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How Animals Find Their Way in Space. Experiments and Modeling

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Abstract. We describe different components of brain's space representation system, such as place cells, grid cells, time cells, and head-direction cells and review the models that suggest and test neural mechanisms on how this system can be used by an animal during navigation.

Key words: *spatial representation system, hippocampus, entorhinal cortex, theta rhythm, phase precession, place cells, grid cells, time cells, head direction cells.*

1. INTRODUCTION

Nobel Prize for physiology and medicine in 2014 was awarded to John O'Keefe, Edward I. Moser, and May-Britt Moser for their studies of brain's space representation system (SRS). These researchers discovered two very important components of the SRS, *place cells* in the hippocampus and *grid cells* in the entorhinal cortex (EC). In the first part of our review we will describe the amazing properties of these neurons and their role in navigation and spatial memory. We will also describe other components of SRS such as time cells and head-direction cells. Based on experimental results, many mathematical models have been proposed to explain how the SRS allows the animal to code its location in space and to memorize and recall the trajectories that lead to target positions. Some of these models will be the subject of the second part of the review.

The essence of the results of the Nobel Prize winners is rather simple. In 1971 O'Keefe and Dostrovsky recorded the electrical activity of hippocampal neurons of freely moving rats. They found that these neurons start spiking at the moment when a rat reaches a specific position in the experimental platform and its body has a proper orientation [1]. Some years later O'Keefe found hippocampal neurons that fire in a specific place of experimental space independently of animal's orientation. These neurons were not responding to a simple sensory stimulus, nor to a specific motor behavior [2]. O'Keefe called these neurons *place cells*. A place cell has its 'own' place where it generates high frequency trains. The area in physical space where a place cell is active is called the *place field*. Thus, the place field is the receptive field of a place cell. O'Keefe supposed that an animal uses place cells to build the internal spatial map which is not associated with sensory stimuli [3] and which allows the animal to navigate in a given environment. The existence of such a map had been earlier predicted by Edward Tolman [4].

The discovery of place cells aroused enthusiasm of some researchers and skeptical reaction of others. The criticism of methodological aspects of O'Keefe's work gradually subsided as the subsequent experiments of the leading neurobiologists (György Buzsáki,

Howard Eichenbaum, Larry Squire, and others) confirmed O'Keefe's results on place cells and added new unexpected information about their properties. Strong support for these results came in 2005 when Edward and May-Britt Moser together with their colleagues discovered what they called *grid cells* [5–7]. These cells are located in the EC that adjoins the hippocampus and is connected with the hippocampus by feedforward and feedback connections. Thus, it became clear that the researchers were able to find not an epiphenomenon, but essential components of the SRS.

In contrast to place cells, grid cells do not code specific positions of the animal in physical space, but a set of positions that form a hexagonal lattice. Each grid cell has its own lattice of positions in which this cell becomes active and generates high-frequency spike trains. Thus, the animal has a whole set of hexagonal coordinate systems, allowing it to reliably determine its location in physical space.

Later it was found that in addition to place cells and grid cells, other types of neurons participate in the operation of the SRS. These include *head-direction cells* which are active when the animal's head points in a specific direction [8–12]; *boundary cells* that respond to the presence of an environmental boundary at a particular distance and direction from an animal [13]; *spatial view cells* that fire when the animal looks at a certain part of the spatial environment [14]; *time cells* that fire at successive moments in temporally structured experiences [15]; and *speed cells* whose activity codes the speed of animal movements [16, 17]. There are also neurons that code the distance to an object and the direction to this object [18]. Recently, the bat's neurons have been found that code positions in three-dimensional space [19]. It is premature to judge whether all the neural components necessary for animal navigation are known.

It is worth to note that place cells and grid cells were only found in mammalians: mice, rats, monkeys, and humans. The knowledge about neural implementation of SRS of birds and fishes is much more restricted (some data about the navigation system of birds can be found in [20]). All further exposition is applied only to mammalians.

The theory of spatial navigation of O'Keefe and Mosers does not comply with the traditional notions about the role of neurons in the realization of cognitive functions. Conventionally, it is believed that the activity of individual neurons does not have cognitive content: information carriers are not individual neurons, but large neural ensembles. This is why the neural memory is often metaphorically described as a hologram. The most popular mathematical model of associative memory of John Hopfield is a single-layer recurrent neural network in which the memory is implemented as a set of stable states of the whole neuronal ensemble constituting a network [21]. The discovery of place cells and grid cells undermines this concept, since information about the position in space is the final result of complex coding which is completed at the highest level in the hierarchy of brain structures (in the EC and the hippocampus).

Of course, one should not think that a place cell is a repository of memory about a particular place in space. First, the place fields of different place cells can overlap, so one place in physical space is coded by many place cells in different parts of the hippocampus. Second, place cells are at the top of the pyramid of spatial event representation in the brain. All layers of this pyramid are important for memory storage. Apparently, place cells are related to working memory, while long term memory (including the memory about spatial events) is stored in the neocortex.

The interest to the SRS is not only of theoretical, but also of medical nature. Place cells and grid cells are located in the structures of the brain which primarily suffer from Alzheimer's disease [22]. Therefore, in patients with Alzheimer's disease not only the processes of memorizing and recall are disrupted, but also spatial navigation. It is assumed that the studies of O'Keefe and Mosers can be useful both for the early diagnosis of

Alzheimer's disease and for understanding the pathological processes that occur in this disease in the hippocampal and entorhinal neurons.

In the next section we describe experimental data related to the SRS, in Section 3 we consider some mathematical models that aim to reproduce and explain these data. In Section 4 we summarize the state of the art in this field and outline the prospects of future research.

2. EXPERIMENTAL DATA

2.1. The hippocampus and entorhinal cortex. Structure and functions

The hippocampus is a brain structure in the depth of the temporal lobes of the neocortex. Its two parts are located symmetrically in the medial temporal areas of the hemispheres. The shape of this structure slightly resembles a seahorse (hippocampus), for which it received its name (Fig. 1).

In the cross-section the hippocampus is subdivided into several fields, the main fields are denoted as CA1 and CA3. Figure 2 presents a scheme of the interaction of the hippocampus with other brain areas suggested by Olga Vinogradova [23].

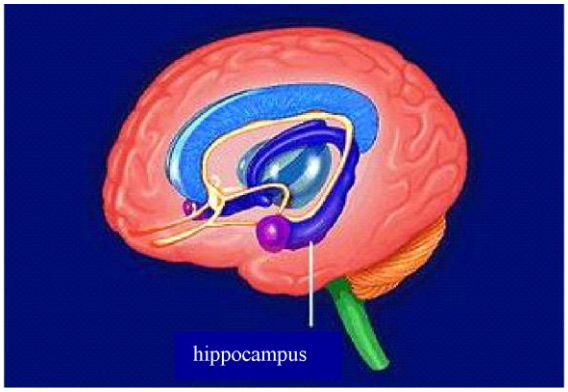

Fig. 1. Location of the hippocampus in the brain. The hippocampus is shown in dark lilac, the brainstem is green, and the amygdalae are lilac.

The complexity of this scheme should not hide the important fact that the hippocampus receives two flows of input signals, one from the EC and the other from the medial septum-diagonal band of Broca (MS-DB). The first input is formed in the medial and lateral parts of the EC (partially going through the subiculum) which in their turn receive the input signal from associative regions of the neocortex. The signal from the EC is divided into two flows: some connections go directly to the field CA1, while other connections go to the dentate gyrus and then to the field CA3. This is the so-called perforant path. The field CA3 projects connections to the CA1 via Schaffer collaterals.

Locating at the top of the pyramid of convergent connections from primary regions of the cortex to higher levels of information processing [24], the hippocampus plays a central role in many brain functions. The information in the hippocampus is represented in a very condensed and integrated form, therefore hippocampal neurons respond to a wide variety of stimuli. In contrast to other brain areas, reliable identification of hippocampal functions still causes discussions. Various researchers specify such functions of the hippocampus as working memory storage, participation in formation and recall of the long term memory, novelty detection of external stimuli, conditioning of complex stimuli, integration of stimuli of different modalities, orientation in space. It is amazing, how this small and relatively simple structure can participate in so different types of behavior (some considerations about how the hippocampus combines memory and space navigation functions can be found in the papers [25, 26]).

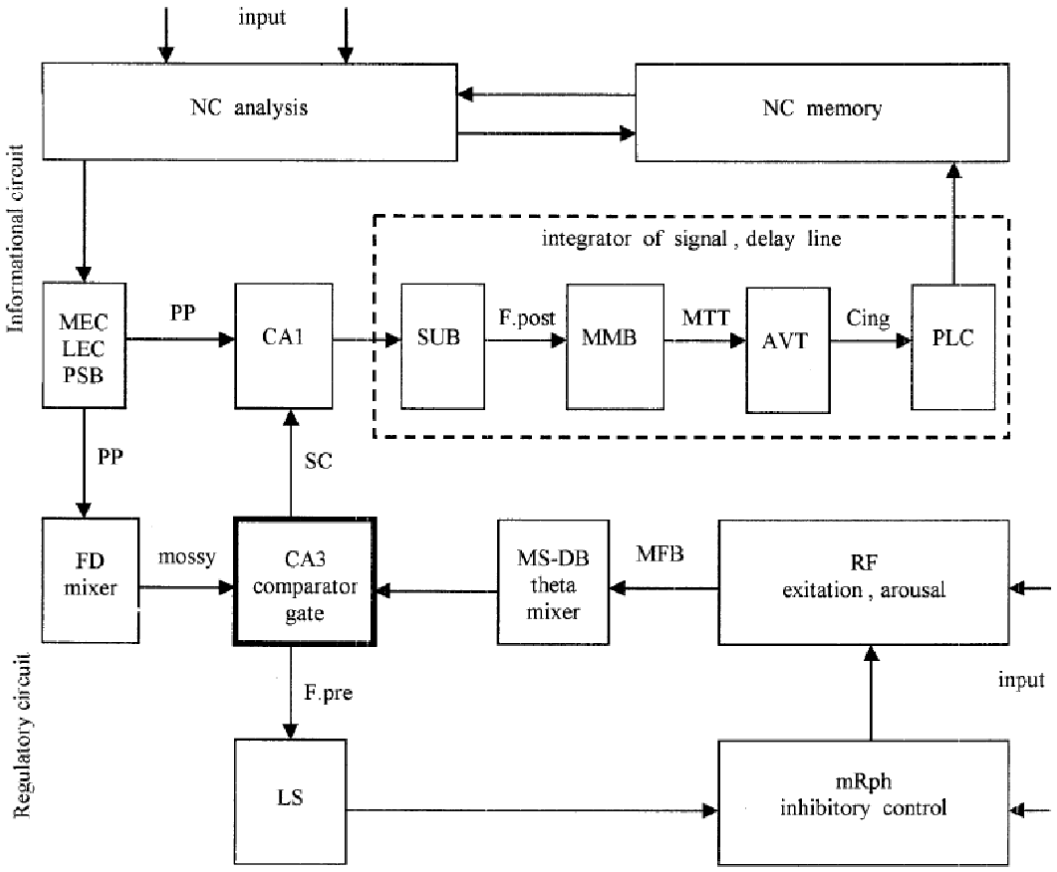

Fig. 2. A scheme of hippocampal interaction. NC, neocortex; FD, fascia dentata (dentate gyrus); MEC, medial EC; LEC, lateral EC; PSB, presubiculum; CA1, CA3, hippocampal fields; MS-DB, medial septum-diagonal band of Broca; LS, lateral septum; RF, reticular formation of the brainstem; mRph, raphe nucleus; SUB, subiculum; MMB, medial mammillary body; MFB, medial forebrain bundle; AVT, anteroventral thalamic nucleus; PLC, posterior limbic cortex; PP, perforant path; mossy, mossy fibers; SC, Schaffer collaterals; F.pre, precommissural fornix; F.post, postcommissural fornix; MTT, mammillothalamic tract; Cing, cingulum [23].

The main types of neurons in the hippocampus are excitatory pyramidal neurons and inhibitory interneurons. Place cells are represented by pyramidal neurons.

The main types of oscillatory activity in the hippocampus are the theta rhythm (4–8 Hz for humans, 4–12 Hz for rodents), gamma rhythm (40–90 Hz), and ripple oscillations (90–150 Hz). It seems that the gamma rhythm and ripple oscillations are generated in the hippocampus autonomously; the theta rhythm is projected to the hippocampus from the MS-DB and then spreads in various regions of the brain including the EC.

The EC is subdivided into lateral and medial parts, which have similar histological organization, but significantly different functions [27]. The medial EC is important for animal navigation; this is the area, where grid cells and head direction cells are found. The lateral EC does not contain such neurons.

The EC has a six-layer structure which is typical for the neocortex. Each layer is formed by principal neurons which send their collaterals to their own layer and the layers above (the neurons of layer V send their connections to layers V, VI, III, the neurons of layer III send their connections to layers III, II, I). Neurons of layer II are an exception: they send their connections up to layer I and down to layers III and V (the latter is innervated with less intensity). Thus, the neural networks of the EC have significant recurrence [27].

Since grid cells have been found in the second layer of the medial EC, this region attracted much attention of the researchers. Functionally and morphologically, two types of principle

neurons are distinguished in the second layer: pyramidal neurons and stellate cells [28, 29]. Grid cells are presumably stellate cells. Stellate neurons do not directly innervate each other, they interact through inhibitory interneurons only. It is believed that pyramidal neurons excite stellate neurons, but their connections with each other and with other types of neurons are little known [28].

2.2. Place cells

After 1971, numerous experiments have been conducted to study the spiking activity of grid cells. The results of some experiments are shown in Figs. 3, 4. Figure 3,A shows schematically the activity of four place cells when the animal moves in a linear track. Figure 3,B shows the real activity of 80 place cells when the animal moves in a square enclosure. Each panel in Figure 3,B presents the experimental field, color denotes the level of activity of different neurons. Most of the recorded neurons are place cells, six neurons are interneurons whose activity is not associated with a particular place.

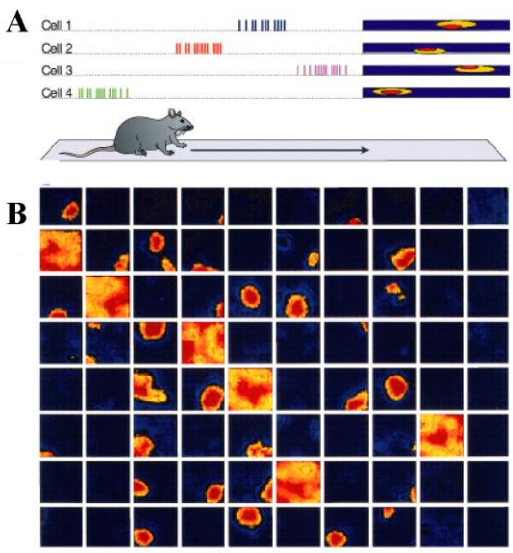

Fig. 3. The activity of hippocampal place cells. **A**. The activity of place cells when the rat moves in a linear track. Each place cell is active when the animal comes to a particular part of the track which is called the place field. On the right there is a schematic representation of the activity of the place cell depending on the position of the rat in the track (dark blue – lack of activity, yellow – low activity, red – high activity). **B**. 80 maps of neural activity simultaneously recorded in the CA1 when the rat was moving in a square enclosure. Six neurons with constant activity are apparently interneurons [30, 31].

Fig. 4. The activity of a place cell. Black lines denote the trajectories of animal movements. Red color is associated with positions where this place cell demonstrates high activity [32].

It can be seen from the figure that each place cell is activated when the animal hits a certain place in the experimental field and stops spiking when the animal leaves this place. Figure 4 shows the activity of a place cell when the rat was running in the experimental field.

It has been shown that 30 %–50 % of pyramidal neurons in the CA1 are place cells with specific place fields. Place cells are also present in the CA3 (and even in the EC), but in a smaller amount than in the CA1. When an animal is put in a new environment, its place cells quickly (within 5 minutes) adapt to new place fields which then remain stable in the given environment. With a slight change in the environment, place cells retain their place fields, although they can to some extent change their activity.

Space topography is not reflected in place fields: place cells with neighboring or overlapping place fields can be located in the hippocampus far from each other. Each place is coded by a population of place cells which are simultaneously active when the rat comes to a particular place. The order in which place cells are activated when the animal moves in a track can be reproduced either at the moment when the end of the track is reached [33] or during non-REM (slow-wave) and REM sleep [34]. The place cells firing can be played in forward and reverse order. In the latter case the rat 'recalls' its movements from the end to the start. Note that recalls are much faster than real movements. It is believed that such recalls serve for the formation of long term memory.

2.3. Phase precession

An unexpected and important phenomenon about place cell activity was discovered in the last decade of the XX century [35, 36], that is more than 20 years after place cells had been discovered. This phenomenon is called *phase precession*. It is schematically illustrated in Fig. 5. Note that receptive fields of different place cells in the CA1 and CA3 may overlap (more or less). When an animal is in exploring behavior, the local field potential registered in its hippocampus contains a strong theta rhythm component. It turned out that the moment when a place cell generates a spike train is bound to the phase of the theta rhythm and depends on the position of the animal relative to the center of the place field.

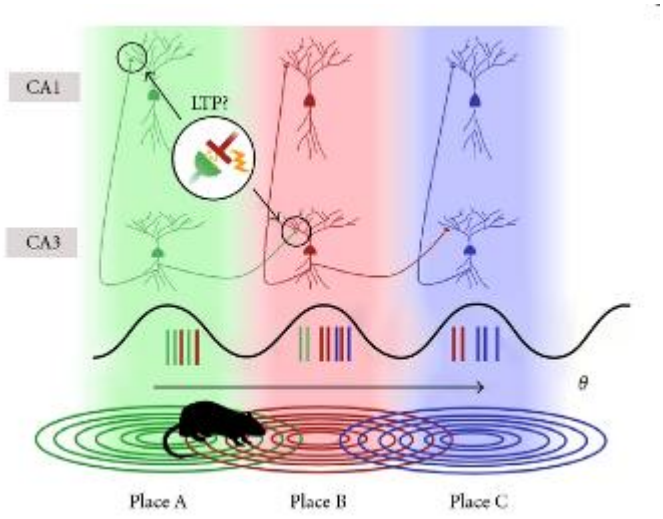

Fig. 5. Phase precession. A place cell generates spikes at the moments, advancing or lagging behind the peaks of the theta rhythm, depending on the position of the animal relative to the center of the place field. This phenomenon allows for the formation of spatial memory via synaptic plasticity [37].

Consider an animal moving in a linear track. If the animal is in the center of the place field of the 'green' place cell, this cell generates spikes for some time immediately after the moment when the theta wave reached its maximum (Fig. 5). Moving further, the animal enters the

place where the receptive fields of the 'green' and 'red' place cells intersect. The 'green' place cell may continue spiking, but now the 'red' place cell becomes active. Spikes generated by the 'red' place cell are lagging behind the maximum of the theta wave. By the time when the animal moves to the center of the field of the 'red' place cell, the next wave of theta rhythm appears. Now the 'red' place cell begins spiking at the moment of the maximum of the theta wave. Spiking of the 'green' place cell goes ahead of this peak, and spiking of the 'blue' place cell is behind this peak. In the same way, when the animal approaches to the center of the 'blue' place cell, this cell starts spiking at the moment when the theta wave reaches its maximum. The 'green' place cell is already silent at that moment, since the animal is out of its place field, while spiking of the 'red' place cell goes ahead of the maximum of the theta wave.

It is assumed that such a temporal organization of the activity of place cells is necessary for the creation (strengthening) of proper connections (synapses) between place cells in the course of learning to orient in space. Due to synaptic plasticity, the connections between place cells in the fields CA1 or CA3, which are discharged with a short time delay, are amplified. This mechanism allows the animal to memorize and recall the sequence of movements in direct order. Anti-plasticity (when the connection from a neuron that discharges a little later to a neuron that fired a little earlier) allows for memory storage and recall of the sequence of positions in reverse order [38]. Moreover, synchronous firing of place cells with similar place fields in the CA1 and CA3 which are connected by Schaffer collaterals must lead to strengthening the connections between these neurons and hence to coordination of their activity. All this creates conditions for encoding motion trajectories and formation of spatial memory.

2.4. Grid cells

Grid cells have been discovered in layer 2/3 of the medial EC of rats [5]. The activity of these neurons is conditioned by space location of the animal, namely these neurons generate spikes when the animal is at the nodes of a hexagonal lattice (Fig. 6). Later grid cells were found in other mammals: mice [39], bats [40], monkeys [41] and humans [42].

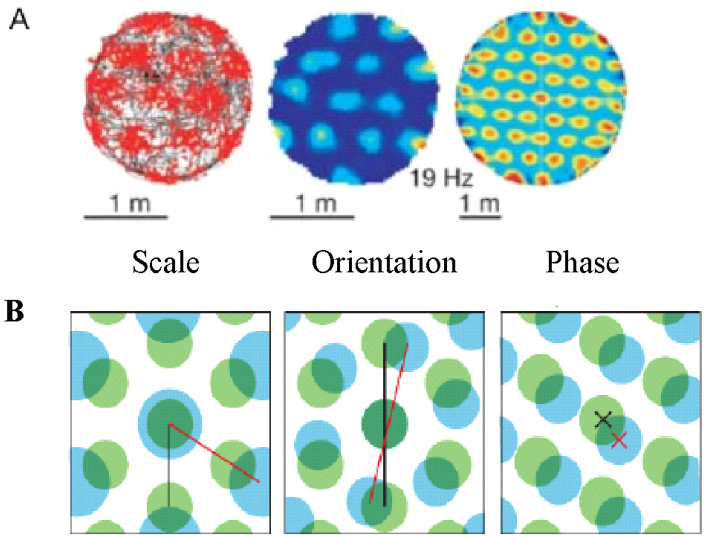

Fig. 6. Basic properties of grid cells. **A**. Firing fields of a grid cell during 30 min of running in a large circular enclosure. Left, trajectory of the rat (gray) with superimposed spike locations (red). Middle, color-coded rate map with the peak rate indicated. Red is maximum, dark blue is zero. Right, spatial autocorrelation for each rate map. The color scale is from blue through green to red. **B**. Cartoons of firing patterns of pairs of grid cells (shown in blue and green), illustrating the differences between grid scale, grid orientation and grid phase. Lines in left and middle panels indicate two axes of the grid pattern (which define grid orientation); crosses in the panel on the right indicate grid phase (x–y location of grid fields) [7].

The proportion of grid cells in the second layer of the EC ranges from 68 % [43] to 26 % [44] and even to 18 % [45]. Both grid and nongrid cells can be characterized as spatially selective [16, 45]. Grid cells are also found in presubiculum and parasubiculum [46]. Pyramidal and stellate neurons are identified morphologically in layer 2/3 of the medial EC. Grid cells are represented by stellate neurons in this region [29, 47]. About 25 % of stellate neurons show themselves as grid cells [47].

Besides grid cells, there are many other types of functionally different neurons in the medial EC, the activity of about 96 % of them is modulated by a position of the animal in space [45].

The grid of each grid cell is characterized by three parameters:

1. *Orientation*, angular deviation from the reference direction.

2. *Phase*, the vector of lattice displacement relative to the reference point.

3. *Scale*, the distance between adjacent grid vertices.

Adjacent grid cells have similar values of scale and orientation, but they can have different phases [5]. The grid scale gradually increases in the direction from dorsal to ventral parts of the EC [48]. The grid scale changes discretely so that scale values form clusters. The distance between the centers of these clusters is approximately a multiple of 1.4 [49].

It has been shown that grid cells and the neurons of other types are arranged into spatial and functional groups. In particular, this means that the correlation between spiking activity of grid cells as a function of the physical distance between these cells has the form of a Mexican hat: nearby neurons fire synchronously, while spike sequences of more distant neurons are anti-correlated [29, 50].

The stable activity of grid cells is maintained independently of visual stimuli and persists even in the darkness. On the other hand, the activity of grid cells can be evoked by the visual input [41]. The activity of grid cells appears nearly immediately after the animal is put in a new environment. Based on this fact, it is assumed that the system of grid cells does not require learning (adaptation to the new environment).

If visual cues or environment are changed, the grid scale of a particular grid cell and its activity remain unchanged [5], but the orientation and phase are anchored to the new system of space coordinates. Distortion of the known environment (by shifting a wall of the box where the rat foraged) leads to the change of the activity of grid cells whose place fields are near the distorted boundary, while the activity of other grid cells is kept unchanged [51].

The important aspect of experimental data is concerned with the relations between the activity of grid cells and the theta rhythm. The theta rhythm may be projected to the EC not only from the hippocampus, but also directly from the MS-DB. The MS-DB as a pacemaker of the theta rhythm generates the input to the hippocampus from the side of the brainstem [52, 53]. However, the connections from the MS-DB also go to the EC. The medial part of projections from the MS-DB is approximately two times larger than the lateral part. The main rhythmic output from the MS-DB is produced by GABAergic neurons which selectively innervate interneurons of the EC [54]. Beside GABAergic connections, the EC obtains cholinergic projections from the MS-DB. Cholinergic neurons of the septum nonselectively innervate all neural populations of the EC. The density of cholinergic receptors on stellate cells (assumed to be grid cells) of layer 2/3 of the EC is two times lower than on the pyramidal neurons of this layer [29]. Thus, it can be concluded that grid cells do not directly receive a rhythmic input at the theta frequency, but only through other neuronal populations of the EC.

It is known that glutamatergic neurons of the MS-DB can play the role of speed cells, therefore they can participate in the formation of grid cells due to their projections in the upper layers of the medial EC [55–57]. In the paper [58], it is shown that the frequency of the theta rhythm in the hippocampus linearly depends on the spiking frequency of glutamatergic neurons of the MS-DB. This effect is mediated by the intraseptal switching through

GABAergic neurons. This evidence complies with the well known fact that the frequency and the power of the theta rhythm in the hippocampus are correlated with the animal's speed [59, 60]. Thus, one can expect that not only the glutamatergic input, but also the GABAergic input to the EC contains the information about the animal speed.

As for place cells, phase precession has been observed for grid cells in relation to the local theta rhythm [61]. Moreover, under pharmacological blockade of the theta rhythm by the inhibitors of cholinergic transmission or under the blockade of the MS-DB, the normal activity of grid cells is usually broken [62, 63]. However, in some special cases it can survive. Such cases are described for bats [40] and for grid cells in deep layers of the medial EC [43].

Functional interaction between place cells and grid cells is still unclear. From one hand, it would be reasonable to suppose that the activity of place cells is controlled by the activity of grid cells, since the former give higher representation of space. This point of view is supported by the fact that stellate cells of layer 2/3 of the EC send their connections to the hippocampus both directly to the fields CA1 and CA3 and indirectly through the dentate gyrus. Thus, one can think that grid cells are the direct source of excitation for place cells. However, from the other hand, there are many data evidencing that the activity of place cells is leading in relation to grid cells. This concept is supported by the fact that the hippocampus sends its connections to deep layers of the EC. In their turn, the neurons from these layers send signals to the second layer. Besides, it is shown that during ontogenesis the grid cells are the last to appear. For example, for the rats they appear on the 17–20th day of postnatal development when all other neural systems associated with navigation (head-direction cells, boundary cells, and place cells) are already formed [64].

Before grid cells become mature, the place fields of hippocampal place cells are lager than after maturing, therefore they provide less exact information about animal position. Grid cells loose their activity if the activity of the hippocampus is suppressed [65]. The remapping of place cells in the hippocampus can successfully go if the input to the hippocampus from the medial EC is blocked [66]. The most convincing data came from optogenetics. It has been shown that the inhibition of neurons in the medial EC does not lead to the disappearance of the activity of hippocampal place cells [44]. To explain these data, the hypothesis is put forward that place cells are supported by non-spatial information from the lateral EC [67]. In summary, we can say that place cells are not exclusively formed by the input from grid cells and that grid cells receive the input from place cells, which improves and stabilizes spatially coordinated activity of grid cells.

2.5. Head direction cells

Head direction (HD) cells are another important component of the SRS. They were discovered in the rat dorsal presubiculum by James B. Ranck, Jr. in 1984, but substantial papers on this subject were published by Ranck and co-authors in 1990 [8, 9]. Later HD cells have been found in many brain structures of the cortex (retrosplenial cortex and EC) and subcortex (thalamus, lateral mammillary nucleus, dorsal tegmental nucleus, and striatum). A striking feature of HD cells is that they discharge when the animal's head is facing in the cell's 'preferred' direction (Fig. 7). All preferred directions are equally represented within a population of head direction cells. The activity of HD cells is independent of animal's position in space, the position of the animal's body relative to its head, and the animal's on-going behavior. Some HD cells can predict what the animal's head direction will be in the nearest future (25–95 ms in advance). The alignment of the HD system is preserved even in the darkness for some time, and restores a few minutes after the light is switched on.

The HD system uses the environmental cues as its reference frame. When head direction cells are recorded in a cylinder-shaped environment that contains a prominent visual cue attached to the inside wall, the rotation of the salient visual landmark can lead to the corresponding shift in the head direction cell’s preferred firing direction. This indicates that

head direction cells can be controlled by landmarks (Fig. 8). In the paper [68], it is shown that in fact the situation is even much more complex. HD cells in the retrosplenial cortex can be of at least three types: the cells that keep their preferred direction in two bi-directionally oriented compartments, the cells that change their preferred direction to the opposite one in these compartments, and the cells that have bi-directional firing patterns.

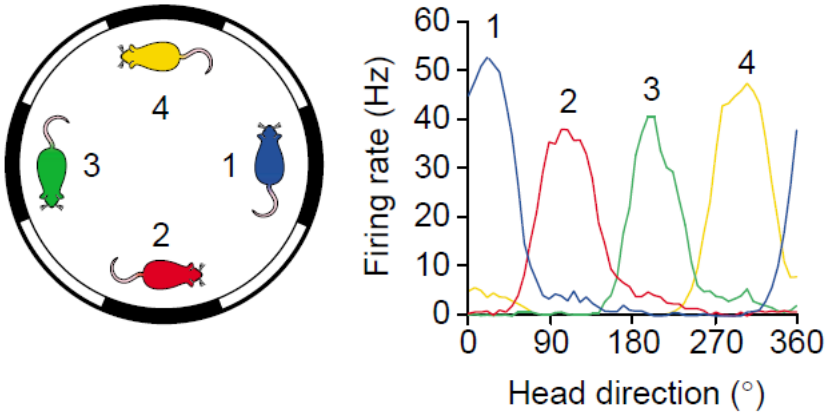

Fig. 7. Firing rate of four HD cells corresponding to four directions of the rat's head [69].

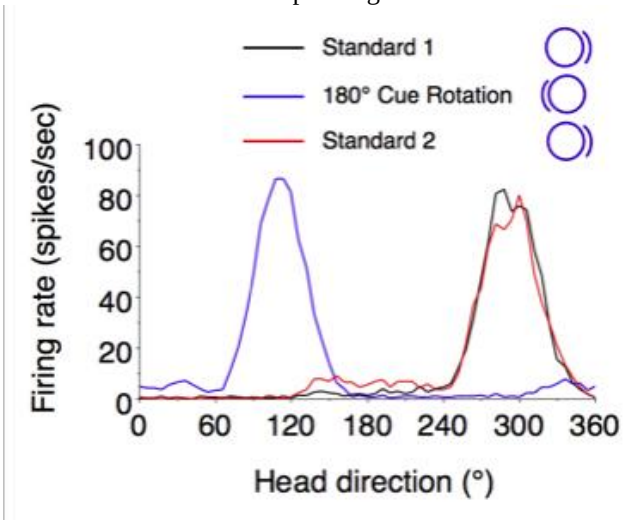

Fig. 8. HD cell response to 180° cue rotation [70].

2.6. Time cells

While place cells fire when an animal occupies a particular location in an environment, time cells fire when an animal is at a particular moment in a temporally structured experience. The researchers anticipated that there should be time cells in the hippocampus, because the hippocampus is involved in memorizing the order of sequential events and in classical trace conditioning when the duration of the gap between conditional and unconditional stimuli is a central component of memory representation.

Time cells have been discovered in the laboratories of Howard Eichenbaum [71] and Gyorgy Buzsáki [72] (see a review [15]). Figure 9,A shows an idealized plot of time cell spiking activity in three experiments. Different cells fire in a sequence with longer duration of activity (longer 'time fields') for later-firing time cells. The periods of firing of each time cell are approximately the same for different trials. Figure 9,B shows a real activity of CA1 neurons of a rat running in a wheel. The neurons are ordered according to the moments of their maximal firing rate: the neurons with higher numbers are active earlier in time. Importantly, each neuron is active during a brief time interval and the neurons' firing covers the entire period of wheel running. It has also been established that a sequence in which time

cells fire is linked to the content of the trial. Firing sequences of time cells during wheel running were observed only after rats had been trained to remember particular paths through a maze and not during wheel running outside the memory task.

The same neurons can play the role of place cells and time cells [73]. This is confirmed by the experiment when a rat performs a spatial alternation task that also includes running on a treadmill. It has been shown that the same neurons that fired at particular moments in time (time cells) on the treadmill also fired when the rat passed through specific locations of the maze outside the treadmill (place cells).

3. MODELS

The mathematical modeling of navigation is popular and promising field of research, since it has important applications in neurobiology, medicine, and robotics. The studies of O'Keefe and Mosers gave a powerful impetus to hundreds of publications. The modeling covers the following subjects:

– How place cells and grid cells are used for the navigation and search of a goal?
– What is the role of oscillations and phase relations for spatial information processing in the hippocampal system? How phase precession appears? What is the role of phase precession in coding positions in space?
– How different neural components of the SRS interact with each other?
– What neural mechanisms are used when an animal or a robot is trained to navigate in space?
– Is the space navigation supported by special neural mechanisms or the memory formation has common forms for any type of declarative memory?

Our review does not aim to provide a full coverage of these subjects. We confine ourselves to a small number of generic examples which should give general ideas of mathematical problems arising in this field and how they are solved.

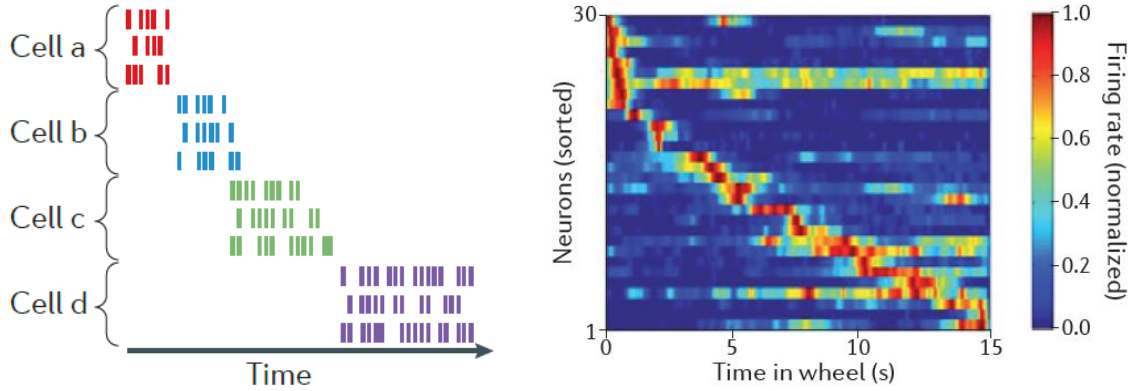

Fig. 9. Time cells. **A.** A raster display of spiking activity from idealized, simultaneously recorded time cells (each shown in a different color). For each cell, activity is shown as a raster of spikes for three example trials in which the cell fires for a brief period at approximately the same moment in each trial, with later-firing time cells being active for longer periods (indicating scalar coding of time). **B**. The ensemble firing-rate during the wheel running period of a rat. The plot shows the normalized firing rates of 30 neurons (each row shows the activity of one neuron). The plot reveals that different hippocampal neurons fired at different times, and that together, the neurons' firing covered the entire period [15].

3.1. A model of navigation in the Morris water maze

A popular experimental paradigm used in spatial learning and memory is the Morris water maze [74]. The water maze is a large pool filled with milky water. There is a fixed submerged platform in the pool. The aim of the experiment is to train the animal (a rat or a mouse) that swims in water (these animals can swim, but water is an alien medium for them) to escape on

the platform by using space cues. There is a large amount of experimental data on the learning process and its disorders under various pathologies of the brain.

The paper [75] describes a neurorobotic model Darwin X that is able to find the platform after some learning trials (Fig. 10). Darwin X moves on a hard surface, but his visual system does not allow the robot to see the 'hidden' platform. The platform can be detected if the robot is located directly on it or in the immediate vicinity. Spatial landmarks (cues) that are used by Darwin X for navigation are colored panels hung along the boundaries of the 'pool'.

Darwin X is a brain-based device that interacts with real environment whose behavior is guided by a simulated nervous system, incorporating aspects of the detailed anatomy and physiology of the hippocampus and its surrounding regions. The information is processed in two channels ('what' and 'where'). The hippocampus plays the role of a coordinator of navigation. It is also the storage of the working memory. Darwin X is trained by the modification of connection strengths between the neocortex and the hippocampus, as well as in the hippocampus itself.

A remarkable and unexpected result of experiments with Darwin X is that its training leads to the automatic formation of place cells in the field CA1 (Fig. 11). This was not planned in advance in the design of the neural network of the robot and, apparently, is a natural consequence of spatial orientation learning in an artificial system with a biologically plausible architecture of the interaction between the hippocampus and neocortex.

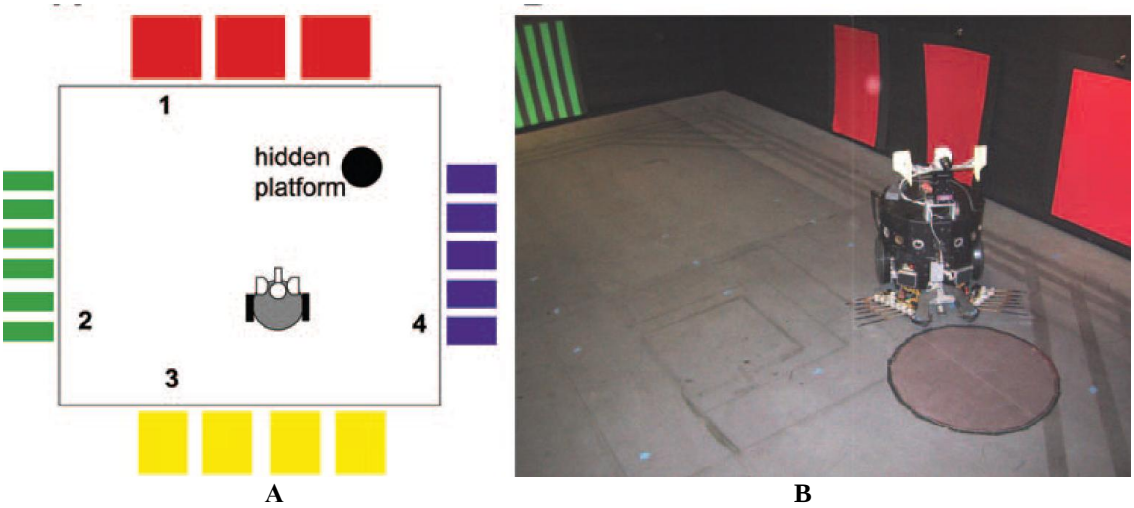

Fig. 10. Neurorobotic model of navigation of the Morris water maze. **A –** Schematic representation of the pool with a hidden platform. Numbers 1–4 denote four starting locations. **B –** Snapshot of Darwin X in its environment [75].

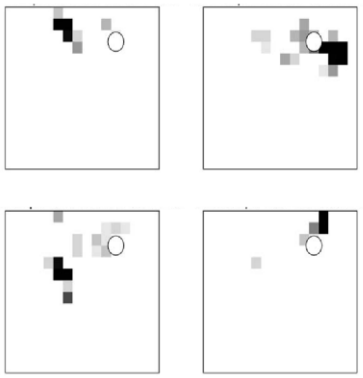

Fig. 11. The activity of place cells in the CA1 of the 'hippocampus' of Darwin X. The charts show the activity of four neurons (place cells) when the robot intersects their place fields. A pixel corresponds to one foot of physical space. The gray scale represents the activity of a given CA1 neuron and is normalized from quiescent (white) to maximal firing rate (black). The circle denotes the location of the hidden platform [75].

3.2. Path planning in a target search model

The idea that synaptic plasticity between place cells can be used as a mechanism for the target search (see Section 2.3) has been realized as a mathematical model in the paper [76]. In this model, a training scheme is proposed that allows the animal to find the target object (for example, a food bowl). It is assumed that synaptic connections between place cells with overlapping place fields are formed in advance, so the training task is to strengthen certain synaptic connections in the network of place cells.

This task is solved by a method reminiscent of dynamic programming, according to which the optimal path in the graph is found by moving from the end of the path to the beginning. In other words, one should start from the target vertex and move consistently to increasingly remote neighborhoods from it until the process reaches the initial vertex. In terms of the model, this procedure is implemented as follows.

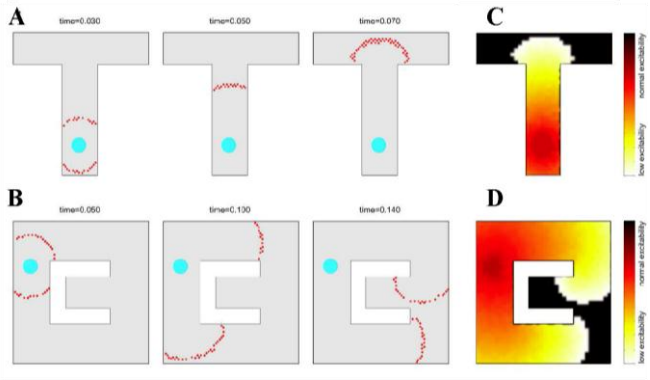

Fig. 12. Wavefront propagation in the Ponulak–Hopfield model for two different environments **A** and **B**. Cyan rings are the initiation points of the wavefronts. Red dots are the action potentials that occurred in a short time window, centered at the times indicated above the charts. Plots **C** and **D** show color maps of the average level of a neural adaptation in the particular regions of the network after a single wavefront passage up to the states illustrated in the right-far plots in **A** and **B**, respectively. Brighter colors represent lower excitability of the neurons at the corresponding locations [76].

First, the animal finds the location of the target object as a result of exploratory behavior. At this moment, the place cell, in whose receptive field the target object is located, sends an exciting spike to all neighboring place cells (here the term 'neighborhood' means the neighborhood in the graph of connectivity), which in turn send spikes to their neighbors, etc. (Fig. 12). To form a traveling excitation wave and to prevent the propagation of the excitement 'backward', a restriction is introduced: after excitation the place cell becomes inactive for some time. The excitation wave is gradually moving farther and farther from its source. Its propagation stops when it has passed through all the place cells or if its further spread is hampered by a barrier from place cells that had lost the ability to excite for a time.

The rule for the modification of synaptic connections is of the anti-STDP (anti-spike-time-dependant plasticity) type [77, 78]. It is formulated as follows. The synaptic connection increases if it goes from the place cell, which the excitation wave has just reached, to the place cell from which this excitation wave came. As a result, a vector field of amplified synaptic connections is formed in the network of place cells (Fig. 13). This field 'prompts' to the animal in which direction to move to reach the target object from any initial position. The animal must move in the direction indicated by the vector field of the strengthened synaptic connections.

We described only the simplest navigation strategy within the Ponulak–Hopfield model. In fact, this model keeps its capacity to work under multiple targets, in the presence of noise in the activity of neurons, and when the context (environment) changes. More details can be found in the paper [76].

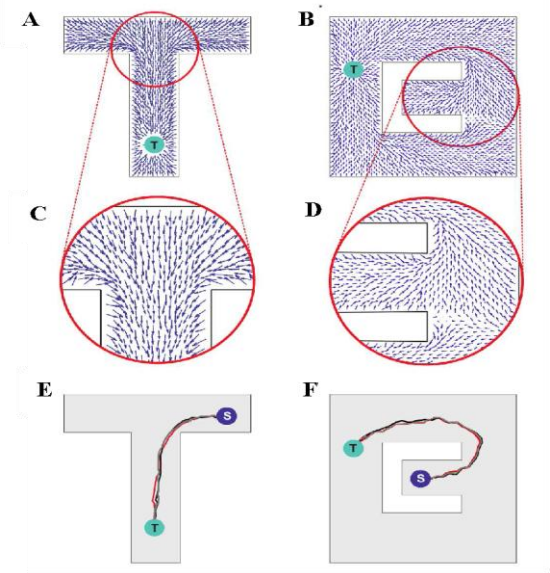

Fig. 13. Synaptic vector fields resulting from the excitation wave and the typical movement trajectories in the environments of Fig. 12. S, starting point; T, target (final) point. **A, B,** vector fields; **C, D,** zoom of the vector fields around the bifurcations in the simulated mazes; **E, F,** movement trajectories [76].

3.3. A model of memorizing and recalling sequences of spatial events

As we already mentioned in Section 2.3, the spatial memory can be reproduced as a sequence of activations of place cell populations in forward or backward order when the animal finished its movement [33] or during sleep [34], as well as in people when recalling an episode of the movement in virtual space [79]. This fact was put in the basis of the model of memorizing the sequence of events, which, in particular, describes the memorization and recall of animal positions in a linear track (Fig. 14) [38].

In the model, there are 8 populations of place cells, each containing 80 neurons. Place cells belonging to the same population have highly intersecting place fields. Place fields of different populations do not intersect and cover the entire space of the linear track in which the animal moves. To conveniently represent the place cell activity, the populations are numbered so that they are sequentially activated when the animal moves from left to right. The activation time of each population is chosen so that the population remains active for approximately one period of the theta rhythm. The recall of the whole sequence takes one period of the theta rhythm after the animal reaches the end of the track. Fig. 14 shows an example where spatial positions are recalled in reverse order from the eighth population to the first one.

Two independent neural mechanisms are used in the model to memorize sequences of positions: STDP (spike-time-dependant plasticity) and anti-STDP (anti-spike-time-dependant plasticity). According to STDP (anti-STDP), synaptic connections between two neurons are amplified if the postsynaptic neuron fires shortly after (before) presynaptic neuron. STDP between the populations of place cells is used to learn a sequence of positions in direct order, while anti-STDP allows for the recall of positions in reverse order. Figure 14 corresponds to the case of reverse memorization and recall which is based on anti-STDP.

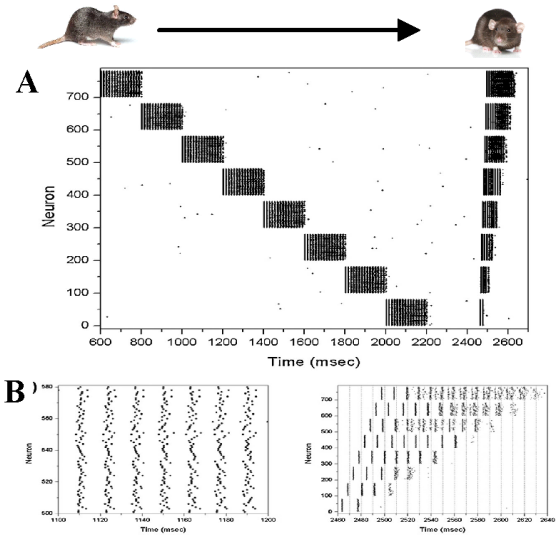

Fig. 14. Memorization and backward recall of a sequence of positions when a rat moves in a linear track. Each small dot represents a spike. **A.** Storage and recall of eight positions of a rat along the track, represented by eight populations of neurons. The left part (time period 600–2200 ms) shows the activation of neurons (the encoding period). The right part (time period 2400–2600 ms) shows the reverse recall which is initiated by the activity pattern corresponding to the end of the track (the recalling period). **B.** A magnified picture of the encoding period shows noisy but coherent firing of neurons. The recall period shows the firing of neural populations one after another with a short delay between the firing of different populations [38].

3.4. Models of grid cells

It is generally accepted that the grid cell system performs the function of path integration. This is a common opinion shared by the leading experimentalists in this field, such as Buzhaki and Moser [25], and the authors of the most influential models [80–82]. Three basic concepts for the formation of grid cells have been proposed: oscillatory interference, self-organizing maps (SOM), and attractor maps. We consider them below.

1. ***Oscillatory interference model.*** This model is promoted by the team of Neil Burgess and co-authors [82–85]. It is based on the assumption that there exist the so-called velocity-controlled oscillators (VCO). A VCO is a neural population that generates a rhythmic signal whose frequency is proportional to the projection of animal's moving velocity on the preferred direction of the VCO. In the model, the preferred directions are chosen with the step of 60°. Grid cells receive an excitatory input from the VCO, as well as an excitatory rhythmic input with a stable frequency in the range of the theta rhythm.

Signals that code the velocity of the animal in different directions interfere on grid cells (Fig. 15). The grid scale depends on the relation between the velocity and the frequency of the VCO. The grid orientation is determined by the preferred direction of the VCO. An advantage of this model is the fact that phase precession arises in the model without any additional conditions.

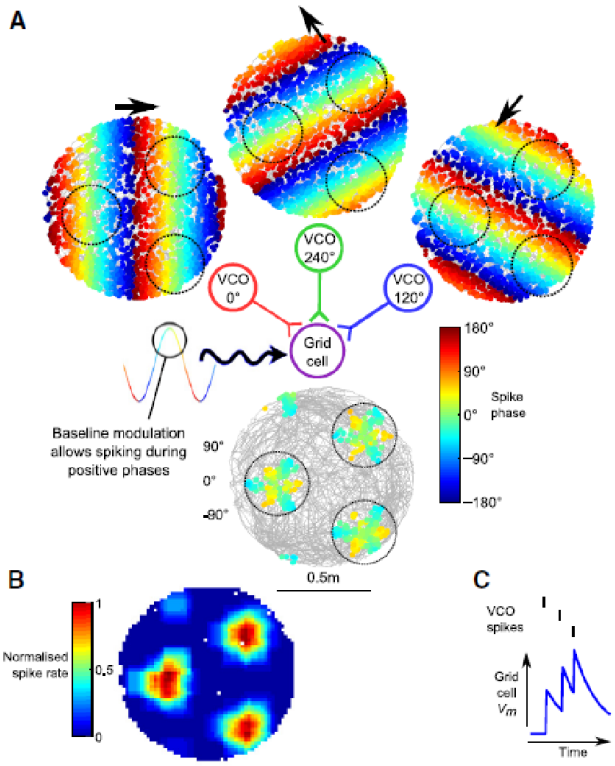

Fig. 15. The oscillatory interference model of grid cell firing. **A**. VCOs (red, green, and blue circles) spike periodically such that their spiking phases relative to a baseline oscillation (colored sinusoid) reflect translation along their preferred directions (black arrows) as the animal navigates its environment. Spike phase maps for a simulated run in a circular environment are shown above their respective cells (spike locations indicated by dots, color coded by baseline phase; see phase color bar). A grid cell is driven by VCOs with different preferred directions, and acts as a coincidence detector for spikes arriving from those inputs. The grid cell is additionally subject to modulation by the baseline oscillation (black sinusoidal arrow). These combined inputs cause the grid cell to fire when all VCOs spike during similar positive baseline phases (which occurs within the ringed regions on each spike phase map), giving the grid cell its spatial firing fields (grid cell, spike phase map is shown below the cell). The animal's trajectory is shown as a gray line. **B**. Firing rate map of the grid cell. Multiples of 60° spacing (here 120°) between VCO preferred directions cause the firing fields to be arranged in a regular triangular grid. **C**. Leaky integration of VCO spikes by the grid cell [83].

2. ***Models based on self-organizing maps***. This model was proposed by Stephen Grossberg and Praveen Pilly [81, 86]. The main assumption of the model is the existence of 'stripe cells' in deep layers of the EC. The properties of stripe cells are similar to the properties of VCO in the oscillatory interference model described above. The firing frequency of a stripe cell is proportional to the projection of the animal's movement velocity on the preferred direction of the stripe cell. The layer of stripe cells excites the layer of grid cells (Fig. 16), the matrix of weights between these layers is tuned according to the rules similar to the Hebb rule. As a result of the learning process, a stable combination of active grid cells is formed that corresponds to a certain velocity of the animal. The authors also consider the projection of the layer of grid cells on the layer of place cells. The corresponding matrix of weights is also trained according to the Hebb rule.

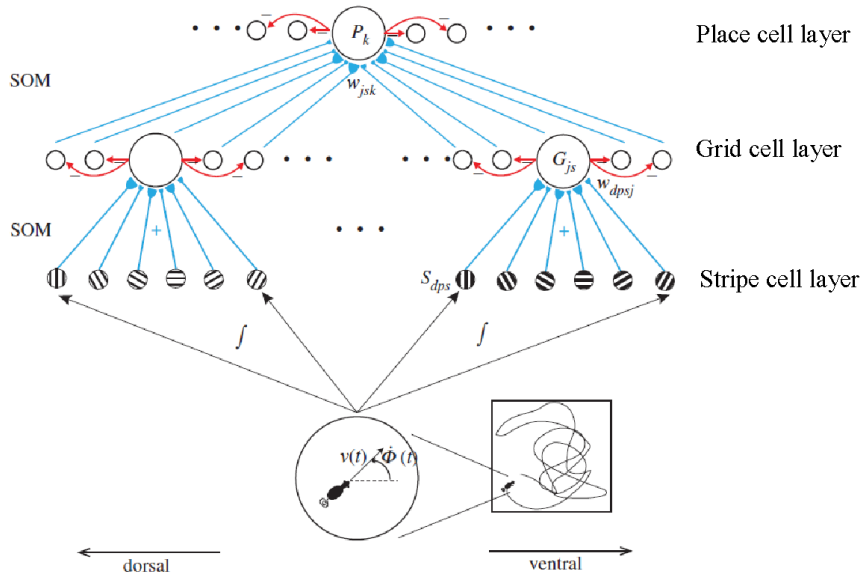

Fig. 16. Self-organizing map hierarchy of grid and place cell activation and learning: stripe cells in either the parasubiculum or the deeper layers of medial EC, self-organizing grid cells in layer II and self-organizing place cells in hippocampal area CA3 learn to represent position in increasingly large spaces based on internally generated signals corresponding to translational and rotational movements during navigation [81].

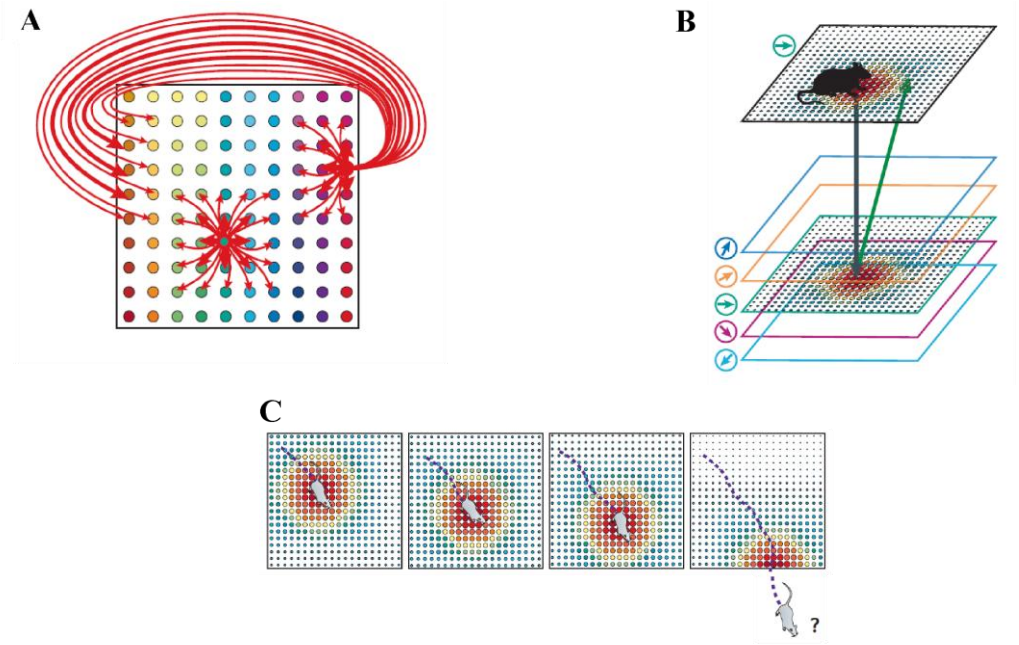

Fig. 17. An attractor model of formation of grid cells. **A.** Architecture of connections within a cluster (see the text). **B**. Controlling attractor movements. A signal about the direction of the movement comes from head direction cells. **C**. Position of a 'bump' of activity in the neural network that encodes a position of the animal [91].

3. ***Models based on attractor neural networks.*** There is a large variety of attractor type models proposed by different authors [80, 87–92]. We will describe the main ideas in this field put forward in the last years. Attractor models are based on the assumption that there exist continuous attractors in the EC. By attractors we mean stable states of a neural network, in other words, states in which, in the absence of external stimuli, the same neurons remain active for a long time. Continuity of attractors implies that transitions between attractors can occur either with the passage of time or under the influence of external stimuli. Thus, at each

moment the attractor network contains active neurons that code the current position. Moving from one attractor to the other encodes the movement of the animal in space.

A popular attractor model has been developed by McNaughton and co-authors [91, 92]. The main assumption of the model is that neurons in the EC form functional clusters. There are no connections between the clusters. Within a square cluster, the connections are wrapped around in a tor, that is the neurons at the boundaries innervate the neurons at the opposite side of the square (Fig. 17). Neurons have local synaptic connections, the strength of connections decreases with the distance between neurons. All neurons receive tonic inhibition. It is assumed that neighboring neurons have similar phases of their grids. The movement of the center of activity takes place not so much in physical space as in the space of phases of the grids.

Various types of connections between grid cells depending on their phases have been proposed (Fig. 18), but the main ideas of attractor model construction are similar among all authors (see review [7]).

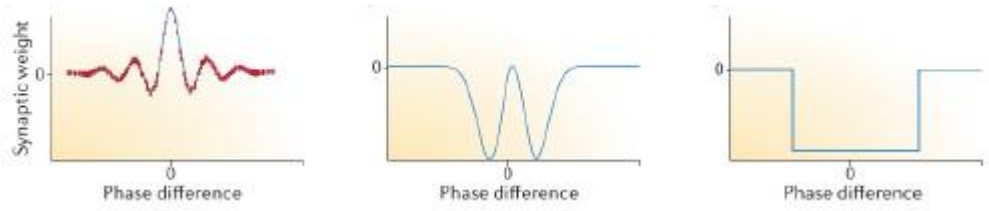

Fig. 18. The dependence of synaptic weights between neurons on the phase difference of their grids in different attractor models [7].

Since connections between neurons are symmetric and decrease rapidly with distance, stable states of activity are possible which have the form of moving bumps. Under the influence of an external input, exciting neighboring neurons, the bump of activity can move to neighboring regions (Fig. 17,C). Such input signal can be produced by head direction cells that encode the direction of animal's movement.

There are some problems in the adequate reflection of experimental data by the model [91]. In particular, the role of the theta rhythm is not clear. There is a possibility to introduce phase precession in the model by introducing an additional rhythmic input [92], but the role of such a signal is vague. Nonetheless, lately the attractor models received a significant support from the works that show spatial and functional clusterization of neurons in the EC [29, 50].

Another problem for attractor models is the speed of activity movement between adjacent states which theoretically must be proportional to the speed of the animal. The excitation in a neural network can move with more or less constant speed, while the speed of animal's movements can vary in a large range. It is believed that this problem can be solved by using grids with different scales.

In conclusion we would like to attract attention to a recent paper whose basic ideas differ from those described above. In this paper, grid cells are formed via special rules of adaptation of connection strengths between the neurons of the EC [93]. There are excitatory and inhibitory neurons in the model (Fig. 19).

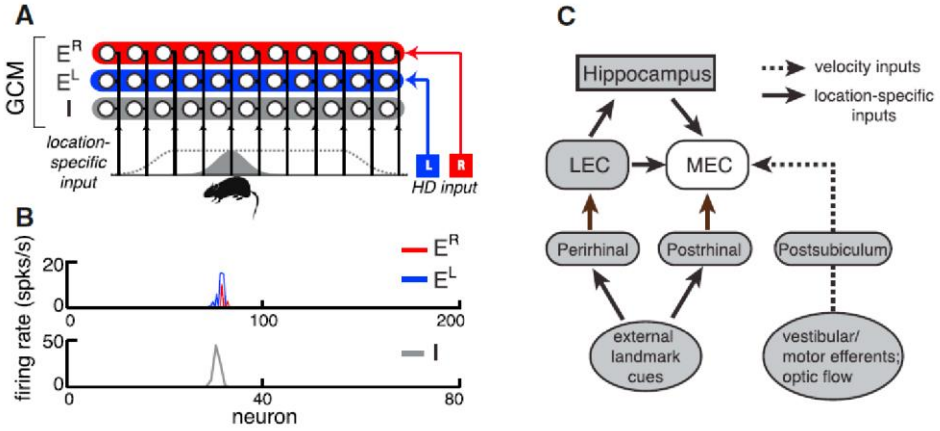

Fig. 19. Architecture of the model [93]. **A**. The 1D grid cell network consists of inhibitory and velocity-sensitive excitatory cells. All cells are assigned location-specific inputs (gray bell-shaped curve: schematic of a location-specific input; dotted gray envelope suppresses location-specific inputs near the environment boundaries). **B**. Snapshot of population activity during the plasticity phase. **C**. Possible pathways for velocity and location-specific inputs to entorhinal grid cells [83].

Excitatory neurons do not project directly to each other. They interact only via inhibitory neurons. Connections from excitatory neurons to inhibitory neurons are modified according to the STDP rule. Connections between inhibitory neurons and from inhibitory to excitatory neurons are modified according to the anti-STDP rule. All excitatory neurons receive a specific input that encodes a position of the animal in space. Excitatory neurons are divided into two subpopulations, L and R, reacting to the turn of the animal, respectively, to the left and right side. Inhibitory neurons do not receive any spatially modulated input. After a short learning period that starts with randomly generated initial values of connection strengths, stable grid cells are formed in the model.

It is also reasonable to attract attention to the papers, showing that the representation of space by grid cells is optimal in some sense. In the paper [94], the author gives an analytic proof that memory capacity of neurons that encode multiple spatial transitions is maximized by a hexagonal pattern. In the paper [95], deep reinforcement learning was used to train a recurrent neural network to perform path integration and goal finding in unfamiliar and changeable environments. It is shown that grid, border, and head direction cells automatically emerge in the model. Spatial scale of grid-like units is clustered as it is observed in the EC. Though the training procedure by backpropagation of errors does not seem biologically plausible, the model provides arguments in favor of computational efficiency of grid cells in coding space information.

3.5. Models of interaction between place cells and grid cells

Among the experimentalists, there is no consensus on the interaction of grid cells and place cells. As a consequence, various approaches have been put forward in modeling works. One of the first models in which it was assumed that place cells appear as a result of grid cell influence was suggested by the pioneers of grid cell investigation and their co-authors [96] (Fig. 20).

Since grid cells directly excite place cells, the idea arises that the information on the position of the animal is simply recoded from one representation to another. Such transformation is demonstrated in the cited work. It is shown that the weighted sum of signals from grid cells with different parameters of orientation, phase, and scale leads to the formation of stable activity of place cells. This idea is shared by many authors of theoretical works [80, 81, 90].

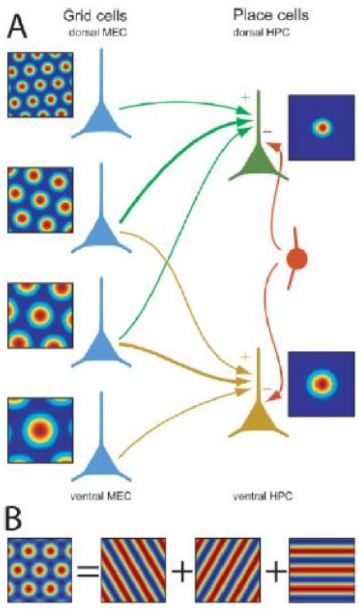

Fig. 20. Model for place-field formation. **A.** Assumed anatomical connectivity between grid cells in the medial EC (MEC) and place cells in the hippocampus (HPC). Grid cells (blue) are illustrated with small grid spacings in the dorsal pole of MEC and with larger grid spacings at more ventral levels. All place cells receive input from grid cells of similar spatial phase, but a diversity of spacings and orientations. Hippocampal place cells with a small firing field (green) are innervated by grid cells from more dorsal parts of the EC than place cells with a larger field (yellow). Connection weights are indicated by the thickness of the arrows. Interneurons (red) provide nonspecific inhibition to keep overall firing rates at physiological levels. The color code for the rate maps ranges from blue (0 Hz) to red (peak rate). **B.** Grid functions are constructed from a sum of three sinusoidal grating functions with 60 and 120 degrees angular difference, and can take any specified spatial phase, orientation, and spacing [96].

The inputs from place cells come into the second layer of the EC through deep layers, so place cells are capable of significantly modulating the activity of grid cells. Models of the transformation of the activity of place cells into the activity of grid cells are not popular in the literature, however, a spatially modulated input is used in many grid cell models. Its purpose is to stabilize the grid parameters in time and to avoid the accumulation of errors in the presence of a noise component in the input (see review [97]).

The idea of a loop in the interaction between place cells and grid cells was developed in detail in the paper [98]. In this paper, grid cells were modeled by several disconnected attractor neural networks of different scales. Place cells were modeled by a recurrent network. Place cells received additional information about space cues which simulated the input from the lateral EC. Grid cells received the input modulated by the animal speed from speed cells. Feedforward and feedback connections were modified according to the Hebb rule (Fig. 21). It has been shown that place cells can be formed autonomously without the input from grid cells. However, the grid cell input to place cells helps stabilize their code under noisy and inconsistent sensory input. The realignment of grid cells in different environments can be explained by remapping of place cells, but not vice versa. This is in agreement with experimental data that remapping of place cells can go without the input from the EC [66].

Not all the researchers share a compromise idea about a loop in the interaction of grid cells and place cells. Some authors of theoretical works on this subject believe that place cells do not simply modulate and correct errors in the activity of grid cells, but play a leading role in the formation of grid cells. This idea is developed in a computer model [99], where grid cells are formed by the signals from inhibitory and excitatory neurons that demonstrate the features of place cells (Fig. 22), as supposed in the paper [100]. The main assumption of the model is that the inhibition is smoother than excitation when the animal moves in space. From

a physiological point of view, this means that inhibitory neurons demonstrate the activity of place cells, but their place fields are larger that place fields of excitatory neurons (an experimental confirmation of this fact can be found in [101]). Both inhibitory and excitatory signals are mixed at the input of a grid cell, but since the excitation acts more locally, the grid cell only fires in the center of the place field. During animal's movement, another place cell and the corresponding interneurons are activated. As a result, the grid cell fires in the center of another pair of excitatory and inhibitory place cells. If the number of place cells is large enough, a periodic structure of grid cells is formed. The STDP of excitatory synapses and the plasticity of inhibitory synapses, that keeps a constant frequency of spikes of excitatory neurons [102], lead to strengthening and adoption of grid cell activity. It is interesting to compare the idea of different smoothness of excitation and inhibition with the mechanism of formation of a regular structure in a chemical reaction of two substances with different diffusion coefficients which has been studied by Alan Turing [103].

At present, the general opinion is that place cells in the hippocampus and grid cells in the medial EC are the key components in path integration and goal finding. It is also assumed that the activity of these cells is modulated by head direction cells. The important question that is under discussion in experiments and modeling concerns the principles of the interaction between place cells and grid cells.

If it is true that place cells are leading in the formation of grid cells, then it would be reasonable to think that grid cells in the subicular complex and in the higher layers of the EC may have different origins. The subicular complex receives strong input from the CA1 field of the hippocampus, where most place cells are present. In the upper layers of the EC the hippocampal signal comes after switching in the subiculum and deep layers of the EC. Based on anatomical and model data, we can hypothesize that grid cells in the presubiculum and parasubiculum are formed due to influences from place cells, while in the EC they are formed by the signals from speed cells and other spatially modulated cells.

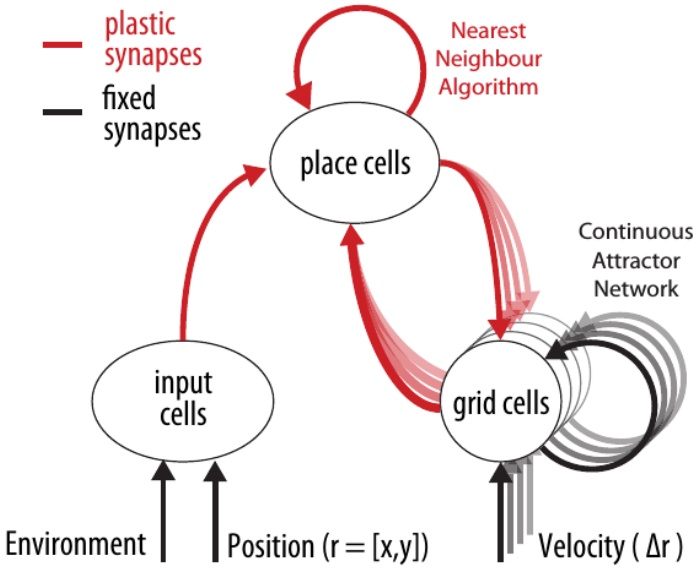

Fig. 21. Model of place and grid cell network with bi-directional connectivity. Circles denote neuronal populations. Arrows represent synaptic connections. Synapses are either fixed (black) or plastic (red). Place cells recurrent collaterals are modeled implicitly by a pattern completion process. Grid cells recurrent collaterals are fixed and implement a continuous attractor network model [98].

The idea that place cells and grid cells are different representations of spatial information found an interesting interpretation and development in the paper [104]. In this paper, the authors contend that two representations of space in the form of spatial coordinates and in the

form of hexagonal lattices are the analogues of a function and its Fourier transform. In other words, the representation of space in terms of grid cell activity is an analogue of frequency representation, while place cells provide space representation in physical coordinates. Under this assumption, the transformation from grid cells to place cells can be considered as backward Fourier transform. The authors prove that there is a one-to-one mapping of these two space representation.

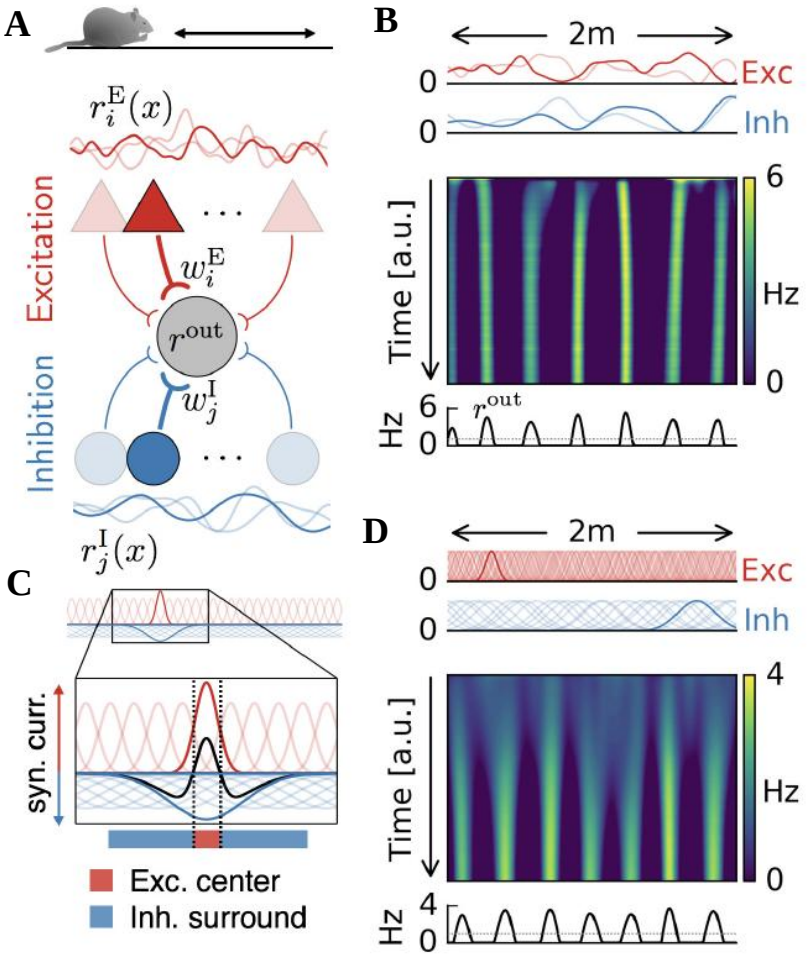

Fig. 22. Emergence of periodic, invariant and single field firing patterns. **A.** Network model for a linear track. A threshold-linear output neuron (gray) receives input from excitatory (red) and inhibitory (blue) cells, which are spatially tuned (curves on top and bottom). **B.** Spatially tuned input with smoother inhibition than excitation. The fluctuating curves (top) show two exemplary spatial tunings (one is highlighted) of excitatory and inhibitory input neurons. Interacting excitatory and inhibitory synaptic plasticity gradually changes an initially random response of the output neuron (firing rate rout) into a periodic, grid cell-like activity pattern. **C.** The mechanism illustrating place cell-like input. When a single excitatory weight is increased relative to the others, the balancing inhibitory plasticity rule leads to an immediate increase of inhibition at the associated location. If inhibitory inputs are smoother than excitatory inputs, the resulting approximate balance creates a center surround field: a local overshoot of excitation (firing field) surrounded by an inhibitory corona. The next firing field emerges at a distance where the inhibition has faded out. Iterated, this results in a spatially periodic arrangement of firing fields. **D.** Inputs with place field-like tuning. Gaussian curves (top) show the spatial tuning of excitatory and inhibitory input neurons (one neuron of each kind is highlighted, 20% of all inputs are displayed). A grid cell firing pattern emerges from an initially random weight configuration [99].

4. CONCLUSION

Space representation and space navigation system of mammals is a complex network of special neural detectors located in many brain areas. In the last years several important components of the SRS have been discovered. Also, partial understanding of the role of brain rhythms in spatial information processing has been obtained. However, the question of how spatial cognition is realized in the brain is far from being solved [105].

The advanced models of the SRS include place cells, grid cells, and head direction cells, trying to describe in more detail cell interaction when spatial tasks are solved by animals. The problem with the models is that they often rely on radically different and mutually contradictable hypotheses. Right now there is no possibility neither to select a single correct model nor to combine a unite model that would absorb positive aspects of existing approaches.

The difficulties in understanding the SRS are related to more general problems that are not solved in the neurobiology: how objects and events are represented in the brain, how this representation changes when the information flows up to the higher levels of processing, how long term memory is formed and recalled, how attention and emotions interfere in information processing and decision making. The advantage of spatial tasks is that they provide us with particular examples of complex cognitive functions that are easier to explore. However, if we study goal planning, decision making, and spatial cues recognition, we have to extend our observations and modeling to the brain regions outside the hippocampus, EC, and subiculum.

There are more specific problems that should be solved in the near future. First, boundary cells should be an object of additional research in order to understand what kind of information about the boundary is accumulated by these cells. Second, the lateral EC should be studied as a source of non-spatial information for the hippocampus. Third, the role of the hippocampal rhythms and their combination should be elucidated in spatial tasks. Fourth, the relation and interaction between spatial and non-spatial tasks in the hippocampal activity is waiting a solution. Fifth, a definite decision must be made about the circuit and interaction principles of grid cells and place cells. Finally, a large scale model of the SRS is needed that would unite all the known details about this system construction and functioning.

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