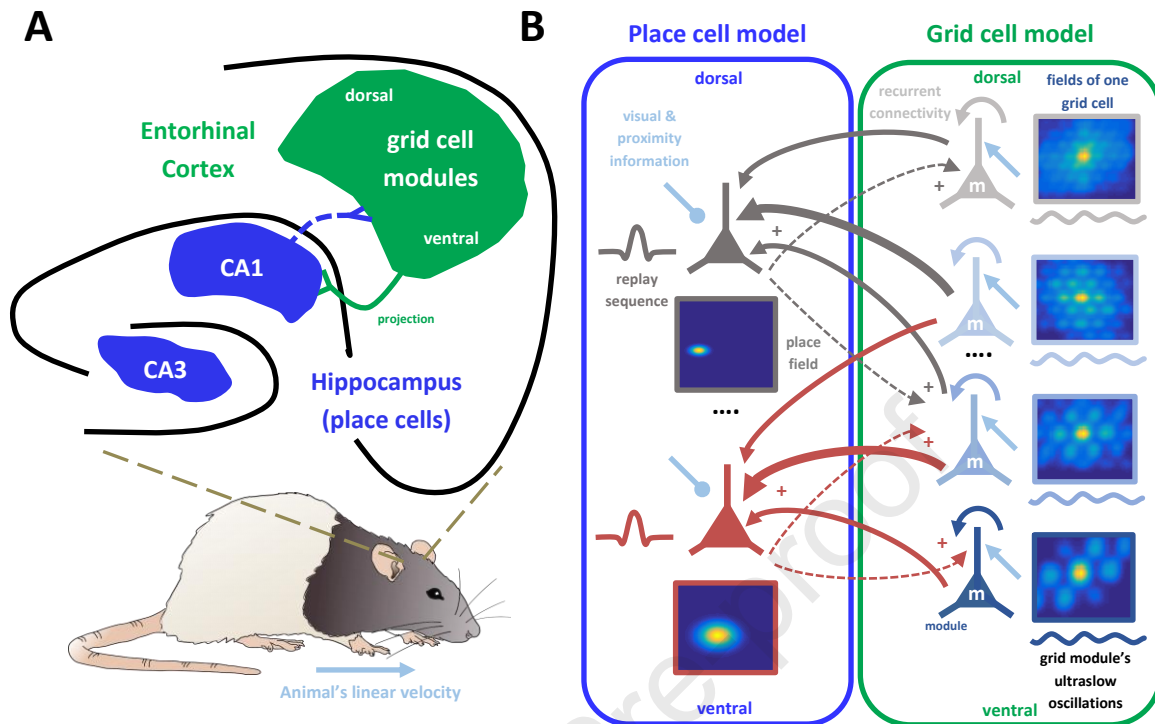
122 activities producing intrinsic grid cell activity in the face of oscillations (Waaga et al., 2022) (**Fig. 1B**).  
123 The first case has been extensively discussed and analyzed (Pfeiffer and Foster, 2013), but the latter  
124 one seems better suited to explain the revealed periodic sequences of neuronal activation in grid cells.  
125 Importantly, Cogno et al. (2022) argue that these oscillations have the potential to coordinate neurons  
126 for extended periods, serving as a possible mechanism for processes that unfold at behavioral time  
127 scales.

128 It has been demonstrated that in grid cell CANs (Witter and Moser, 2006), theta sequences and replay  
129 are produced intrinsically, generating distinct modulation of external input and causing attractor  
130 dynamics to oscillate in speed and size (Kang and Deweese, 2019). Thus, we must evaluate whether  
131 these oscillations, amongst other, have a crucial role for being considered as part of a normative  
132 mechanism for grid cells dynamics. We hypothesize that the interplay between place cell replay  
133 sequences and intrinsic grid cell oscillations may be the core of the hippocampal-entorhinal navigation  
134 system, including spatial and visual navigational spaces.

135 We certainly do not know yet the full scope of Sorscher et al.'s claims, but we recognize that the  
136 proposed normative model should explain further evidence that seems crucial for the emergence of  
137 grid cells coupled to place cells. Given other works on place and grid cell dynamics (e.g., (Almog et al.,  
138 2019; Bush and Burgess, 2014; Gardner et al., 2022; Moser et al., 2008)), it is expected that Sorscher  
139 et al.'s normative model can be extended by stating the conditions needed for coding grid cell  
140 sequences perhaps through requiring coordination mechanisms between grid cell modules. Future  
141 works should explore the role of grid-place oscillations on biological or simulated spatial navigation  
142 and whether hippocampal replay facilitates the formation of grid cells and viceversa (see also (Zhang  
143 and Liu, 2023)). This coupling mode between grid- and place-cells seems irreducible and crucial in  
144 cognitive mapping.

145

146 FIGURE



147

148 **Figure 1. Model main components and grid-place cell connectivity map.** (A) Schematics depicting the  
 149 connectivity of the main components for a possible place-grid cell normative model; (B)  
 150 Representation of recurrent (putative) connections within and between grid cell modules, where each  
 151 module receives the linear velocity input of the simulated animal. A grid cell within a module (m)  
 152 project to place cells as proposed in (Solstad et al., 2006). Place cells could process multisensory  
 153 information such as visual, proximity information, and grid cell information for place coding.  
 154 Projections from place-to-grid cells can be represented following (Dordek et al., 2016) for grid cell  
 155 definition and spatial anchoring. The grid cells can show intrinsic grid module ultraslow oscillations  
 156 (Cogno et al., 2022). The synaptic weight can be adapted to improve path integration during the  
 157 simulated animal's exploration as discussed in (Sorscher et al., 2023). Note that grid module ultraslow  
 158 oscillations could eventually influence place cell's replay, and vice versa, for sequence coding. Mouse  
 159 drawing extracted from SciDraw.io.

160



161 **STATEMENTS AND DECLARATIONS**

162 **Conflicts of interest/Competing interests.** The authors declare that the research was conducted in  
163 the absence of any commercial or financial relationships that could be construed as a potential conflict  
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172 **Code or data availability.** No custom code was used in this paper.

173 **Ethics approval.** This article does not contain any studies with human participants performed by any  
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175 **Consent to participate.** Informed consent was obtained from all individual participants (authors)  
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177 **Consent for publication.** The authors affirm that human research participants or related data were  
178 not included in this article.

179 **Declaration of generative AI in scientific writing.** This article did not use AI and AI-assisted  
180 technologies in the writing process.

181

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