6. Rieder, C.L. (2005). Kinetochore fiber formation in animal somatic cells: dueling mechanisms come to a draw. Chromosoma *114*, 310–318.

7. Dong, Y., Vanden Beldt, K.J., Meng, X., Khodjakov, A., and McEwen, B.F. (2007). The outer plate in vertebrate kinetochores is a flexible network with multiple microtubule interactions. Nat. Cell Biol. *9*, 516–522.

8. Wu, J., Larreategui-Aparicio, A., Lambers, M.L.A., Bodor, D.L., Klaasen, S.J., Tollenaar, E., de Ruijter-Villani, M., and Kops, G.J.P.L. (2023). Microtubule nucleation from the fibrous corona by LIC1-pericentrin promotes chromosome congresssion. Curr. Biol. *33*, 912–925.

9. Roostalu, J., and Surrey, T. (2017). Microtubule nucleation: beyond the template. Nat. Rev. Mol. Cell Biol. *18*, 702–710.

10. Ferreira, L.T., and Maiato, H. (2021). Prometaphase. Sem. Cell Dev. Biol. *117*, 52–61.

11. Prosser, S.L., and Pelletier, L. (2017). Mitotic spindle assembly in animal cells: a fine balancing act. Nat. Rev. Mol. Cell Biol. *18*, 187–201.

12. Kirschner, M., and Mitchison, T. (1986). Beyond self-assembly: from microtubules to morphogenesis. Cell *45*, 329–342.

13. Mitchison, T., and Kirschner, M. (1984). Dynamic instability of microtubule growth. Nature *312*, 237–242.

14. Tulu, U.S., Fagerstrom, C., Ferenz, N.P., and Wadsworth, P. (2006). Molecular requirements for kinetochore-associated microtubule formation in mammalian cells. Curr. Biol. *16*, 536–541.

15. O'Connell, C.B., Loncarek, J., Kalab, P., and Khodjakov, A. (2009). Relative contributions of chromatin and kinetochores to mitotic spindle assembly. J. Cell Biol. *187*, 43–51.

16. Witt, P.L., Ris, H., and Borisy, G.G. (1980). Origin of kinetochore microtubules in Chinese hamster ovary cells. Chromosoma *81*, 483–505.

17. Snyder, J.A., and McIntosh, J.R. (1975). Initiation and growth of microtubules from mitotic centers in lysed mammalian cells. J. Cell Biol. *67*, 744–760.

18. Euteneuer, U., and McIntosh, J.R. (1981). Structural polarity of kinetochore microtubules in PtK1 cells. J. Cell Biol. *89*, 338–345.

19. Kitamura, E., Tanaka, K., Kitamura, Y., Antony, C., and Tanaka, T.U. (2010). Kinetochores generate microtubules with distal plus ends: their roles and limited lifetime in mitosis. Dev. Cell *18*, 248–259.

20. Euteneuer, U., Ris, H., and Borisy, G.G. (1983). Polarity of kinetochore microtubules in Chinese hamster ovary cells after recovery from a colcemid block. J. Cell Biol. *97*, 202–208.

NeuroAI: If grid cells are the answer, is path integration the question?

Markus Frey, Mackenzie W. Mathis, and Alexander Mathis
École Polytechnique Fédérale de Lausanne (EPFL), Brain Mind Institute & Neuro-X Institute, Geneva, Switzerland
Correspondence: markus.frey@epfl.ch (M.F.), mackenzie.mathis@epfl.ch (M.W.M.), alexander.mathis@epfl.ch (A.M.)
https://doi.org/10.1016/j.cub.2023.01.031

Spatially modulated neurons known as grid cells are thought to play an important role in spatial cognition. A new study has found that units with grid-cell-like properties can emerge within artificial neural networks trained to path integrate, and developed a unifying theory explaining the formation of these cells which shows what circuit constraints are necessary and how learned systems carry out path integration.

Imagine you are a squirrel scurrying through a forest, trying to find your way to a tasty acorn. As you navigate the twists and turns, your brain is working hard to keep track of where you are and where you are going. This ability to accurately estimate and integrate distances and directions as an animal moves through its environment is crucial for successful navigation and is called path integration. In biological neural networks, this is thought to be accomplished through spatially modulated cells[1], such as place or head direction cells, which together compose a cognitive map of the environment. Of particular importance are grid cells, which exhibit a striking periodic activity pattern to represent an animal's position within its environment[2]. Grid cells have been observed across many different species, such as rats, mice, bats and humans[3], and more recently units with characteristic grid-like properties have been detected in certain artificial neural networks (ANNs)[4,5]. This phenomenon has now been explored in more detail in a paper published recently in *Neuron*, in which Sorscher *et al.*[6] develop an elegant normative framework, explaining the emergence of grid-like units within artificial neural networks trained to path integrate.

In order to fully appreciate the significance of the Sorscher *et al.*[6] study, it is important to appreciate prior grid cell models. In the past, researchers have used a variety of techniques to model grid cells (reviewed in Giocomo *et al.*[7]): these include oscillatory inference in single cell models, creating hexagonal firing fields; self-organization based on Hebbian plasticity; and continuous attractor models with a center–surround connectivity structure[8–10]. While these models have provided valuable insights, they focused solely on replicating the firing properties of grid cells. In contrast to these mechanistic models, artificial neural networks (ANNs) can be trained in a normative manner using a variety of objective functions that aim to recover biologically plausible single-cell responses. ANNs have shown impressive performance in predicting neural activity in sensory[11] and motor areas[12]. Following this approach, recent grid cell models have been trained on path integration,

and grid-like responses have been observed in units of the trained network. Interestingly, these studies have revealed a diversity in the lattice structure of single-cell responses, with some models exhibiting four-fold symmetry[4] ('square grids') and others displaying regular six-fold symmetric grid-like units in the activations of their neural networks[5].

Sufficient conditions for the emergence of grid cells

Sorscher *et al.*[6] proposed a normative framework for the emergence of grid cells based on three core constraints. For this normative model, it is important to understand the functional and anatomical context of grid cells. Firstly, they project to place cells[3], which are also spatially selective neurons, but ones that only fire when the animal is at one particular place (hence their name). Secondly, grid cells are recurrently connected[3,13]. And thirdly, the entorhinal cortex, where grid cells are located, receives synaptic input related to the speed and heading direction of the moving animal[3,14] (Figure 1A). Sorscher *et al.*[6] asked whether grid cells emerge in this circuit, when the synaptic weights are trained to perform path integration. In order for the model to implement this task the circuit's weights are adapted to minimize the difference between the actual location of a simulated agent and the one predicted by the circuit (Figure 1B).

Thus, the model also comprises an agent scurrying through bounded two-dimensional space, like a box, and receives the agent's two-dimensional velocity vector. The network, made up of recurrent connections among (putative) grid cells, is tasked with predicting the agent's location indirectly through the activation of place cells. In other words, rather than directly predicting the agent's (X,Y) coordinates, the network predicts the activity of the place cell population (Figure 1A). Through this framework, the authors aimed to establish a comprehensive understanding of the underlying mechanisms that give rise to the observed properties of grid cells, allowing them to unify all previous normative path integration models.

The key insights drawn by Sorscher *et al.*[6] are as follows. First, when place fields are modeled using a broad receptive field the observed grid cells will have a four-fold symmetry. Second, a receptive field with a center–surround structure,

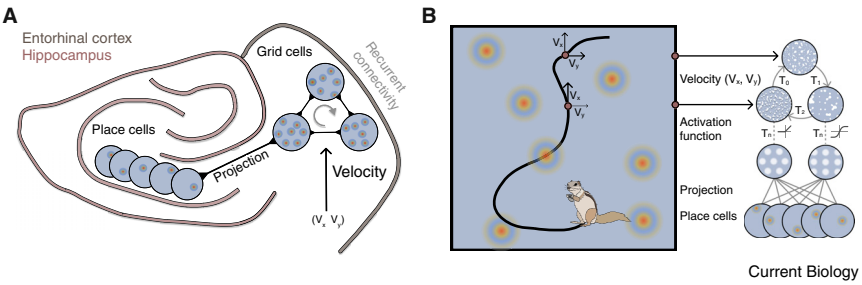

Figure 1. Model architecture and learning dynamics.
(A) Scheme depicting the ingredients of the normative model comprising recurrently connected (putative) grid cells, which receive a velocity vector input representing the instantaneous velocity of the agent. These grid cells project to place cells located in the hippocampus. The grid cells are in the entorhinal cortex. (B) Learning dynamics for a single ANN cell over time. The synaptic weights are changed to improve path integration accuracy as the agent explores a square arena. The cell increasingly has a grid-cell-like firing pattern. Note that, depending on the activation functions, the model learns square-shaped or hexagonal-shaped grid cells. Squirrel adapted from SciDraw.io.

such as a difference of Gaussians, results in amorphous 'grid cells'. And third, these amorphous cells become hexagonal grid cells on the introduction of a non-negativity constraint on the hidden unit activations[9]. Through these initial experiments, the authors have successfully identified the precise implementation choices that give rise to hexagonal firing fields, thereby clarifying the results of previous models. They further validated their findings by reformulating learning to path integrate as a pattern formation problem, for which they can apply analytical methods. In this simplified setting, they can neatly illustrate the emergence of hexagonal grid cells.

Comparing emerging models to hand-crafted attractor models

As mentioned, attractor models emerged early as possible mechanistic models of grid cells[7,10,15], and indeed subsequent experimental work lends a lot of support to those models[16,17]. In these models, the position of the animal is encoded by attractor states, which are activity patterns of a neural network, towards which the system's dynamics like to evolve. In order for the dynamics of those models to form attractors and be able to path integrate, the anatomical connections in these hand-crafted models have two strong properties. First, to stabilize the attractor, when the animal is not moving, the connectivity has a center–surround structure[7,10,15] (i.e. neighboring cells are excited and neurons further away are inhibited). And second, the recurrent connectivity is such that the attractor moves 'correctly' when the agent moves, for example towards the attractor state that represents the updated position[7,10,15].

So how do the learned models of Sorscher *et al.*[6] stack up against the earlier idealized models? In order to look at the connectivity patterns, the authors had to come up with a way to place the units of their ANN in a virtual, two-dimensional 'neural sheet'. Once they overcame this hurdle, they found that their model learned a similar solution to the engineered systems. Namely, as in the idealized models, the population activity looks like a hexagonal pattern on the neural sheet and two-dimensional attractor dynamics also underlie the dynamics of path integration in the normative models. Given the experimental support for attractor models[16,17], this further corroborates their approach.

Where to navigate next?

Overall, Sorscher *et al.*[6] provide a comprehensive work that generalizes and combines multiple threads of modeling grid cells. They unify previous normative approaches for the emergence of grid cells and neatly explain how the learned systems work by linking them to engineered attractor models, which are classic computational neuroscience models and very well understood[15]. Sometimes, ANNs are criticized as models of the brain, because they are accused of swapping one complex system for another complex system. Sorscher *et al.*[6] provide a great case study for NeuroAI research of how one can then break down the artificial, learned system to gain insights into the biological system of interest.

So, what is missing? Firstly, the current model only learns a single grid scale, and one wonders how multiple scales could emerge in this framework? This crucial question goes back to early conceptual models. Secondly, while the circuit itself is biologically plausible, the learning mechanism (backpropagation) and task formulation are not[18]. How could one train a model to path integrate in a biologically plausible fashion? Last but not least, the hippocampal formation does many tasks beyond navigation[19,20]. This begs the question if grid cells are the answer, is path integration with anatomical constraints the only question?

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Gil, M., Ancau, M., Schlesiger, M.I., Neitz, A., Allen, K., De Marco, R.J., and Monyer, H. (2018). Impaired path integration in mice with disrupted grid cell firing. Nat. Neurosci. *21*, 81–91.

2. Hafting, T., Fyhn, M., Molden, S., Moser, M.B., and Moser, E.I. (2005). Microstructure of a spatial map in the entorhinal cortex. Nature *436*, 801–806.

3. Moser, E.I., Roudi, Y., Witter, M.P., Kentros, C., Bonhoeffer, T., and Moser, M.B. (2014). Grid cells and cortical representation. Nat. Rev. Neurosci. *15*, 466–481.

4. Cueva, C.J., and Wei, X.X. (2018). Emergence of grid-like representations by training recurrent neural networks to perform spatial localization. Preprint at arXiv, https://doi.org/10.48550/arXiv.1803.07770.

5. Banino, A., Barry, C., Uria, B., Blundell, C., Lillicrap, T., Mirowski, P., and Kumaran, D. (2018). Vector-based navigation using grid-like representations in artificial agents. Nature *557*, 429–433.

6. Sorscher, B., Mel, G.C., Ocko, S.A., Giocomo, L.M., and Ganguli, S. (2022). A unified theory for the computational and mechanistic origins of grid cells. Neuron *111*, 121–137.

7. Giocomo, L.M., Moser, M.B., and Moser, E.I. (2011). Computational models of grid cells. Neuron *71*, 589–603.

8. Burgess, N., and O'Keefe, J. (2011). Models of place and grid cell firing and theta rhythmicity. Curr. Opin. Neurobiol. *21*, 734–744.

9. Dordek, Y., Soudry, D., Meir, R., and Derdikman, D. (2016). Extracting grid cell characteristics from place cell inputs using non-negative principal component analysis. eLife *5*, e10094.

10. Burak, Y., and Fiete, I.R. (2009). Accurate path integration in continuous attractor network models of grid cells. PLoS Comput. Biol. *5*, e1000291.

11. Yamins, D.L., and DiCarlo, J.J. (2016). Using goal-driven deep learning models to understand sensory cortex. Nat. Neurosci. *19*, 356–365.

12. Hausmann, S.B., Vargas, A.M., Mathis, A., and Mathis, M.W. (2021). Measuring and modeling the motor system with machine learning. Curr. Opin. Neurobiol. *70*, 11–23.

13. Couey, J.J., Witoelar, A., Zhang, S.J., Zheng, K., Ye, J., Dunn, B., Czajkowski, R., Moser, M.B., Moser, E.I., Roudy, Y., and Witter, M.P. (2013). Recurrent inhibitory circuitry as a mechanism for grid formation. Nat. Neurosci. *16*, 318–324.

14. Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B.L., Witter, M.P., Moser, M.B., and Moser, E.I. (2006). Conjunctive representation of position, direction, and velocity in entorhinal cortex. Science *312*, 758–762.

15. Khona, M., and Fiete, I.R. (2022). Attractor and integrator networks in the brain. Nat. Rev. Neurosci. *23*, 744–766.

16. Gu, Y., Lewallen, S., Kinkhabwala, A.A., Domnisoru, C., Yoon, K., Gauthier, J.L., Fiete, I.R., and Tank, D.W. (2018). A map-like micro-organization of grid cells in the medial entorhinal cortex. Cell *175*, 736–750.

17. Gardner, R.J., Hermansen, E., Pachitariu, M., Burak, Y., Baas, N.A., Dunn, B.A., Moser, M.B., and Moser, E.I. (2022). Toroidal topology of population activity in grid cells. Nature *602*, 123–128.

18. North, G. (1987). A celebration of connectionism. Nature *328*, 107.

19. Eichenbaum, H. (2017). On the integration of space, time, and memory. Neuron *95*, 1007–1018.

20. Bellmund, J.L., Gärdenfors, P., Moser, E.I., and Doeller, C.F. (2018). Navigating cognition: Spatial codes for human thinking. Science *362*, eaat6766.

Sleep: Not getting enough diminishes vaccine responses

Mark R. Opp
Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80301, USA
Correspondence: mark.opp@colorado.edu
https://doi.org/10.1016/j.cub.2023.02.003

Vaccine failure is a multifactorial global public health problem. A new meta-analysis underscores the role of sleep history as a factor involved in antibody responses to vaccination and subsequent protection against disease.

The development of vaccines is arguably the most beneficial global public health advance in history[1]. For example, it is estimated that more than 200 million lives have been saved since smallpox was eradicated by vaccination[2] and that four million deaths worldwide are prevented annually by childhood vaccination[3]. Furthermore, vaccination against measles and hepatitis B could save ~33 million lives during this decade[3]. These historical numbers and projections reinforce the importance of vaccines and vaccination programs for reducing deaths from infectious diseases. The World Health Organization now lists 25 diseases for which vaccines are currently available and an additional 15 for which they are being developed [4]. Due to these efforts, the number of vaccine-preventable diseases continues to increase as does the potential to reduce vaccine-preventable deaths.